Exercise therapy and cardiac, autonomic and systemic function in patients with chronic heart failure

Melissa Jane Pearson

Bachelor of Exercise & Sports Science
(Clinical Exercise Physiology) (Honours, Class 1)

A thesis submitted in fulfilment for the degree of

Doctor of Philosophy

School of Science and Technology

University of New England, NSW Australia

June 2018

Declaration

I declare that this work has not been and is not being submitted for any other degree to this or any other University. To the best of my knowledge it does not contain any materials previously published or written by another person except where due reference is made in the text; and all substantive contributions by others to the work presented, including jointly authored publications is clearly acknowledged.

Signed

20th June 2018

Date

Acknowledgments

To my Principal Supervisor Professor Neil Smart, I would like to acknowledge and express my sincere thanks for your guidance, advice, support, knowledge and patience. Reflecting back to the start of the journey I really wasn't sure what to expect, however, I can honestly say that I am extremely grateful for the opportunity and experience. It did not go the original way it was planned, but that's life and all part of the journey. I am taking a lot more away from this journey then I expected. I would also like to thank Associate Professor Gudrun Dieberg for your support, advice and friendship over the years.

Most importantly, I would like to acknowledge my husband Warwick. Words cannot fully express how I feel. It was not in our plan for me to undertake such a commitment, but when the opportunity arose you were encouraging and supportive as you always are. There have been ups and down (probably a nice way of putting it), but your unconditional love, encouragement and support have kept me going. You are the most patient person I have ever known. Thank you for reading all the papers, even though they are way outside your field of research. Yes you deserve a PhD as well (oh wait you already have one). Finally, while he cannot read, Bucky kept me company while sitting at the computer all those hours and helped me keep my sanity.

Financial Support

This body of work was supported by an Australian Postgraduate Award Scholarship (APA) funded by the Australian Federal Government.

Thesis Format

This thesis is presented as a thesis by publication. The listed publications have been inserted into the thesis as chapters. Each of the following has been accepted and published in peer reviewed journals, in press or submitted for peer-review.

Pearson, M. J., & Smart, N. A. (2017). Effect of exercise training on endothelial function in heart failure patients: a systematic review meta-analysis. *International Journal of Cardiology*, *231*, 234-243, https://doi.org/10.1016/j.ijcard.2016.12.145

Pearson, M. J., & Smart, N. A. (2017). Aerobic training Intensity for Improved Endothelial Function in Heart Failure Patients: A Systematic Review and Meta-Analysis. *Cardiology Research and Practice*, *2017*. Article ID 2450202, https://doi.org/10.1155/2017/2450202

Pearson, M. J., & Smart, N. A. (2018). Exercise therapy and autonomic function in heart failure patients: a systematic review and meta-analysis. *Heart Failure Reviews*, *23*(1), 91-108. https://doi.org/10.1007/s10741-017-9662-z

Pearson, M. J., Mungovan, S. F., & Smart, N. A. (2018). Effect of aerobic and resistance training on inflammatory markers in heart failure patients: systematic review and meta-analysis. *Heart Failure Reviews*, *23*(2), 209-223. https://doi.org/10.1007/s10741-018-9677-0

Pearson, M. J., King, N., & Smart, N. A. (2018). Effect of exercise therapy on established and emerging circulating biomarkers in heart failure patients: A systematic review and meta-analysis. *Open Heart*. **ARTICLE IN PRESS** http://dx.doi.org/10.1136/openhrt-2018-000819.

Pearson, M. J., Mungovan, S. F., & Smart, N. A. (2017). Effect of exercise on diastolic function in heart failure patients: a systematic review and meta-analysis. *Heart Failure Reviews, 22(2), 229-242.* https://doi.org/10.1007/s10741-017-9600-0

Pearson, M. J., & Smart, N. A. (2018). Reported methods for handling missing change standard deviations in meta-analyses of exercise therapy interventions in patients with heart failure: a systematic review. **Submitted to PLOS ONE 25th May 2018 Under review**

Publications arising from thesis:

Chapter 3:

Pearson, M., & Smart, N. (2017). Effect of exercise training on endothelial function in heart failure patients: A systematic review meta-analysis. *International Journal Of Cardiology*, *231*, 234-243. doi: 10.1016/j.ijcard.2016.12.145

Chapter 4:

Pearson, M., & Smart, N. (2017). Aerobic Training Intensity for Improved Endothelial Function in Heart Failure Patients: A Systematic Review and Meta-Analysis. *Cardiology Research And Practice*, *2017*, 1-10. doi: 10.1155/2017/2450202

Chapter 5:

Pearson, M., & Smart, N. (2017). Exercise therapy and autonomic function in heart failure patients: a systematic review and meta-analysis. *Heart Failure Reviews*, *23*(1), 91-108. doi: 10.1007/s10741-017-9662-z

Chapter 6:

Pearson, M., Mungovan, S., & Smart, N. (2018). Effect of aerobic and resistance training on inflammatory markers in heart failure patients: systematic review and meta-analysis. *Heart Failure Reviews*, *23*(2), 209-223. doi: 10.1007/s10741-018-9677-0

Chapter 7:

Pearson, M., King, N., & Smart, N. (2018). Effect of exercise therapy on established and emerging circulating biomarkers in patients with heart failure: a systematic review and meta-analysis. *Open Heart*, *5*(2), e000819. doi: 10.1136/openhrt-2018-000819

Chapter 8:

Pearson, M., Mungovan, S., & Smart, N. (2017). Effect of exercise on diastolic function in heart failure patients: a systematic review and meta-analysis. *Heart Failure Reviews*, *22*(2), 229-242. doi: 10.1007/s10741-017-9600-0

Chapter 9:

Pearson, M., & Smart, N. (2018). Reported methods for handling missing change standard deviations in meta-analyses of exercise therapy interventions in patients with heart failure: A systematic review. *PLOS ONE*, *13*(10), e0205952. doi: 10.1371/journal.pone.0205952

Table of Contents

List of Figures

List of Tables

Abbreviations

ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
ACEI	Angiotensin-converting-enzyme inhibitor
ADL	Activities of daily living
AHA	American Heart Association
AT	Anaerobic threshold
β-Blockers	Beta blockers
BNP	Brain-type natriuretic peptide
CCS	Canadian Cardiovascular Society
CO	Cardiac output
CPX	Cardiopulmonary exercise test
CRP	C-reactive protein
cTnT	Cardiac Troponin
CT-proAVP	Copeptin
DBP	Diastolic blood pressure
DT	Deceleration time
E/A	Ratio of early to late ventricular filling
EACPR	European Association of Cardiovascular Prevention and Rehabilitation
ECG	Electrocardiogram
ESC	European Society of Cardiology
EDV	End diastolic volume
E/E’	Ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity
EPCs	Endothelial progenitor cells
ESSA	Exercise and Sports Science Australia
ESV	End systolic volume
EF	Ejection fraction
FES	Functional electrical stimulation
FMD	Flow-mediated dilation
Gal-3	Galectin 3

GH	Growth hormone
HF	Heart failure
HF_{nu}	High frequency normalised units
HFpEF	Heart failure preserved ejection fraction
HFmrEF	Heart failure mid-range ejection fraction
HFrEF	Heart failure reduced ejection fraction
HIIT	High intensity interval training
HR	Heart rate
HR_{peak}	Peak heart rate
HR_{rest}	Heart rate at rest
HRR	Heart rate recovery
HRR_1	Heart rate recovery at 1 minute
HRR_2	Heart rate recovery at 2 minutes
HRV	Heart rate variability
ICAM	Intercellular adhesion molecule
IGF-1	Insulin like growth factor 1
IMT	Inspiratory muscle training
IL-6	Interleukin 6
IPD	Individual patient data
KNGF	Dutch Royal Society of Physiotherapy
LF_{nu}	Low frequency normalised units
LVAD	Left ventricular assist device
LVEDD	Left ventricular end diastolic diameter
LVEF	Left ventricular ejection fraction
METS	Metabolic equivalents
MCT	Moderate intensity continuous training
MIP	Maximal inspiratory pressure
MLHFQ	Minnesota living with heart failure questionnaire
MRA	Mineralocorticoid receptor antagonists
MR-proANP	Mid-regional pro-atrial natriuretic peptide
MR-proADM	Mid-regional pro-adrenomedullin
MSNA	Muscle sympathetic nerve activity

NMD	Nitroglycerine mediated dilatation
NMES	Neuromuscular electrical stimulation
NP	Natriuretic peptides
NT-proBNP	N-terminal portion brain-type natriuretic peptide
NYHA	New York Heart Association
PI	Maximal inspiratory pressure
PNS	Parasympathetic nervous system
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
QoL	Quality of life
RAAS	Renin–angiotensin–aldosterone system
RCT	Randomised controlled trial
RMSSD	Root mean square of the successive differences
SBP	Systolic blood pressure
SD	Standard deviation
SDNN	Standard deviation of normal to normal R-R intervals
SNS	Sympathetic nervous system
ST2	Suppression of tumorigenicity 2
SV	Stroke volume
SVR	Systemic vascular resistance
TNF-α	Tumor necrosis factor alpha
TUG	Timed up and go
VAD	Ventricular assist device
VAT	Ventilatory anaerobic threshold
VCAM	Vascular adhesion molecule
V_E	Minute ventilation
V_E/VCO_2	Ventilatory equivalent for carbon dioxide
VO_{2AT}	Oxygen uptake at anaerobic threshold
VO_{2peak}	Peak oxygen uptake
6MWD	Six-minute walk distance

Abstract

Background

Exercise training is now accepted as a safe, adjunct therapy in stable heart failure patients. Acceptance of exercise training or therapy within this population is due to the benefits that have been demonstrated over the past three decades in trials and data syntheses presented in systematic reviews and meta-analyses. As new concepts emerge and with an increase in the number of trials comes the challenge of keeping up-to date with all the information, deciphering what's relevant, deciding how to interpret and apply the findings and what should happen next. Fortunately, the research methodologies of systematic review and meta-analysis provide a suitable platform for collecting, analysing and critically appraising studies.

Methods

An initial evidence mapping exercise identified the current level of research activity in regard to the synthesis of evidence focusing on the broad question of the benefits and/or effects of exercise training in heart failure patients. The objective of the exercise was to identify gaps in research synthesis and areas in which research synthesis would be valuable. A series of research syntheses were then conducted based on the identified gaps, using systematic reviews as the research methodology, and applying the statistical technique of meta-analysis where possible.

Results

While some of the effects of exercise training are now well established, e.g., improved functional capacity and quality of life, new trials and new concepts continue to emerge. Evidencing mapping highlighted a number of areas in which research synthesis was limited or out dated. The identified areas addressed the effect of exercise training on specific areas of cardiac, autonomic and systemic inflammatory markers in chronic heart failure patients; all associated with the pathogenesis and progression of heart failure. Evidence from systematic reviews and meta-analyses demonstrated that exercise training/therapy resulted in statistically significant improvements in: 1) endothelial function (FMD and EPCs), 2) direct (MSNA) and indirect (HRR, HRV) measures of autonomic function, 3) cardiac biomarkers

(BNP, NT-proBNP) and 4) diastolic function, measured as E/E'. However, the evidence for improvements in a number of inflammatory markers was inconclusive, and limited evidence is currently available to allow for any conclusion to be drawn on the effect of exercise on emerging heart failure biomarkers.

Conclusion

This thesis utilised systematic reviews and meta-analyses as the research methodology to answer questions in relation to exercise training in heart failure patients. This work adds to the current evidence base by providing a robust synthesis of data in regard to effects of exercise training and therapy on endothelial function, autonomic function, inflammatory markers, biomarkers and diastolic function in heart failure patients.

1 Chapter 1 Introduction - Thesis Overview

Heart Failure remains a worldwide leading cause of morbidity and mortality, with significant social and financial consequences. While there is no cure for heart failure, pharmacological therapy is the mainstay of treatment for heart failure patients. However, exercise training is now a recommendation in numerous countries and several published guidelines exist to inform exercise prescription. Due to its ability to improve functional capacity, symptoms and reduce risk of hospitalisation, the most recent European Society of Cardiology (ESC) guidelines for diagnosis and treatment of chronic heart failure identify aerobic exercise training as a Class 1A recommendation in stable heart failure patients (Ponikowski et al., 2016).

Over the past three decades the amount of research in this area has expanded. Given that we are still learning about the pathophysiology of this complex syndrome, studies will continue to emerge and at a more rapid pace, adding to and strengthening current evidence or refuting previous evidence. As the volume of studies increases, the garnishing of relevant and useful information becomes a time consuming task for those involved in patient management. Fortunately, methods exist by which information can be accumulated and data from studies combined, allowing us to evaluate the effect of these interventions, thereby providing evidence to inform decisions. Additionally, reviews and analyses combining a number of studies at one time aid in the identification of areas that require more research, in order to consolidate, strengthen or clarify particular areas of already existing evidence. Systematic review and meta-analyses allow us to do these things.

This thesis had two main aims:

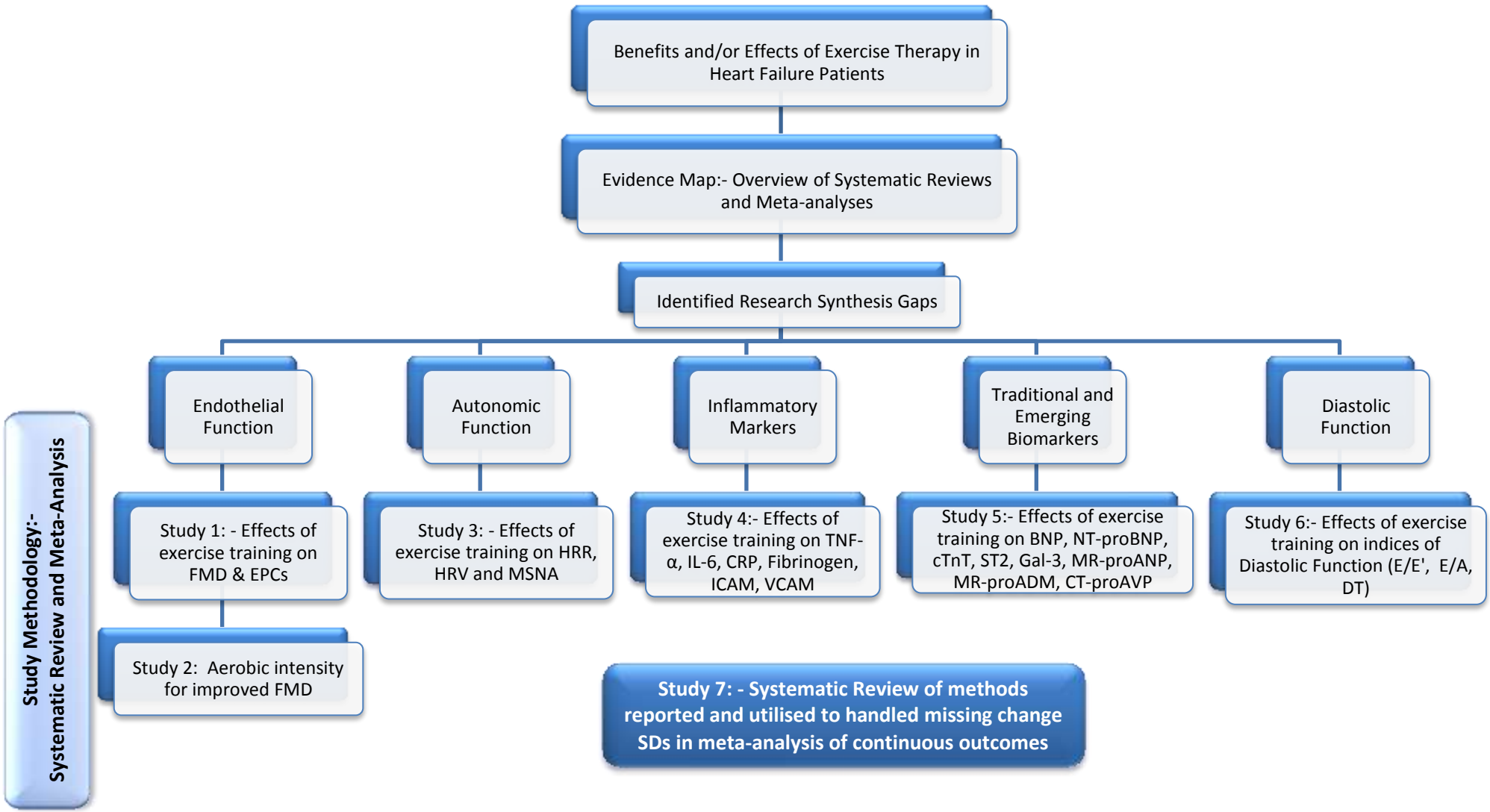
1) Firstly to identify the current level of systematic review and meta-analysis research activity dealing with the benefits and/or effects of exercise training; informing research synthesis gaps; and
2) To undertake research synthesis using systematic review as the research methodology and where appropriate apply meta-analysis to determine an effect

size, based on the identified areas considered a valuable addition to the current literature.

Literature Review - Chapter 2

Chapter two provides a brief overview of the burden, diagnosis, pathophysiology and treatment of chronic heart failure. A brief history of exercise training in heart failure patients is presented. An overview of systematic reviews and meta-analyses in this area was conducted via evidence mapping to determine the research activity within this area. As a result of the information garnished from the evidence map and the identified gaps, research questions were formulated upon which the remaining chapters of this work are based. Chapters 3 to 9 are a series of studies using systematic reviews and meta-analysis as the research methodology (Figure 1).

Figure 1– Thesis Flow Diagram



Peer reviewed publication - Chapter 3 - Effect of exercise training on endothelial function in heart failure patients: a systematic review meta-analysis

Pearson, M. J., & Smart, N. A. (2017). Effect of exercise training on endothelial function in heart failure patients: a systematic review meta-analysis. *International Journal of Cardiology*, *231*, 234-243, https://doi.org/10.1016/j.ijcard.2016.12.145

Endothelial dysfunction is associated with the pathogenesis and progression of heart failure. The endothelium plays a major role in the regulation of vascular homeostasis and exercise training has demonstrated improvements in endothelial function across different populations. A number of studies have now investigated endothelial function and exercise in heart failure patients. This chapter is a systematic review and meta-analysis conducted to answer the following questions:

Research questions and aims

a. Does exercise training improve endothelial function in heart failure patients with reduced ejection fractions? If so, can the improvement be quantified?
b. Does exercise training promote mobilisation of endothelial progenitor cells (EPCs) in this population?

Peer reviewed publication - Chapter 4 - Aerobic Training Intensity for Improved Endothelial Function in Heart Failure Patients: A Systematic Review and Meta-Analysis.

Pearson, M. J., & Smart, N. A. (2017). Aerobic Training Intensity for Improved Endothelial Function in Heart Failure Patients: A Systematic Review and Meta-Analysis *Cardiology Research and Practice*, *2017*. Article ID 2450202. https://doi.org/10.1155/2017/2450202

Identification of training characteristics which produce the most optimal benefits is an ever expanding area of research and this is no different in the heart failure setting. While all

training characteristics will influence results to some degree, the area of training intensity in cardiac rehabilitation has received increased attention over the last decade. In light of the findings of the results on improved endothelial function in chapter 3, this chapter is a systematic review and meta-analysis conducted to answer the following questions:

Research questions and aims

a. Is there an optimal training intensity for the improvement of endothelial function in heart failure patients with reduced ejection fractions?

Peer reviewed publication - Chapter 5 - Exercise therapy and autonomic function in heart failure patients: a systematic review and meta-analysis.

Pearson, M. J., & Smart, N. A. (2018). Exercise therapy and autonomic function in heart failure patients: a systematic review and meta-analysis. *Heart Failure Reviews*, *23*(1), 91-108. https://doi.org/10.1007/s10741-017-9662-z

Autonomic imbalance, reflected by increased Sympathetic Nervous System (SNS) activity and reduced Parasympathetic Nervous System (PNS) activity, is a hallmark of heart failure. A number of different tools, providing a range of indices, are utilised to access autonomic function. This chapter is a systematic review and meta-analysis conducted to answer the following questions:

Research questions and aims

a. What evidence exists for improved heart rate recovery (HRR) from exercise training in heart failure patients? Can the level of improvement be quantified?
b. What evidence exists for improved heart rate variability (HRV) from exercise training in heart failure patients? Can the level of improvement be quantified?
c. What evidence exists for improved muscle sympathetic nerve activity (MSNA) in heart failure patients? Can the level of improvement be quantified?
d. Does exercise training improve autonomic balance in patients with heart failure?

Peer reviewed publication - Chapter 6 - Effect of aerobic and resistance training on inflammatory markers in heart failure patients: systematic review and meta-analysis.

Pearson, M. J., Mungovan, S. F., & Smart, N. A. (2018). Effect of aerobic and resistance training on inflammatory markers in heart failure patients: systematic review and meta-analysis. *Heart Failure Reviews*, *23*(2), 209-223. https://doi.org/10.1007/s10741-018-9677-0

Heart failure is characterised by increased levels of pro-inflammatory markers and exercise is widely considered to have an "anti-inflammatory" effect. This chapter is a systematic review and meta-analysis conducted to answer the following questions:

Research questions and aims

a. Have the latest training studies helped clarify the effect of exercise training on circulating pro-inflammatory cytokines Tumor Necrosis Factor alpha (TNF-α) and Interleukin 6 (IL-6) in heart failure patients?
b. To what extent, if any, can aerobic and resistance training improve circulating levels of TNF-α and IL-6 in heart failure patients?
c. To what extent, if any, can aerobic and resistance training improve acute-phase reactants, C-reactive protein (CRP) and Fibrinogen in heart failure patients?
d. To what extent, if any, can aerobic and resistance training improve the adhesion molecules, vascular adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM) in heart failure patients?

Peer reviewed publication - Chapter 7 - Effect of exercise therapy on established and emerging circulating biomarkers in heart failure patients: A systematic review and meta-analysis.

Pearson, M. J., King, N., & Smart, N. A. (2018). Effect of exercise therapy on established and emerging circulating biomarkers in heart failure patients: A systematic review and meta-analysis. *Open Heart* http://dx.doi.org/10.1136/openhrt2018-000819

Levels of circulating biomarkers are important in the diagnosis and risk stratification of heart failure patients. However, the role of biomarkers has evolved over the last decade with the discovery and emergence of "new" biomarkers aiding in our understanding of the numerous pathophysiological pathways involved in heart failure. It is suggested that biomarker profiles may be effective in improving and guiding treatment strategies. This chapter is a systematic review and meta-analysis conducted to answer the following questions:

Research questions and aims

a. Have the more recent exercise training studies strengthened the evidence for improvements in traditional heart failure biomarkers, BNP and NT-proBNP?
b. To what extent do traditional and non-traditional modes of exercise training improve BNP and NT-proBNP in heart failure patients?
c. Can exercise therapy improve the levels of emerging heart failure biomarkers that reflect different pathophysiological pathways?

Peer reviewed publication - Chapter 8 - Effect of exercise on diastolic function in heart failure patients: a systematic review and meta-analysis.

Pearson, M. J., Mungovan, S. F., & Smart, N. A. (2017). Effect of exercise on diastolic function in heart failure patients: a systematic review and meta-analysis. *Heart Failure Reviews, 22(2), 229-242.* https://doi.org/10.1007/s10741-017-9600-0

Diastolic dysfunction is associated with the development and progression of heart failure. While most frequently referred to in the context of patients with preserved ejection

fraction, diastolic dysfunction often coexists with systolic function and is hence evident in patients with reduced ejection fractions. This chapter is a systematic review and meta-analysis conducted to answer the following questions:

Research questions and aims

a. What evidence exists for the use of exercise training to improve diastolic function in heart failure patients with reduced ejection fractions?
b. What evidence exists for the use of exercise training to improve diastolic function in heart failure patients with preserved ejection fractions?

Peer reviewed publication - Chapter 9 - Reported methods for handling missing change standard deviations in meta-analyses of exercise therapy interventions in patients with heart failure: a systematic review

Pearson, M.J., & Smart, N.A. (2018). Reported methods for handling missing change standard deviations in meta-analyses of exercise therapy interventions in patients with heart failure: a systematic review. *Submitted to PLOS ONE 25th May 2018 - Under review*

During the research and writing of this thesis a number of issues arose which created difficulties. The most common issue encountered throughout the series of analyses was the absence of a reported change in standard deviation. This chapter is a review of current methods reported and utilised in heart failure and exercise training studies to deal with missing change standard deviations when these cannot be obtained directly from authors.

Research questions and aims

a. What methods are currently reported by researchers performing meta-analyses, to deal with missing change standard deviations?
b. What methods are currently utilised by researchers performing meta-analyses, to impute a change in standard deviation?

c. Is there any consistency in standard deviation imputation in current heart failure and exercise meta-analyses?

Conclusion - Chapter 10

This chapter brings together the findings from all manuscripts within this thesis. Systematic reviews synthesise results from all studies that fit the stated inclusion criteria, and where possible meta-analyses provide statistical analysis, in an effort to provide quality evidence that can guide clinicians and shape future research. Results from the manuscripts in this thesis add to the current evidence base for exercise training in heart failure patients. Furthermore, they highlight the need and importance of updating previously published evidence, as new studies and new research methodologies applied in studies can change the conclusion of a review.

2 Chapter 2 - Literature Review

2.1 Introduction

The following is a brief overview of the burden, diagnosis, classification, pathophysiology and current treatment of chronic heart failure.

2.1.1 Epidemiology and Burden of Heart Failure

Heart failure is a major global health problem. Worldwide it is estimated to affect 37.7 million people (Ziaeian & Fonarow, 2016). The lifetime risk of developing heart failure is 20% and even greater in people with hypertension (Metra & Teerlink, 2017). Despite improvements in therapy, mortality rates and hospitalisation remain high (Ponikowski et al., 2016). Currently the majority of incidence and prevalence data comes from North America and Europe, with an estimated prevalence of 1-2% of the adult population (Ponikowski et al., 2016). In the United States of America (USA) approximately 960,000 new cases of heart failure are diagnosed per year and an estimated 6.5 million adults live with heart failure (Benjamin et al., 2017). This is projected to increase to more than 8 million by 2030 (Benjamin et al., 2017). Concurrently, the cost associated with heart failure is expected to rise, increasing from $30.7 billion in 2012, of which 68% is attributable to direct medical costs, to an estimated $69.7 billion in 2030 (Heidenreich et al, 2013). In the USA one in eight deaths had heart failure mentioned on the death certificate in 2014 (Benjamin et al., 2017). Previous global estimates published in 2014, put the cost of heart failure at $108 billion per year, a value which will undoubtedly rise (Cook, Cole, Asaria, Jabbour & Francis, 2014).

The picture in Australia is similar, with the estimated prevalence of heart failure ranging from 1-2% (Sahle, Owen, Mutowo, Krum & Reid, 2016). Prevalence however, increases with age, is higher in indigenous Australians and greater in rural and remote locations (Sahle et al., 2016). However, while the 2014-2015 National Health

Survey by the Australian Bureau of Statistics estimated that 111,000 adult Australians were living with heart failure, this is based on self-reported data, which likely underestimates the true burden of the disease (Australian Institute of Health and Welfare, 2017). In fact, comprehensive data to describe the burden of heart failure in Australia is lacking (Chan et al., 2016a). Most recently it was estimated that in excess of 67,000 Australian adults 45 years of age or older are diagnosed with heart failure every year and that an estimated 511,000 Australians (~2.1% population) are currently living with heart failure (Chen, Booley, Keates & Stewart, 2017). However, this estimate is for heart failure patients with reduced ejection fraction. It is estimated that a further 536,000 have heart failure with preserved ejection fraction (Chen et al., 2017). Currently it is estimated that 61,000 deaths per year are heart failure related (Chen et al., 2017). With an estimated number of hospital admissions in excess of 158,000, equating to more than 1.1 million days in hospital per year, the estimated annual community and in-patient health costs of heart failure in Australia are AUD $3.1 billion (Chen et al., 2017). With a predicted increase in the next 10-15 years of the number of patients living with heart failure to 750,000, the cost is predicted to increase to an estimated AUD $3.8 billion per annum (Chan et al., 2016a).

2.1.2 Definition, Diagnosis and Classification

Chronic heart failure is a complex clinical syndrome with typical signs and symptoms that occur at rest or during exertion (Ponikowski et al., 2016). It is the result of structural and/or functional cardiac abnormalities, impairing the heart's ability to fill with blood at normal pressure or eject sufficient blood to support the body's physiological needs (Ponikowski et al., 2016; Yancy et al., 2013). While it is defined by typical symptoms, quite often these are non-specific (Ponikowski et al., 2016). The cardinal symptoms of heart failure are dyspnoea, fatigue and exercise intolerance (Yancy et al., 2013). In heart failure patients, exercise tolerance, measured as peak oxygen uptake (VO_{2peak}) is approximately 35% lower than in healthy individuals (Tucker et al., 2018) and peak VO_2 is an independent predictor of

prognosis (Alba et al., 2016). As heart failure progresses, these symptoms impact on the ability to perform activities of daily living (ADLs) and contribute to poor quality of life. The condition is considered one of complexity given its impact on multiple organs within the body.

A heart failure diagnosis is based on the clinical assessment of the patient's medical history, signs (e.g., elevated jugular venous pressure, peripheral oedema, tissue wasting) and symptoms (e.g., breathlessness, fatigue, ankle swelling, orthopnea), and a number of medical and imaging investigations including assessment of natriuretic peptides (NPs), electrocardiogram (ECG) and echocardiography (Ponikowski et al., 2016). The updated 2016 ESC Guidelines (Ponikowski et al., 2016) provide an algorithm for the diagnosis of heart failure in the non-acute setting outlining tests and when these should be utilised. Application of the ESC criteria, further establishes the type of heart failure based on the results of investigations, with heart failure phenotypes primarily described according to left ventricular ejection fraction (LVEF).

Formerly known as systolic heart failure, heart failure with reduced ejection fraction (HFrEF) is defined by signs and symptoms and a LVEF of <40% (Ponikowski et al., 2016). Heart failure with normal or preserved ejection fraction (HFpEF), formerly known as diastolic heart failure, is defined by the presence of signs and symptoms of heart failure, a LVEF of ≥50%, elevated levels of NPs (BNP and/or NT-proBNP) and evidence of relevant structural heart disease or diastolic dysfunction (Ponikowski et al., 2016). The key structural alterations are: left ventricular hypertrophy, increased left ventricular mass index or left atrial volume index, with an increased E/E' ratio and E' as the main functional alterations (Ponikowski et al., 2016). However, timely diagnosis of HFpEF remains a challenge (Ponikowski et al., 2016) and comorbidities can be a confounder in the diagnosis. The recent 2016 ESC guidelines introduced a new classification, heart failure with mid-range ejection fraction (HFmrEF), defined as signs and symptoms of heart failure with a LVEF of 40-49%, elevated levels of NPs and either relevant structural heart disease or diastolic dysfunction as per HFpEF (Ponikowski et al., 2016). While not defined as a separate phenotype in the USA

guidelines (ACCF/AHA), it is stated that the characteristics and treatment patterns in this population (LVEF 41-49%) represent an intermediate group (Yancy et al., 2013). However, whether HFmrEF is a distinct clinical entity is currently a matter of debate (Rickenbacher et al., 2017).

In addition to defining and classifying heart failure according to LVEF, heart failure is also classified according to the level of severity of symptoms. The New York Heart Association (NYHA) functional classification table is the most commonly used method to grade the severity of heart failure. Categorising patients into one of four classes according to functional limitations, with severity ranging from asymptomatic (NYHA Class I; ordinary physical activity does not cause undue fatigue, dyspnoea or palpitations) to severe (NYHA Class IV; symptoms of heart failure present even at rest, mostly bedbound) (Yancy et al., 2013).

2.1.3 Aetiology and Pathophysiology

The aetiologies of heart failure are quiet diverse, with structural and/or functional changes resulting from a myriad of causes and events (Yancy et al., 2013; Ponikowski et al., 2016). Many patients with chronic heart failure have a history of coronary artery disease, hypertension, cardiomyopathies, valve disease or a combination (Metra & Teerlink, 2017). Additionally, many people with heart failure have comorbid conditions.

Traditionally heart failure was considered to be purely a hemodynamic disorder (Van Linthout & Tschöpe, 2017). However, over the past few decades our understanding of the development and progression of heart failure has significantly improved and a number of pathophysiological models or “hypotheses” have emerged (Braunwald, 2013). However, no single model has been able to fully explain the pathophysiological mechanisms. Therefore, it is now accepted that heart failure is a complex multifactorial syndrome involving different pathways and pathological processes (Chow et al., 2017), with adaptations involving many body organs and

systems, including cardiovascular, neuroendocrine, musculature, renal, hemostatic, immune and inflammatory responses (Piepoli & Coats, 2013).

HFrEF

After the initial myocardial injury or stress, the pumping capacity of the heart is impaired, however, a number of compensatory mechanisms are activated to restore cardiovascular homeostasis (Hartupee & Mann, 2017). To date the main compensatory mechanisms described involve neurohormonal adaptations, which include activation of the sympathetic nervous system (SNS) and renin-angiotensin aldosterone systems (RAAS); increased secretion of natriuretic peptides (NPs), antidiuretic hormone and endothelin; alterations in nitric oxide (Hartupee & Mann, 2017) and inflammatory mediators (Mann, 2015). In the short-term compensatory mechanisms help to restore cardiac output by increasing heart rate, cardiac contractility, vascular resistance and renal sodium and fluid retention (Hartupee & Mann, 2017). Therefore, these mechanisms are initially beneficial; however a sustained response leads to further damage to the heart, kidneys and peripheral vasculature (Hartupee & Mann, 2017). The structural changes occurring in response to cardiomyocyte loss and increased neurohormonal activation are referred to as left ventricular remodelling (Metra & Teerlink, 2017) and these changes further contribute to disease progression (Hartupee & Mann, 2017).

The nature of heart failure does not lend itself to one single pathophysiological model. However, in HFrEF the predominant mechanism leading to left ventricular remodelling is considered to be the result of the progressive loss of cardiomyocytes due to various modes of cell death and increased myocardial strain (Paulus & Tschöpe, 2013), with neurohormonal activation and eccentric remodelling dominating the pathophysiology after an initial myocardial insult (Shah, 2017). Furthermore, heart failure severity and clinical prognosis have been correlated with neurohormonal activity (Hartupee & Mann, 2017; Florea & Cohn, 2014). The role of neurohormonal mechanisms in HFrEF is evident with pharmacological treatment in HFrEF targeting inhibition of SNS and RAAS, with demonstrated improvements in morbidity and mortality (Ponikowski et al., 2016).

HFpEF

About 50% of patients with heart failure have HFpEF and it is more prevalent in older, female patients (van Heerebeek & Paulus, 2016). Although diastolic dysfunction (impaired relaxation and increased diastolic stiffness) is the most prevalent and typical pathophysiological finding in HFpEF patients (van Heerebeek & Paulus, 2016), it is now recognised as a far more complex syndrome associated with multiple cardiac, vascular and non-cardiac factors (Borlaug, 2014; Borlaug 2016). Other contenders in the pathophysiology of HFpEF are: impaired systolic reserve function, abnormal ventricular-arterial coupling, chronotropic incompetence, inflammation, endothelial dysfunction, pulmonary arterial hypertension, renal insufficiency and altered myocardial energetics and skeletal muscle metabolism and perfusion (Borlaug, 2016; Shah, Katz & Deo, 2014). However, HFpEF is a highly heterogeneous syndrome and its pathophysiology is still not completely understood.

Traditionally, the pathophysiology of HFpEF was attributed to hypertensive left ventricular remodelling, with pressure overload leading to concentric hypertrophy, diastolic dysfunction and fibrosis (Redfield, 2016). However, in HFpEF there exists a high prevalence of cardiovascular and non-cardiovascular comorbidities, with systemic inflammation and endothelial dysfunction hallmarks of these comorbidities (van Heerebeek & Paulus, 2016). In 2013, a novel paradigm of HFpEF proposed that myocardial remodelling and associated dysfunction is driven by comorbidities (e.g., obesity, hypertension, diabetes mellitus, metabolic syndrome, COPD and iron deficiency), which induce a systemic pro-inflammatory state, oxidative stress, microvascular and endothelial dysfunction (Paulus & Tschöpe, 2013). This cascade of events leads to myocardial and vascular stiffness (Giamouzis, Schelbert & Butler, 2016). Systemic inflammation is evident from elevated levels of inflammatory biomarkers, and the chronic inflammation affects not only the myocardium, but skeletal muscles, lungs and kidneys leading to diverse HFpEF phenotypes (Shah et al., 2016). The mechanisms leading from the pro-inflammatory state to myocardial fibrosis also promote arterial stiffening (Samson, Jaiswal, Ennezat, Cassidy & Le Jemtel, 2016). Furthermore, the high-incidence of HFpEF among the elderly

highlights age as a risk factors for HFpEF, with age-related increases in arterial stiffness likely a trigger for left ventricular remodelling (Samson et al., 2016). Given the heterogeneity of the HFpEF population it is likely a number of pathophysiological abnormalities support a multifactorial aetiology (Zakeri & Cowie, 2018).

Currently, it is estimated that approximately up to 20% of patients have HFmrEF (Nauta et al., 2017). However, at this point in time with the limited data available, the underlying pathophysiology of HFmrEF is still not completely elucidated (Nauta et al., 2017). The establishment of this new category has stimulated research into characteristics, pathophysiology and treatment for patients (Rickenbacher et al., 2017). However, emerging data is inconsistent as to whether HFmrEF is closer to HFrEF or HFpEF (Lund et al., 2018). Patients with HFmrEF have a high prevalence of Ischemic heart disease and therefore in terms of aetiology are more similar to HFrEF than HFpEF (Nauta et al., 2017).

Simplistically, in HFrEF, a direct sudden insult triggers cardiomyocyte damage and loss, and a neurohormonal cascade, however, HFpEF is considered a slower progressive process driven by age and comorbidities (Lourenco et al., 2018). Regardless of HF phenotype, neurohormonal activation (including autonomic dysfunction, with increased SNS activity), inflammation and endothelial dysfunction are involved in the pathophysiology of HF, however, the role each plays likely differs according to phenotype (Giamouzis et al., 2016; Van Linthout & Tschöpe, 2017; Verloop et al., 2015), in addition to possible differing roles in “sub phenotypes” in HFpEF (Shah et al., 2016; Samson et al., 2016)

Overall, a number of mechanisms and pathways operating at varying levels (e.g., cellular, molecular) are involved in the development and progression of heart failure. Fortunately, biomarker research has improved our understanding of the pathophysiology of heart failure, with biomarkers classified according to the associated pathophysiological processes; e.g., biomarkers of myocardial stretch, myocyte injury, fibrosis, matrix remodelling, inflammation, oxidative stress, neurohumoral activation and renal dysfunction (Correale et al., 2018). This

classification of biomarkers also helps distinguish the pathophysiological differences between heart failure phenotypes (Tromp et al., 2017; Sanders-van Wijk et al., 2015). The importance of biomarkers in the heart failure setting is evidenced by their recommended use in heart failure guidelines (Ponikowski et al., 2016; Yancy et al., 2013, Yancy et al., 2017), with BNP and/or NT-proBNP the "gold standard" biomarkers. Not only providing diagnostic information, they also provide important clinical information in regard to heart failure severity, risk stratification and prognosis (Correale et al., 2018). Furthermore, biomarker profiles which provide a more in-depth knowledge of the pathophysiology may prove beneficial in guiding heart failure therapy (Correale et al., 2018).

2.1.4 Heart Failure Management

Current heart failure management involves pharmacological and non-pharmacological therapies. The aim of treatment is to improve clinical status, symptoms, quality of life and survival time and reduce hospitalisation (Ponikowski et al., 2016). In patients with HFrEF, mortality and morbidity are improved with pharmacological therapies, including, angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers (β-blockers) and mineralocorticoid receptor antagonists (MRAs), while diuretics may reduce congestion (Ponikowski et al., 2016). However, in HFpEF evidence of reduced mortality and hospitalisation from pharmacological therapy remains unclear. While to date no pharmacological therapies in HFpEF have convincingly demonstrated improvements in morbidity or mortality (Ponikowski et al., 2016), meta-analyses of pharmacological trials have demonstrated improvements in clinical and surrogate endpoints from a number of drugs (Tschöpe et al., 2018) including beta-blockers and MRAs (Bonsu, Arunmanakul, Chaiyakunapruk, 2018; Zheng et al., 2018). Hence, treatment strategies currently focus on relief of symptoms, improving quality of life and management of risk factors and comorbidities (Tschöpe et al., 2018). Furthermore, given HFpEF is a highly heterogeneous syndrome, management and treatment strategies require an

individualised approach based on the specific HFpEF phenotype (Tschöpe et al., 2018).

Non-pharmacological management of heart failure focusing on lifestyle changes and exercise training is recommended regardless of heart failure phenotype (Ponikowski et al., 2016; Yancy et al., 2013). Medical devices and surgical therapies are also utilised in the management of heart failure and include implantable cardiac defibrillators, cardiac resynchronisation therapy, left ventricular assistive devices, and heart transplantation (Ponikowski et al., 2016; Yancy et al., 2013).

2.2 Exercise Training and Heart Failure

While pharmacological therapy is the mainstay of treatment for heart failure patients, exercise training is now widely considered a safe, adjunct treatment in stable heart failure patients. The most recent ESC guidelines for diagnosis and treatment of chronic heart failure identify aerobic exercise training as a Class 1A recommendation in stable heart failure patients (Ponikowski et al., 2016).

2.2.1 History

Avoidance of physical activity and bed rest were initially prescribed for heart failure patients due to concerns it would worsen cardiac function further reducing exercise capacity and quality of life. In 1988, Sullivan and colleagues reported improved exercise tolerance in addition to a number of other physiological improvements, after training in a small cohort (n=12) of chronic heart failure patients. Not long after, Coats and colleagues (1990) reported on the results of a prospective controlled trial. Using a crossover design, eleven patients completed eight weeks of home-based aerobic training and eight weeks of restricted activity. Exercise training was not only safe, with no recorded adverse events, but it improved exercise duration, VO_{2peak}, and heart failure related symptoms (Coats, Adamopoulos, Meyer, Conway & Sleight, 1990). In 1999, Belardinelli and colleagues published the first study demonstrating improved prognosis in heart failure patients after cardiac

rehabilitation. Ninety-nine heart failure patients were randomised to training or no training for 14 months. In addition to improved exercise capacity and quality of life (QoL), exercise training was associated with lower mortality [RR 0.37 (95% CI, 0.17 to 0.84), p=0.01] and lower rates of hospital readmission for heart failure [RR 0.29 (95% CI, 0.11 to 0.88), p=0.02] (Belardinelli, Georgiou, Cianci & Purcaro, 1999).

A common problem with the majority of studies investigating this population however, relates to the small sample sizes. To date the largest exercising training study in heart failure patients is the HF-ACTION Trial (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise) (Whellan et al., 2007); a large (n=2331) multicentre trial designed to assess the efficacy and long term safety of aerobic training in participants with an LVEF≤35%. Patients were randomised to usual care or usual care plus 36 supervised aerobic sessions followed by home-based training. The median follow-up time was 30 months and initial results failed to produce any significant findings in regard to mortality or hospitalisation. However, after adjustments for prognostic factors, exercise training was associated with modest but significant reductions in all-cause mortality and hospitalisation as well as cardiovascular mortality and heart failure hospitalisation (O'Connor et al., 2009). Furthermore, at both three and 12 months VO_{2peak} demonstrated modest but significant improvements (O'Connor et al., 2009). There have been a number of ancillary studies from the HF-ACTION trial, with modest but significant improvements observed in self-reported health status (Flynn et al., 2009), depressive symptoms (Blumenthal et al., 2012) and global health status (Ambrosy et al., 2017) in exercise training patients compared to usual care controls, although questions remained as to whether the results were clinically meaningful . In another ancillary study, Keteyian et al. (2012) reported that only a moderate level of exercise (3-7 MET hrs per week) was needed to obtain a clinical benefit. However, while considered to provide strong evidence on the effects of exercise training due to its design, the trial suffered from a number of limitations, including crossover of patients between usual care and exercising groups, as well as issues with exercise adherence (O'Connor et al., 2009; Flynn et al., 2009). These issues may have reduced the potential benefits and needs to be considered when interpreting the results.

Over the past three decades numerous trials of varying design have investigated the effects of exercise training in this population. Furthermore, over the years our understanding of the development and progression of heart failure has become progressively clearer. With acknowledgement that heart failure is a multisystem disorder involving not only the heart, but a number of organ systems and, due to the fact that exercise training likely exerts its beneficial effects at different levels, studies have investigated and analysed a diverse range of outcomes. These outcomes can be categorised as clinical (e.g., mortality and morbidity, exercise or functional capacity), physiological/pathophysiological (e.g., skeletal muscle function, vascular function, inflammation, autonomic function) and psychological effects (e.g., quality of life, depression). Trials and meta-analyses have consistently demonstrated that exercise training improves functional capacity (VO_{2peak}) and quality of life across the heart failure spectrum (Ismail, McFarlane, Nojoumian, Dieberg & Smart, 2013; Dieberg, Ismail, Giallauria & Smart, 2015; Taylor et al., 2014). Furthermore, it appears that there is a reduction in hospitalisation (Taylor et al., 2014). Trials to date have demonstrated the responses and adaptations to exercise training in various organs and systems with the general consensus that the benefits of exercise training are due to central and peripheral adaptations and these underlie the improvements in exercise capacity (Tucker et al., 2018). Over the years trials have demonstrated improvements in cardiac output and stroke volume, attenuation of left ventricular remodelling, and improvements in vascular and skeletal muscle function, with associated improvements in blood flow and oxygen extraction (Tucker et al., 2018). However, while these mechanisms are considered to mediate VO_{2peak} improvements in HFrEF the situation in HFpEF is not as clear (Tucker et al. 2018).

In understanding the current landscape of exercise training in heart failure, it is important to recognise that the majority of trials to date are in patients with HFrEF or an unspecified ejection fraction. Therefore while the evidence for exercise training in HFrEF is well established, evidence in HFpEF is still emerging, with a limited number of trials to date. However, meta-analyses (Chan, Giallauria, Vigorito & Smart, 2016; Dieberg et al., 2015; Pandey et al., 2014) have consistently

demonstrated improvements in VO_{2peak} and quality of life. A limited number of other trials have added to the HFpEF literature. Kitzman et al. (2016) considered the effect of exercise and/or calorie restriction in obese HFpEF; demonstrating increased VO_{2peak} with aerobic exercise or calorie restriction, however, the combination of diet and exercise provided an additive benefit. In a small pilot study Angadi et al. (2014) found that high-intensity interval training (HIIT) significantly improved VO_{2peak} compared to moderate-continuous training. Improvements in diastolic function measured as E/E', the ratio of early mitral inflow velocity and mitral annular early diastolic velocity (Edelmann et al., 2011; Fu et al., 2016), have also been observed.

2.2.2 Exercise Rehabilitation Practices and Guidelines

Over the years as the evidence from heart failure trials expanded a number of recommendations and guidelines for exercise training in this population emerged. Furthermore, as new and robust evidence emerges guidelines and recommendations are updated. Based on the evidence to date, from individual studies and research synthesis, exercise training for stable heart failure patients is currently recommended by the ESC (Ponikowski et al., 2016) and ACC/AHA (Yancy et al., 2013) guidelines (evidence 1A) in the treatment of chronic heart failure. Furthermore, a number of exercise prescription guidelines for cardiac rehabilitation exist across the world; some solely dedicated to heart failure cardiac rehabilitation (Price, Gordon, Bird & Benson, 2016). Specific exercise guidelines for heart failure patients have been issued by a number of authoritative organisations including, Exercise and Sports Science Australia (ESSA), American Heart Association (AHA), European Association of Cardiovascular Prevention and Rehabilitation (EACPR), Dutch Royal Society of Physiotherapy (KNGF) and the Canadian Cardiovascular Society (CCS).

While aerobic training is recommended by all guidelines, currently there is no universal agreement on the best modality of training in chronic heart failure patients. Exercise prescription should therefore be individualised based on clinical evaluation and consideration of patient preferences likely to have a positive impact on exercise adherence. In Australia, the current ESSA position statement for exercise

in stable chronic heart failure recommends that patients undertake low-to-moderate intensity aerobic exercise on most days of the week (4-7 days per week) (Selig et al., 2010). Prescription should be individualised and volume and intensity of training should be based on the patients' characteristics and the severity of the condition (Selig et al., 2010). Aerobic training can be performed as continuous training or interval training, with training duration and intensity progressed gradually according to patient's tolerance (Selig et al., 2010). Additionally, it is recommended that low-to-moderate intensity resistance training is performed at least twice per week (Selig et al., 2010).

2.3 Evidenced-based Medicine in Healthcare Interventions – Systematic Reviews and Meta-analyses

Well-designed RCTs provide high quality evidence; however, single studies may be unrepresentative of all the evidence (Murad et al., 2014). Therefore, by examining the totality of evidence in a particular field with systematic reviews and meta-analyses, a stronger, more comprehensive picture is provided (Gough, Oliver & Thomas, 2017) and the overall usefulness of individual results is enhanced. Furthermore, finding, appraising, interpreting and presenting all relevant available evidence in relation to a particular topic or clinical question is a time consuming and resource intensive task (Higgins & Green, 2011). Well-constructed systematic reviews and meta-analyses are hallmarks of evidenced-based medicine. They play a key role; helping inform clinical guidelines and practice (Liberati et al., 2009). Furthermore, and as importantly, they assist in identifying knowledge gaps, informing future research (Higgins & Green 2011; Shamseer et al., 2015).

The synthesis of research evidence is necessary to understand not only what we know, but also how we know it (Gough et al., 2017). Systematic reviews can also assist in reducing research waste; ensuring new primary research is only done with full knowledge of what has preceded it and interpreted in the context of what is already known (Chalmers et al., 2014). The importance of systematic reviews in

healthcare is evidenced by the creation of international organisations, such as the Cochrane Collaboration, the Joanna Briggs Institute and organisations actively involved in contributing to the development of systematic reviews such as PRISMA, Prospero and Equator.

Starting with a clearly defined question and following rigorous and robust research methodology, systematic reviews bring together the evidence from all relevant primary research, with a synthesis of findings and critical appraisal, resulting in a new result and conclusion (Gough et al., 2017). The key characteristics of a systematic review: clearly stated objectives and criteria, explicit and reproducible methods, systematic searching, assessment of validity, and systematic presentation and synthesis of studies and findings (Higgins & Green, 2011) are what define the robustness of this type of research. In the same manner as is the case for a primary research study, the research question(s) helps determine the appropriate method for the systematic review. In the case of a research question about the effect of an intervention, the methodology for data synthesis may involve combining studies for statistical analysis, i.e., meta-analysis, in order to estimate an effect size (Higgins & Green, 2011).

Karl Pearson (1904) is considered to have made the first formal attempt at combining results of a medical intervention using a meta-analytic approach (Gurevitch, Koricheva, Nakagawa & Stewart, 2018). However, the term meta-analysis, was first coined by Glass in 1976, and was defined as "the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings". Simply, it's the statistical combination of results from independent studies. This combination of individual study results leads to a pooled result, and more specifically an estimated effect size (Borenstein, Hedges, Higgins & Rothstein, 2011). In the case of a healthcare intervention, this effect size allows for the interpretation of its effectiveness. By combining a number of studies, a meta-analysis has the advantage of increasing precision and statistical power (Borenstein et al., 2011; Higgins & Green, 2011). Furthermore it allows one to understand the

results of any one study in the context of all the other studies (Borenstein et al., 2011).

Not only is the conduct of a new review and analysis of previously unsynthesised evidence important, but updating of systematic reviews is also crucial. Data from new studies can change the conclusion of a previous review, possibly impacting clinical decisions, policy development and new research agendas (Garner et al., 2016). Additionally, as new methodologies emerge, for example in statistical analysis (meta-analysis), these too can impact previous conclusions (Garner et al., 2016).

2.4 Evidence Map of Systematic Reviews and Meta-analyses – Effects and/or benefits of exercise training/therapy interventions in heart failure patients

An evidence map is an overview of the available research, examining the extent and nature of research activity by identifying, organising and summarising evidence on a broad topic (Miake-Lye, Hempel, Shanman & Shekelle, 2016). In addition to providing a mechanism for summarising and disseminating research findings, a key focus is the identification of research gaps in the existing literature prior to conducting a systematic review and/or new research (Miake-Lye et al., 2016). Aspects detailed in an evidence map will depend on the review question (Gough et al., 2017).

In 1998, the European Heart Failure Training Group conducted an "overview" of studies, reviewing data from RCTs involving a total of 134 heart failure patients, concluding that exercise training was safe and beneficial, with improvements in exercise tolerance (Piepoli, Flather & Coats, 1998). While a number of review papers began to emerge focusing on various aspects of exercise training and heart failure (Afzal, Brawner & Keteyian, 1998; Coats, 1998; McKelvie et al., 1995), in what appears to be the first review described and titled as a systematic review, Lloyd-Williams and Colleagues in 2002 published "Exercise training and heart failure: a systematic review of current evidence". In the systematic review of trials carried out between 1966 and December 2000, which totaled 31 (14 RCTs, 8 randomised

crossover trials, 2 non-RCTs and 7 pre-post-test trials), the authors concluded that short-term exercise training had physiological benefits and positive effects on quality of life in selected subgroups of patients with chronic heart failure (Lloyd-Williams, Mair & Leitner, 2002). Since 2002, systematic reviews have become a major research methodology utilised to examine various aspect of exercise therapy in heart failure patients and in 2004 the first Cochrane Review of Exercise-based rehabilitation in heart failure was published (Rees, Taylor, Singh, Coats & Ebrahim, 2004).

Objective

The evidence map is based on an overview of systematic reviews and meta-analyses of exercise therapy interventions in heart failure patients. The objective of the mapping exercise was to determine what systematic reviews and meta-analyses currently exist addressing the broad question of the benefits and/or effects of exercise therapy in heart failure patients. The intent was to describe the main outcomes addressed by these published systematic reviews and meta-analyses in order to ascertain what research syntheses are lacking, and to aid in determining the value of undertaking further systematic reviews and meta-analyses.

Method

A search of the Cochrane Database of Systematic Reviews, PubMed and EMBASE was conducted for systematic reviews and meta-analyses related to exercise training and heart failure using the following criteria.

- End search date 31st December 2016
- Publications must have identified themselves as a systematic review and/or meta-analysis or indicated pooled analysis of data
- Systematic reviews and meta-analyses were only included if the sole focus was heart failure patients

- Systematic reviews and meta-analyses focused on the benefits and/or effects of exercise therapy interventions
- Exercise therapy included both traditional and non-traditional forms of exercise
- Systematic reviews and meta-analyses which included the analysis of other interventions in addition to exercise therapy were not included in the evidence map
- The search was limited to full-text articles available in English

Data Analysis

Tables and graphs are used to display the evidence map of systematic reviews and meta-analyses.

Results

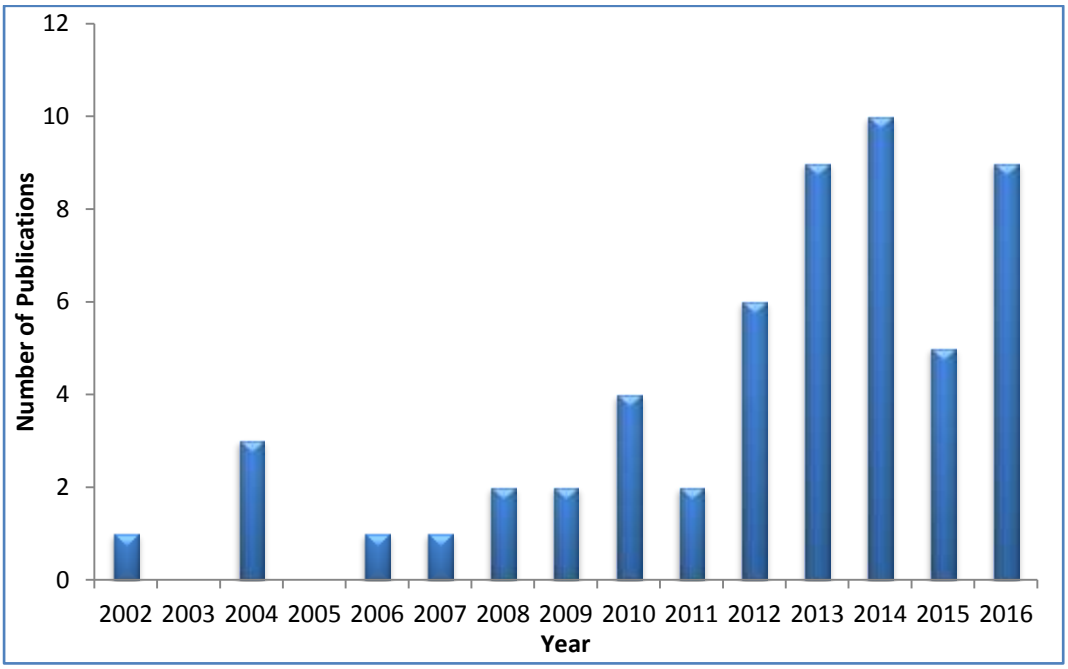
In total 55 systematic reviews and/or meta-analyses were identified. Forty five systematic reviews with meta-analyses were identified (Table 1) and three publications were individual patient data (IPD) analyses (Table 2). An additional seven publications were systematic reviews without meta-analyses (Table 3). The identified reviews and analyses were published between 2002 and 2016 (Figure 2).

Three of the included reviews were Cochrane Reviews. Overall, five reviews focussed solely on HFpEF patients, four of which also included meta-analyses. Exercise training within the various meta-analyses included the following exercise training and therapy modalities:

- Aerobic training; including aquatic (Hydrotherapy)
- Endurance training
- Resistance training
- Yoga
- Tai Chi
- Functional Electrical Stimulation/Neuromuscular Electrical Stimulation

- Inspiratory Muscle Training
- Combinations of one or more modalities

Figure 2 - Systematic Reviews and Meta-analyses by Publication date



The majority of systematic reviews that conducted meta-analyses only included studies within the review that provided data suitable for quantitative analysis (data pooling) of at least one of the stated review outcomes. However, a small number of reviews did include studies that were only suitable for a qualitative analysis in addition to studies suitable for meta-analyses. Where studies were not included in any associated meta-analysis, a descriptive review and/or tabulated data was generally provided.

Table 1 – Characteristics of Systematic Reviews with Meta-analysis included in Evidence Map - as at 31st December 2016

Author (year)	Last search date	Study designs in review	Total n =	HF phenotype(*)	Intervention(s)/ Comparator	Outcome analysed by Meta-Analysis (statistical analysis) (n= no. studies in pooled analysis of outcome)
Adsett (2015)	Mar 2014	RCTs = 5 Pre-Post = 2 Cohort =1	156	HFrEF	Aquatic vs. Land-based or Usual Care or Self-comparator	VO_{2peak} (n=3), 6MWD (n=2) , Peak power (n=3) *Descriptive review of secondary outcomes (BP, HR, SV, CO, SVR, LVEDV, BNP*)
Chan (2016)b	Sep 2015	RCTs = 8	317	HFpEF	Exercise vs. Usual Care	VO_{2peak} (n=5), V_E/VCO_2 (n=4), HR_{max} (n=5), 6MWD (n=5), Diastolic Function: E/A (n=4), E/E' (n=5), DT (n=3), MLHFQ (n=7), SF-36 (n=3) *Descriptive review of adverse events*
Chen (2012)a	Oct 2011	RCTs = 15	813	HF	Aerobic, Resistance or Combined Aerobic/ Resistance vs. Usual Care	LVEF, EDV, ESV Aerobic, Resistance & Combined: LVEF (n=15), EDV (n=15), ESV (n=15) Aerobic: LVEF (n=12), EDV (n=12), ESV (n=11) Combined: LVEF (n=3), EDV (n=3), ESV (n=3)
Chen (2012)b	Jun 2012	RCTs = 4	296	HFrEF	Combined Aerobic/ Resistance vs. Usual Care	6MWD (n=4)
Chen (2013)a	Feb 2012	RCTs = 4	106	HFrEF	IMT vs. Placebo IMT or Aerobic	Submaximal Exercise Capacity (n=4)
Chen (2013)b	Sep 2012	RCTs = 7	530	HFrEF	Aerobic, Resistance or Combined Aerobic/ Resistance vs. Usual Care	All-cause Mortality (n=5), Hospitalisation (n=4), VO_{2peak} (n=3), 6MWD (n=6), QoL (n=5)
Chien (2008)	Jul 2006	RCTs = 10	648	HFrEF	Home-based Exercise vs. Usual Care or FES (n=1)	VO_{2peak} (n=7), 6MWD (n=5), QoL (n=3), Hospitalisations (n=2)
Cipriano (2014)	Feb 2013	RCTs = 9	408	HFrEF	Aerobic vs. Usual Care	V_E/VCO_2 (n=4), NT-proBNP (n=5)

Cornelis (2016)	Oct 2015	RCTs = 20	811	HFrEF	Interval vs. Interval/Strength Continuous vs. Continuous/Strength Continuous vs. Interval Continuous vs. Strength	VO_{2peak}, LVEF, LVEDD, MLHFQ, V_E/VCO_2 Interval vs. Interval/Strength: VO_{2peak} (n=5), LVEF (n=1), LVEDD (n=1) Continuous vs. Continuous/Strength: VO_{2peak} (n=3), V_E/VCO_2 (n=3), LVEF (n=3), LVEDD (n=2), MLHFQ (n=2) Continuous vs. Interval: VO_{2peak} (n=11), V_E/VCO_2 (n=7), LVEF (n=6), LVEDD (n=4), MLHFQ (n=4) Continuous vs. Strength: VO_{2peak} (n=1)
Davies (2010)[1]	Apr 2008	RCTs = 19	3,647	HFrEF	Exercise or Exercise as a component of Cardiac Rehabilitation vs. Usual Care or Placebo	All-cause Mortality ≤12 months FU (n=13), All-cause Mortality >12 months FU (n=4), Hospitalisation ≤12 months FU (n=8), Hospitalisation > 12 months FU (n=4), Hospitalisations HF <12 months FU (n=7) MLHFQ (n=6), QoL (all scales n=10) *Descriptive review of cost effectiveness*
Dieberg (2015)	Oct 2014	RCTs = 7	258	HFpEF	Exercise vs. Usual Care	VO_{2peak} (n=4), V_E/VCO_2 (n=3), HR_{max} (n=4), 6MWD (n=5), Diastolic Function: E/A (n=3), E/E' (n=4), DT (n=3), MLHFQ (n=6), SF-36 (n=2) *Descriptive review of adverse events*
Haykowsky (2007)	2006	RCTs = 14	812	HFrEF	Aerobic and/or Resistance vs. Usual Care	LVEF, EDV, ESV, VO_{2peak} Aerobic and/or Resistance: LVEF (n=14), EDV (n=7), ESV (n=7) Aerobic: LVEF (n=9), EDV (n=5), ESV (n=5), VO_{2peak} (n=9) Resistance: LVEF (n=1) Combined: LVEF (n=4), EDV (n=2), ESV (n=2)
Haykowsky (2013)	2012	RCTs = 7	168	HFrEF	Aerobic Interval vs. Moderate Continuous	VO_{2peak} (n=7), LVEF (n=5)
Hwang (2009)	2008	RCTs = 19	1069	HFrEF	Home-based Exercise vs. Usual Care	VO_{2peak} (n=16), 6MWD (n=6), Exercise Time (n=7)
Hwang (2010)	Sep 2009	RCTs = 8	241	HFrEF	Resistance vs. Usual Care/Sham Combined Aerobic/ Resistance vs. Aerobic	LVEF, VO_{2peak}, 6MWD, MLHFQ Combined vs. Aerobic: LVEF (n=3), VO_{2peak} (n=3), Resistance vs. Usual: LVEF (n=1), VO_{2peak} (n=4), 6MWD (n=2) Combined vs. Resistance: MLHFQ (n=2)

Ismail (2014)[2]	2012	RCTs = 47	4,383	HFrEF	Aerobic vs. Usual Care	VO_{2peak} analysis by training characteristics (energy, frequency, duration, intensity) VO_{2peak} High (n=3), VO_{2peak} Vigorous (n=26), VO_{2peak} Moderate (n=18), VO_{2peak} Low (n=2)
Ismail (2013)a[2]	2012	RCTs =74	5,877	HFrEF	Aerobic vs. Usual Care (High Intensity, Vigorous intensity, Moderate Intensity and Low intensity)	VO_{2peak} High (n=3), VO_{2peak} Vigorous (n=26), VO_{2peak} Moderate (n=18), VO_{2peak} Low (n=2) *Descriptive and statistical analysis of adverse events, withdrawals based on intensity of training*
Ismail (2013)b	2011	RCTs =8	236	HFrEF	Aerobic and/or Resistance (with and without β-Blockers) vs. Usual Care and/or Placebo & Exercise	VO_{2peak}, MLHFQ, V_E/VCO_2 Exercises vs. Usual (both groups using βB): VO_{2peak} (n=6), V_E/VCO_2 (n=2), MLHFQ (n=2) Exercise vs. βB Exercise: VO_{2peak} (n=2), Exercise/Selective. βB vs. Exercise/Non-Sel. βB: VO_{2peak} (n=2) *Descriptive review of adverse events*
Jewiss (2016)	May 2016	RCTs = 27	2,321	HFrEF	Resistance vs. Usual Care Combined Aerobic/ Resistance vs. Usual Care Combined Aerobic/ Resistance vs. Aerobic	Mortality, Hospitalisation, $VO_{2peak,}$ LVEF, MLHFQ, SBP, 6MWD, HR_{rest}, HR_{peak} Combined vs. Usual: Mortality (n=9), Hospitalisation (n=8), VO_{2peak} (n=10), 6MWD (n=7), MLHFQ (n=10), LVEF (n=5), HR_{peak} (n=4), SBP (n=3), HR_{rest} (n=3) Resistance vs. Usual: VO_{2peak} (n=4), 6MWD (n=2), HR_{peak} (n=3) Combined vs. Aerobic: VO_{2peak} (n=6)
Lewinter (2015)	Jan 2013	RCTs = 46	?	HF	Aerobic and/or Resistance Training vs. Usual Care	All-cause Mortality (n=21), Hospitalisation (n=12), Exercise Capacity (n=26)

Montemezzo (2014)	Aug 2013	RCTs = 9	239	HF	IMT vs. Sham/IMT or Usual Care	MIP, Sustained MIP, VO_{2peak}, V_E, 6MWD Overall MIP (n=9) Subgroup analysis: MIP (inspiratory muscle weakness n=4), MIP (normal inspiratory muscle strength n=5), Sustained MIP (n=3), 6MWD (n=4) Subgroup analysis: 6MWD (inspiratory muscle weakness n=1), 6MWD (normal inspiratory muscle strength n=3), VO_{2peak} (n=4) *Subgroup analysis:* VO_{2peak} (inspiratory muscle weakness n=1), VO_{2peak} (normal inspiratory muscle strength n=3), V_E (n=4) *Subgroup analysis:* V_E (inspiratory muscle weakness n=1), V_E (normal inspiratory muscle strength n=3)
Neto (2014)a	Dec 2013	RCTs = 2	59	HF	Yoga vs. Usual Care	VO_{2peak} (n=2), MLHFQ (n=2)
Neto (2014)b	Aug 2013	RCTs = 2	183	HF	Dance vs. Usual Care Exercise vs. Dance	VO_{2peak}, QoL Dance vs. Usual: VO_{2peak} (n=2), QoL (n=2) Dance vs. Exercise: VO_{2peak} (n=2), QoL (n=2)
Neto (2015)	May 2014	RCTs = 6	129	HF	Hydrotherapy vs. Usual Care Hydrotherapy vs. Aerobic	VO_{2peak}, 6MWD, Muscle Strength, MLHFQ Hydrotherapy vs. Usual: VO_{2peak} (n=2), 6MWD (n=2), Muscle Strength (n=2), MLHFQ (n=2) Hydrotherapy vs. Aerobic: VO_{2peak} (n=2)
Neto (2016)a	Jul 2014	RCTs = 13	406	HF	NMES vs. Aerobic NMES vs. Usual Care	VO_{2peak}, QoL, 6MWD, Muscle Strength, FMD, Depressive Symptoms NMES vs. Aerobic: VO_{2peak} (n=6), 6MWD (n=5), QoL (n=2) NMES vs. Usual Care: VO_{2peak} (n=3), 6MWD (n=6), QoL (n=5), Muscle strength (n=2), FMD (n=2), Depressive Symptoms (n=2)
Neto (2016)b	Apr 2015	RCTs = 3	89	HF	IMT/Endurance vs. Endurance	MLHFQ (n=3), PI_{max} (n=3), VO_{2peak} (n=3), Exercise Time (n=2)
Neves (2014)	Mar 2014	RCTs = 9	347	HFrEF	NMES vs. Usual Care NMES vs. Exercise	VO_{2peak}, VO_{2AT}, HR_{peak}, Peak Workload NMES vs. Exercise: VO_{2peak} (n=7), VO_{2AT} (n=4,) HR_{peak}(n=4), PW (n=2) NMES vs. Usual Care: VO_{2peak} (n=9), HR_{peak} (n=5) VO_{2AT} (n=5), PW (n=3)

Pan (2013)	May 2012	RCTs = 4	242	HFrEF	Tai Chi & Tai Chi/Endurance vs. Usual Care or Endurance	6MWD (n=3), MLHFQ (n=13) , NT-proBNP (n=2), SBP (n=2), DBP (n=2), VO_{2peak} (n=2)
Pandey (2014)	NR	RCTs = 6	276	HFpEF	Exercise Training vs. Usual Care	VO_{2peak} (n=4), MLHFQ (n=5), Diastolic Function: E/A (n=4), DT (n=3), LVEF (n=5)
Plentz (2012)	Jul 2011	RCTs = 6	150	HF	IMT vs. Placebo-IMT or Education	VO_{2peak} (n=3), 6MWD (n=3), MIP (n=6)
Rees (2004)[(1)]	Mar 2001	RCTs = 29	1126	HFrEF	Exercise or Exercise as a component of Cardiac Rehabilitation vs. Usual Care or Placebo	6MWD (n=8), VO_{2peak} (n=24), Exercise Duration (n=15), Work Capacity (n=6), Mortality (n=1), MI (n=1), Hospitalisation (n=1) *Descriptive/tabulated review of QoL*
Sbruzzi (2010)	Jan 2009	RCTs = 7	224	HF	FES vs. Aerobic or Usual Care, or Sham FES	$VO_{2peak,}$ Muscle Strength , 6MWD FES vs. Aerobic: $VO_{2peak,}$ (n=2), Muscle Strength (n=2), 6MWD (n=5) FES vs. Usual: VO_{2peak} (n=2)
Smart (2004)	Aug 2003	RCTs = 30 Non-RCTs = 5 Crossover =9 Cohort = 37	2387	HFrEF	RCTs- Exercise Training vs. Non-exercising Controls	Adverse Events (n=14), Mortality (n=11), Composite of Adverse Events and Deaths (n=17) *Change in VO_{2peak} via linear analysis (n=57)*
Smart (2010)	Feb 2009	RCTs = 9	463	HFrEF	Aerobic and/or Resistance Training vs. Usual Care	BNP (n=5), NT-pro-BNP (n=6)
Smart (2013)a	Oct 2011	RCTs = 10	301	HF	FES vs. Usual Care/Sham FES FES vs. Cycling	VO_{2peak} , 6MWD, QoL FES vs. Usual: VO_{2peak} (n=3), 6MWD (n=2), QoL (n=3), Cycling vs. FES: VO_{2peak} (n=5), 6MWD (n=5), QoL (n=2) *Descriptive review of adverse events/withdrawals*
Smart (2013)b	Feb 2012	RCTs = 11	287	HF	IMT vs. Usual Care or Sham-IMT	VO_{2peak} (n=8), 6MWD (n=7), V_E/VCO_2 (n=6), PI_{max} (n=9), MLHFQ (n=4)

Smart (2013)c	Sep 2013	RCTs = 13	446	HF	Intermittent vs. Continuous Exercise, Combined Training, or Usual Care	VO_{2peak} , V_E/VCO_2 Intermittent vs. Usual: VO_{2peak} (n=7), V_E/VCO_2 (n=3) Intermittent vs. Combined: VO_{2peak} (n=4) Intermittent vs. Continuous: VO_{2peak} (n=5), V_E/VCO_2 (n=3) *Descriptive review of adverse events/withdrawals*
Taylor (2012)	Nov 2011	RCTs = 3 Controlled =1 Pre-Post =1	228	HFpEF	Aerobic and/or Resistance vs. Usual Care or Pre-Post Test	VO_{2peak} (n=4), MLHFQ (n=4), Diastolic Function: E/A (n=3), E/E' (n=3), EDV (n=2), LVEF (n=3) *Descriptive review of mortality, hospital admission, adverse events and other QoL measures*
Taylor (2014)[(1)] [Sagar (2015)]	Jan 2013	RCTs = 33	4,740	HF	Exercise or Exercise as a component of Cardiac Rehabilitation vs. Usual care or intervention such as education	All-cause Mortality ≤12 months FU (n=24), All-cause Mortality >12 months FU (n=6), Hospitalisation ≤12 months FU (n=15), Hospitalisation >12 months FU (n=5), Hospitalisation HF only (n=12), MLHFQ ≤12 months FU [n=13), MLHFQ >12 months FU (n=3), MLHFQ + other QoL (n=21) *Descriptive review of cost and cost-effectiveness*
Tu (2014)	Aug 2013	RCTs = 19	3,447	HF	Exercise vs. Usual Care or Placebo Educational Group	Depression (various instruments combined n=16) Subgroup analyses for numerous characteristics with varying no. of associated studies depending on characteristic.
Van der Meer (2012)	Mar 2010	RCTs = 22	3,826	HFrEF	Aerobic and/or Resistance vs. Usual Care	VO_{2max}, (n=14), 6MWD (n=10), $Workload_{max}$, (n=7), Duration Maximal Cycle Test (n=8), MLHFQ (n=9)
Van Tol (2006)	Oct 2004	RCTs = 35	1,486	HFrEF	Aerobic and/or Resistance vs. Usual Care	VO_{2peak} (n=31), 6MWD (n=15), AT (n=13), Watt (n=19), MLHFQ (n=9) Rest: DBP (n=7), SBP (n=11), EDV (n=9), ESV (n=7), LVEF (n=14), HR (n=14), CO (n=4) During maximum exercise: HR (n=18), SBP (n=10), DBP (n=4), CO (n=3)
Vromen (2016)	Apr 2015	RCTS = 17	2935	HF	Aerobic Training vs. Usual Care	VO_{2peak} (n=17) *Meta-regression of training characteristics (n=17 for frequency, duration, length, intensity, energy expenditure)*
Zhang (2016)	2014	RCTs = 28	2533	HF	Short-term Exercise (8-24 weeks) vs. Usual Care	VO_{2max} (n=16), SBP (n=5), CO (n=3) LVEF (n=5), HR (n=6), HRV (n=3), MLHFQ (n=4)

Zwisler (2016)	Dec 2015	RCTS = 19	1290	HF	Home-based Exercise vs. Usual Care Home-based Exercise vs. Centre-based Exercise	$VO_{2peak,}$ Combined Exercise Capacity, MLHFQ, All-cause Mortality, Hospitalisations, HF Hospitalisation Home vs. Usual: $VO_{2peak,}$ (n=10), Combined Exercise Capacity (n=18), MLHFQ (n=7), Mortality (n=12), Hospitalisation (n=4), HF Hospitalisation (n=4), Study Completers (n=14) Home vs. Centre: $VO_{2peak,}$ (n=3), Combined Exercise Capacity (n=4), Mortality (n=3), HF Hospitalisation (n=1), Study Completers (n=4) *Descriptive review of adherence and costs*

AT: anaerobic threshold, βB: beta-blockers, BNP: B-type natriuretic peptide, CO: cardiac output, DBP: diastolic blood pressure, DT: deceleration time, E/A: ratio of early to late ventricular filing velocity, E/E': mitral peak velocity of early filling to early diastolic mitral annular velocity, EDV: end diastolic volume, ESV: end systolic volume, FES: functional electrical stimulation, FU: follow-up, HF: heart failure, HFpEF: heart failure preserved ejection fraction, HFrEF: heart failure reduced ejection fraction, HR: heart rate, HRV: heart rate variability, IMT: inspiratory muscle training, LVEDD: left ventricular end diastolic diameter, LVEF: left ventricular ejection fraction, MIP: maximal inspiratory pressure, MLHFQ: Minnesota living with heart failure questionnaire, NMES: neuromuscular electrical stimulation, NT-proBNP: N terminal portion of BNP, PI_{max}: maximal inspiratory pressure, PW: peak workload, QoL: quality of life, RCT: randomised controlled trial, SBP: systolic blood pressure, SF-36: short form health survey, SV: stroke volume, SVR: systemic vascular resistance, V_E: minute ventilation, V_E/VCO_2: ventilatory equivalent for carbon dioxide, VO_{2peak}: peak oxygen uptake, 6MWD: six minute walk distance, (1) Cochrane reviews, (2) Publications pooled same data , second publication is different analysis, * HF Phenotype – if inclusion criteria of studies were specifically identified as HFpEF or HFrEF, if not then HF noted. ***Appendix Table 5 provides an update to the above with details of meta-analyses published between 1st January 2017 and 30th April 2018***

Table 2 – Characteristics of Individual Patient Data Analysis included in Evidence Map - as at 31st December 2016

Author (year)	Last study date	Study Designs in Review	Total n =	HF phenotype	Intervention(s)/ Comparator	Outcome analysed by Data Pooling (statistical analysis)
ExTraMATCH (2004)	2002	RCTs = 9	801	HFrEF	Exercise vs. Usual Care	Mortality, Death/ Hospitalisation
Smart (2012)	2009	RCTs = 10	565	HFrEF	Aerobic Training vs. Usual Care	BNP, NT-pro-BNP, VO_{2peak} & Correlations
Smart (2011)a	2008	RCTs=1 Pre-Post-test =3	106	HFrEF	Exercise	TNF-α, IL-6

BNP: B-type natriuretic peptide, HFrEF: heart failure reduced ejection fraction, IL-6: interleukin 6, NT-proBNP: N terminal portion of BNP, RCTs: randomised controlled trials, TNF-α: tumor necrosis factor alpha, VO_{2peak}: peak oxygen uptake

Table 3 – Summary of Systematic Reviews with no Meta-analysis (not included in Evidence Map) - as at 31st December 2016

Author (year)	Last search date	Study Designs in Review	Total n =	HF phenotype(*)	Intervention(s)/ Comparator	Outcomes Reviewed
Hsu (2015)	Mar 2015	RCTs = 8	280	HFrEF	Exercise vs. No Training or Usual Care	Heart Rate Recovery and Heart Rate Variability
Lloyd-Williams (2002)	Dec 2000	RCTs =14 Crossover trials =8, Non-RCTs= 2, Pre-Post = 7	1010	HF	Exercise vs. Usual Care Exercise vs. No Control	Improvements in Peak Performance (VO_{2peak}, CO, AT), QoL, Mortality, Cost Effectiveness and Healthcare Service Utilisation
Palau (2016)	Apr 2014	RCTs	279	HFpEF	Exercise vs. Usual Care	Exercise Capacity (VO_{2peak}, 6MWD, METs), QoL (MLHFQ, SF-36), Diastolic Function, Biomarkers
Reiter (2014)	Mar 2011	RCTs = 15	?	HFrEF	Exercise vs. Usual Care	Physiological Function, Functional Capacity, QoL and Health Status
Smart (2011)b	Oct 2011	RCTs = 9 Cohort study = 2	352	HF	Exercise vs. Usual Care or Other Exercise Modality	Pro-inflammatory Cytokines (TNF-α, IL-6)
Spruit (2009)	Aug 2008	RCTs=7 Controlled =3	251	HF	Resistance Training and/or Endurance Training vs. Usual Care or Endurance Training	Cardiovascular Function, Skeletal Muscle Function, Body Composition, Exercise Capacity, QoL, Adverse Events
Tai (2008)	Oct 2006	RCTs = 69	?	HF	Exercise vs. Usual Care or Other Modality	Central Hemodynamic, Blood Flow, Endothelial Function, Neurohormones, Cytokines, Skeletal Muscle, QoL

AT: anaerobic threshold, CO: cardiac output, FES: functional electrical stimulation, HF: heart failure, HFpEF: heart failure preserved ejection fraction, HFrEF: heart failure reduced ejection fraction, IL-6: interleukin 6, METs: metabolic equivalent, MLHFQ: Minnesota living with heart failure questionnaire, RCT: randomised controlled trial, QoL: quality of life, SF-36: short form health survey, TNF-α: tumor necrosis factor alpha, VO_{2peak}: peak oxygen uptake, 6MWD: six minute walk distance, * HF Phenotype – if inclusion criteria of studies were specifically identified as HFpEF or HFrEF, if not then HF noted. ***Appendix Table 6 provides an update to the above with details of systematic reviews published between 1st January 2017 and 30th April 2018.***

Outcomes

Of the 48 publications to pool data, 40 analysed one or more measures of exercise capacity. The most frequently analysed exercise capacity measure was VO_{2peak}. One or more measures of quality of life was analysed in 25 publications, with Minnesota Living with Heart Failure Questionnaire (MLHFQ) the most common outcome analysed. Figure 3 provides a summary of the number of meta-analyses to have assessed outcomes, based on outcome category. Individual results for each outcome category are detailed in Table 4.

Figure 3 – Evidence Map 1 - Outcomes analysed by Meta-analyses, by category

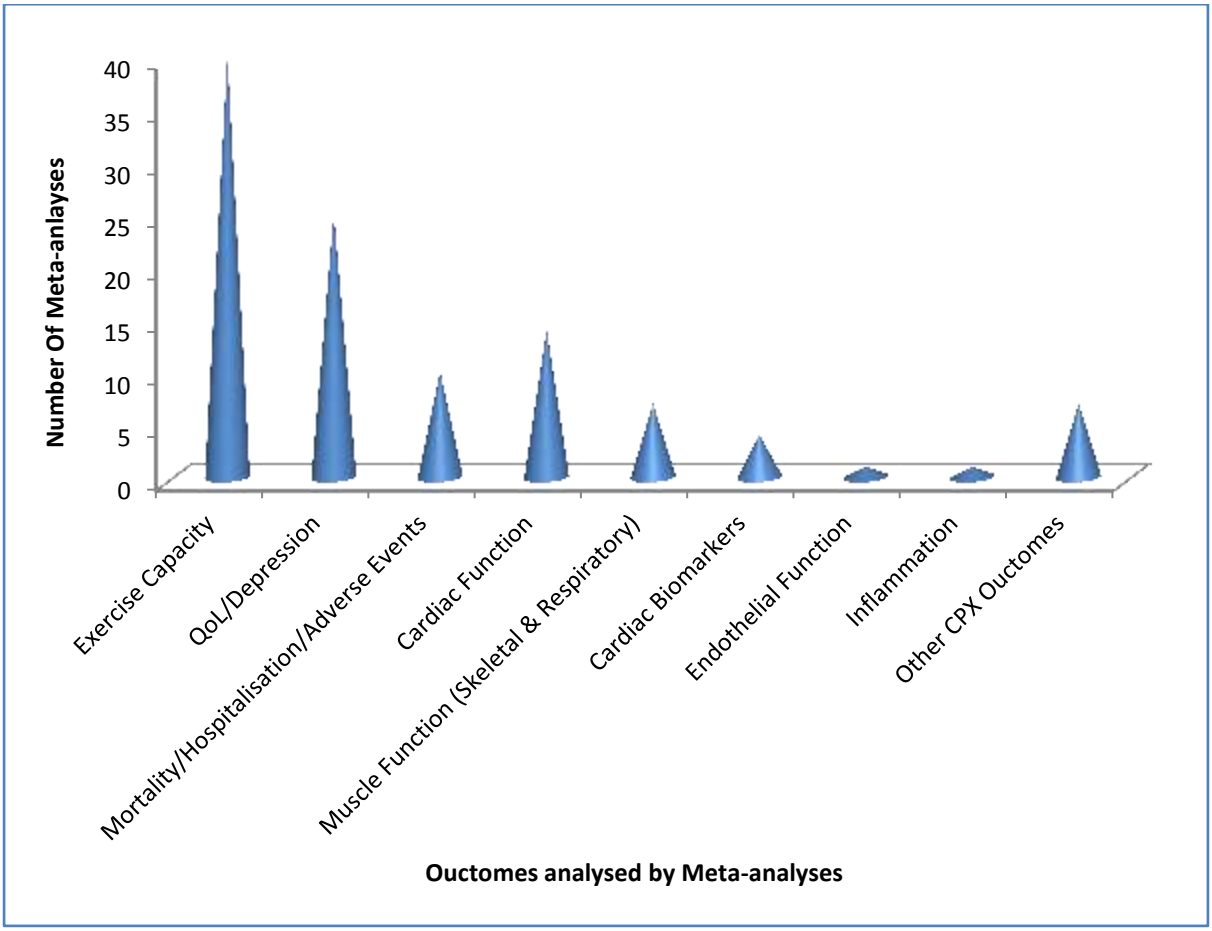


Table 4 – Evidence Map 2 - Outcomes analysed by Meta-analyses

Outcome	Number of Meta-analyses that analysed outcome
Exercise Capacity	
• VO_{2peak}	36
• 6MWD	20
• Other measures (AT, VO_{2AT}) and/or combined exercise capacity	9
Quality of Life and Depression	
• MLHFQ	19
• Other QoL/ Depression/Combined measure	8
Mortality, Hospitalisation	
• Mortality	9
• Hospitalisation/Adverse Events	10
Cardiac Function	
• Diastolic Function (E/E', E/A or DT)	4
• LVEF, LVEDD, EDV or ESV	10
• HR_{peak} or HR_{rest}	5
• Blood Pressure	4
• CO	2
• HRV	1
Muscle Function	
• Skeletal Muscle	3
• Inspiratory Muscle	4
Cardiac Biomarkers	
• BNP and/or NT-proBNP	4
Endothelial Function	
• FMD	1
Inflammation	
• TNF-α, IL-6	1
Other CPX outcomes	
• V_E/VCO_2	6
• V_E	1

AT: anaerobic threshold, BNP: B-type natriuretic peptide, CO: cardiac output, CPX: cardiopulmonary exercise test, DT: deceleration time, E/A: ratio of early to late ventricular filing velocity, EDV: end diastolic volume, E/E': mitral peak velocity of early filling to early diastolic mitral annular velocity, ESV: end systolic volume, FMD: flow-mediated dilation, HRV: heart rate variability, HR: heart rate, IL-6: interleukin 6, LVEDD: left ventricular end diastolic diameter, LVEF: left ventricular ejection fraction, QoL: quality of life, MLHFQ: Minnesota living with heart failure questionnaire, NT-proBNP: N- terminal portion of B-type natriuretic peptide, TNF-α: tumor necrosis factor alpha, V_E: minute ventilation, V_E/VCO_2:ventilatory equivalent for carbon dioxide, VO_{2peak}: peak oxygen uptake, $VO2_{AT}$: peak oxygen uptake at anaerobic threshold, 6MWD: six-minute walk distance.

Key Findings:- Evidence Map of Systematic Reviews & Meta-Analyses

- 55 systematic reviews and/or meta-analyses were identified
  - 45 were systematic reviews with meta-analysis
  - 3 were IPD analyses
  - 7 were systematic reviews with no meta-analysis

- Included reviews were published between 2002 and 2016

- The latest search date of any of the included meta-analyses was May 2016

- Three reviews were Cochrane Reviews

- Most common outcomes measured were exercise capacity and QoL
  - Peak VO_{2peak} was the most common measure of exercise capacity

- Meta-analyses included a range of training modalities, both traditional and non-traditional training or therapies

- Identified gaps in research synthesis:

  - Endothelial Function
    - Only one meta-analysis was identified that has conducted an analysis of this outcome, and this was limited to two studies using NMES/FES
      - *Importance: Endothelial dysfunction is involved in development and progression of heart failure*

  - Autonomic Function
    - No obvious evidence of any meta-analysis analysing heart rate recovery (HRR)
    - No obvious evidence of any meta-analysis analysing muscle sympathetic nerve activity (MSNA)
    - Only one analysis considered HRV
      - *Importance: Autonomic function is impaired in heart failure patients, with increased SNS activity and decreased PNS; and several parameters of autonomic function have prognostic significance*

  - Diastolic Function
    - Diastolic Function has only been analysed in HFpEF
      - *Importance: While generally considered in the context of HFpEF patients diastolic dysfunction often coexists in HFrEF patients and is associated with reduced exercise capacity*

- Inflammatory Markers
  - Only one review has pooled any data on inflammatory markers, and this only included individual patient data from 4 studies with no comparator data
    - *Importance: Inflammation is likely both a cause and consequence of heart failure; elevated levels are associated with severity and adverse outcomes. Exercise training is considered to exert anti-inflammatory effects in healthy and diseased population.*

- Biomarkers
  - Cardiac Biomarkers - Four meta-analyses (1 of which was an IPD) have analysed BNP and/or NT-proBNP, with the last meta-analysis published in 2014 with the last search date of February 2013 (>5 years)
  - Other Biomarkers - To date no meta-analysis or systematic review has considered how exercise may impact emerging heart failure biomarkers
    - *Importance: Biomarkers are a current area of interest in heart failure research given their association with the pathophysiological pathways in heart failure and may be beneficial in guiding treatment strategies including exercise*

2.5 Summary

Systematic reviews and meta-analyses are an important research method; collecting, analysing and critically appraising studies in order to answer a focused research question. As a result of the evidence mapping exercise a number of areas were identified as lacking in research synthesis and considered a valuable addition to the current evidence-base given their role in the development and progression of heart failure, association with disease severity, prognosis and symptomology such as reduced exercise capacity. The following chapters are a synthesis of research in the identified areas, using systematic review and meta-analysis as the research methodology. Each chapter comprises a separate systematic review and meta-analysis. Chapters 3-8 address the identified areas above, while chapter 9 is a systematic review of methods reported and utilised when the change standard deviation (SD), required for meta-analysis of change scores, is missing; a common problem encountered when conducting the meta-analyses in this thesis.

2.6 References

Adsett, J. A., Mudge, A. M., Morris, N., Kuys, S., & Paratz, J. D. (2015). Aquatic exercise training and stable heart failure: A systematic review and meta-analysis. *International Journal of Cardiology*, *186*, 22-28.

Afzal, A., Brawner, C. A., & Keteyian, S. J. (1998). Exercise training in heart failure. *Progress in Cardiovascular Diseases*, *41*(3), 175-190.

Alba, A. C., Adamson, M. W., MacIsaac, J., Lalonde, S. D., Chan, W. S., Delgado, D. H., & Ross, H. J. (2016). The added value of exercise variables in heart failure prognosis. *Journal of Cardiac Failure*, *22*(7), 492-497.

Ambrosy, A. P., Cerbin, L. P., DeVore, A. D., Greene, S. J., Kraus, W. E., O'Connor, C. M., ... & Mentz, R. J. (2017). Aerobic exercise training and general health status in ambulatory heart failure patients with a reduced ejection fraction—Findings from the Heart Failure and A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial. *American Heart Journal*, *186*, 130-138.

Angadi, S. S., Mookadam, F., Lee, C. D., Tucker, W. J., Haykowsky, M. J., & Gaesser, G. A. (2014). High-intensity interval training vs. moderate-intensity continuous exercise training in heart failure with preserved ejection fraction: a pilot study. *Journal of Applied Physiology*, *119*(6), 753-758.

Australian Institute of Health and Welfare (AIHW). Cardiovascular health compendium. *Web report.* Last updated: 22 Dec 2017.

Belardinelli, R., Georgiou, D., Cianci, G., & Purcaro, A. (1999). Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. *Circulation*, *99*(9), 1173-1182.

Benjamin, E. J., Blaha, M. J., Chiuve, S. E., Cushman, M., Das, S. R., Deo, R., ... & Jiménez, M. C. (2017). Heart disease and stroke statistics-2017 update: a report from the American Heart Association. *Circulation, 135(10),* e146-e603.

Blumenthal, J. A., Babyak, M. A., O'Connor, C., Keteyian, S., Landzberg, J., Howlett, J., ... & Whellan, D. J. (2012). Effects of exercise training on depressive symptoms in patients with chronic heart failure: the HF-ACTION randomized trial. *JAMA: Journal of the American Medical Association*, *308*(5), 465-474.

Bonsu, K. O., Arunmanakul, P., & Chaiyakunapruk, N. (2018). Pharmacological treatments for heart failure with preserved ejection fraction—a systematic review and indirect comparison. *Heart Failure Reviews*, *23*(2), 147-156.

Borenstein, M., Hedges, L. V., Higgins, J. P., & Rothstein, H. R. (2011). *Introduction to meta-analysis*. John Wiley & Sons.

Borlaug, B. A. (2014). The pathophysiology of heart failure with preserved ejection fraction. *Nature Reviews Cardiology*, *11*(9), 507.

Borlaug, B. A. (2016). Is HFpEF one disease or many? *Journal of the American College of Cardiology 67(5),* 671-673

Braunwald, E. (2013). Heart Failure. *Journal of the American College of Cardiology 1(1),* 1-20.

Chalmers, I., Bracken, M. B., Djulbegovic, B., Garattini, S., Grant, J., Gülmezoglu, A. M., ... & Oliver, S. (2014). How to increase value and reduce waste when research priorities are set. *The Lancet*, *383*(9912), 156-165.

Chan, Y. K., Tuttle, C., Ball, J., Teng, T. H. K., Ahamed, Y., Carrington, M. J., & Stewart, S. (2016)a. Current and projected burden of heart failure in the Australian adult population: a substantive but still ill-defined major health issue. *BMC Health Services Research*, *16*(1), 501.

Chan, E., Giallauria, F., Vigorito, C., & Smart, N. A. (2016)b. Exercise training in heart failure patients with preserved ejection fraction: a systematic review and meta-analysis. *Monaldi Archives for Chest Disease*, *86*(1-2).

Chen, Y. M., Li, Z. B., Zhu, M., & Cao, Y. M. (2012)a. Effects of exercise training on left ventricular remodelling in heart failure patients: an updated meta-analysis of randomised controlled trials. *International Journal of Clinical Practice*, *66*(8), 782-791.

Chen, Y. M., & Yin, T. (2012)b. Inspiratory muscle training improves submaximal exercise capacity in patients with heart failure: a systematic review of randomized controlled trials. *International Journal of Cardiology*, *158*(2), 294-296.

Chen, Y. M., Zhu, M., & Zhang, Y. X. (2013)a. Combined endurance–resistance training improves submaximal exercise capacity in elderly heart failure patients: A systematic review of randomized controlled trials. *International Journal of Cardiology, 166(1*), 250-252.

Chen, Y. M., & Li, Y. (2013)b. Safety and efficacy of exercise training in elderly heart failure patients: a systematic review and meta-analysis. *International Journal of Clinical Practice*, *67*(11), 1192-1198.

Chen, L., Booley, S., Keates, A.K. & Stewart, S. (2017). *Snapshot of heart failure in Australia.* Mary MacKillop Institute for Health Research, Australian Catholic University, Melbourne, Australia.

Chien, C. L., Lee, C. M., Wu, Y. W., Chen, T. A., & Wu, Y. T. (2008). Home-based exercise increases exercise capacity but not quality of life in people with chronic heart failure: a systematic review. *Australian Journal of Physiotherapy*, *54*(2), 87-93.

Chow, S. L., Maisel, A. S., Anand, I., Bozkurt, B., De Boer, R. A., Felker, G. M., ... & Liu, P. P. (2017). Role of biomarkers for the prevention, assessment, and management of heart failure: a scientific statement from the American Heart Association. *Circulation*, *135*(22), e1054-e1091.

Cipriano, G., Cipriano, V. T., Da Silva, V. Z. M., Cipriano, G. F., Chiappa, G. R., De Lima, A. C., ... & Arena, R. (2014). Aerobic exercise effect on prognostic markers for systolic heart failure patients: a systematic review and meta-analysis. *Heart Failure Reviews*, *19*(5), 655-667.

Coats, A. J. (1998). Optimizing exercise training for subgroups of patients with chronic heart failure. *European Heart Journal*, *19*, O29-34.

Coats, A. J. S., Adamopoulos, S., Meyer, T. E., Conway, J., & Sleight, P. (1990). Effects of physical training in chronic heart failure. *The Lancet, 335(8681),* 63-66.

Cook, C., Cole, G., Asaria, P., Jabbour, R., & Francis, D. P. (2014). The annual global economic burden of heart failure. *International Journal of Cardiology*, *171*(3), 368-376.

Correale, M., Monaco, I., Brunetti, N. D., Di Biase, M., Metra, M., Nodari, S., ... & Gheorghiade, M. (2018). Redefining biomarkers in heart failure. *Heart Failure Reviews*, *23*(2), 237-253.

Cornelis, J., Beckers, P., Taeymans, J., Vrints, C., & Vissers, D. (2016). Comparing exercise training modalities in heart failure: a systematic review and meta-analysis. *International Journal of Cardiology*, *221*, 867-876.

Davies, E. J., Moxham, T., Rees, K., Singh, S., Coats, A. J., Ebrahim, S., ... & Taylor, R. S. (2010). Exercise based rehabilitation for heart failure. *The Cochrane Library*.

Dieberg, G., Ismail, H., Giallauria, F., & Smart, N. A. (2015). Clinical outcomes and cardiovascular responses to exercise training in heart failure patients with preserved ejection fraction: a systematic review and meta-analysis. *Journal of Applied Physiology*, *119*(6), 726-733.

Edelmann, F., Gelbrich, G., Düngen, H. D., Fröhling, S., Wachter, R., Stahrenberg, R., ... & Herrmann-Lingen, C. (2011). Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. *Journal of the American College of Cardiology*, *58*(17), 1780-1791.

ExtraMATCH Collaborative: Piepoli, M.F., Davos, C., Francis, D.P., & Coats, A.J. (2004). Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ*, *328*(7433), 189.

Florea, V. G., & Cohn, J. N. (2014). The autonomic nervous system and heart failure. *Circulation Research*, *114*(11), 1815-1826.

Flynn, K. E., Piña, I. L., Whellan, D. J., Lin, L., Blumenthal, J. A., Ellis, S. J., ... & Kraus, W. E. (2009). Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA: Journal of the American Medical Association*, *301*(14), 1451-1459.

Fu, T. C., Yang, N. I., Wang, C. H., Cherng, W. J., Chou, S. L., Pan, T. L., & Wang, J. S. (2016). Aerobic interval training elicits different hemodynamic adaptations between heart failure patients with preserved and reduced ejection fraction. *American Journal of Physical Medicine & Rehabilitation*, *95*(1), 15-27.

Garner, P., Hopewell, S., Chandler, J., MacLehose, H., Akl, E. A., Beyene, J., ... & Lefebvre, C. (2016). When and how to update systematic reviews: consensus and checklist. *BMJ*, *354*, i3507.

Giamouzis, G., Schelbert, E. B., & Butler, J. (2016). Growing evidence linking microvascular dysfunction with heart failure with preserved ejection fraction. *Journal of the American Heart Association, 5*, E003259.

Glass, G. V. (1976). Primary, secondary, and meta-analysis of research. *Educational Researcher*, *5*(10), 3-8.

Gough, D., Oliver, S., & Thomas, J. (Eds.). (2017). *An Introduction to Systematic Reviews*. Sage.

Gurevitch, J., Koricheva, J., Nakagawa, S., & Stewart, G. (2018). Meta-analysis and the science of research synthesis. *Nature*, *555*(7695), 175.

Hartupee, J., & Mann, D. L. (2017). Neurohormonal activation in heart failure with reduced ejection fraction. *Nature Reviews Cardiology*, *14*(1), 30.

Haykowsky, M. J., Liang, Y., Pechter, D., Jones, L. W., McAlister, F. A., & Clark, A. M. (2007). A meta-analysis of the effect of exercise training on left ventricular remodelling in heart failure patients: the benefit depends on the type of training performed. *Journal of the American College of Cardiology*, *49*(24), 2329-2336.

Haykowsky, M. J., Timmons, M. P., Kruger, C., McNeely, M., Taylor, D. A., & Clark, A. M. (2013). Meta-analysis of aerobic interval training on exercise capacity and systolic function in patients with heart failure and reduced ejection fractions. *American Journal of Cardiology*, *111*(10), 1466-1469.

Heidenreich, P. A., Albert, N. M., Allen, L. A., Bluemke, D. A., Butler, J., Fonarow, G. C., ... & Nichol, G. (2013). Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circulation: Heart Failure*, *6*(3), 606-619.

Higgins, J. P., & Green, S. (Eds.). (2011). *Cochrane handbook for systematic reviews of interventions (Vol. 4).* John Wiley & Sons.

Hsu, C. Y., Hsieh, P. L., Hsiao, S. F., & Chien, M. Y. (2015). Effects of exercise training on autonomic function in chronic heart failure: systematic review. *BioMed Research International*. Article ID 591708, http://dx.doi.org/10.1155/2015/591708

Hwang, R., & Marwick, T. (2009). Efficacy of home-based exercise programmes for people with chronic heart failure: a meta-analysis. *European Journal of Cardiovascular Prevention & Rehabilitation*, *16*(5), 527-535.

Hwang, C. L., Chien, C. L., & Wu, Y. T. (2010). Resistance training increases 6-minute walk distance in people with chronic heart failure: a systematic review. *Journal of Physiotherapy*, *56*(2), 87-96.

Ismail, H., McFarlane, J. R., Nojoumian, A. H., Dieberg, G., & Smart, N. A. (2013)a. Clinical outcomes and cardiovascular responses to different exercise training intensities in patients with heart failure: a systematic review and meta-analysis. *Journal of the American College of Cardiology: Heart Failure*, *1*(6), 514-522.

Ismail, H., McFarlane, J., & Smart, N. A. (2013)b. Is exercise training beneficial for heart failure patients taking β-adrenergic blockers? a systematic review and meta-analysis. *Congestive Heart Failure*, *19*(2), 61-69.

Ismail, H., McFarlane, J. R., Dieberg, G., & Smart, N. A. (2014). Exercise training program characteristics and magnitude of change in functional capacity of heart failure patients. *International Journal of Cardiology*, *171*(1), 62-65.

Jewiss, D., Ostman, C., & Smart, N. A. (2016). The effect of resistance training on clinical outcomes in heart failure: a systematic review and meta-analysis. *International Journal of Cardiology*, *221*, 674-681.

Keteyian, S. J., Leifer, E. S., Houston-Miller, N., Kraus, W. E., Brawner, C. A., O'Connor, C. M., ... & Cohen-Solal, A. (2012). Relation between volume of exercise and clinical outcomes in patients with heart failure. *Journal of the American College of Cardiology*, *60*(19), 1899-1905.

Kitzman, D. W., Brubaker, P., Morgan, T., Haykowsky, M., Hundley, G., Kraus, W. E., ... & Nicklas, B. J. (2016). Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA: Journal of the American Medical Association*, *315*(1), 36-46.

Lewinter, C., Doherty, P., Gale, C. P., Crouch, S., Stirk, L., Lewin, R. J., ... & Bland, J. M. (2015). Exercise-based cardiac rehabilitation in patients with heart failure: a meta-analysis of randomised controlled trials between 1999 and 2013. *European Journal of Preventive Cardiology*, *22*(12), 1504-1512.

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P., ... & Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Medicine*, *6*(7), e1000100.

Lloyd-Williams, F., Mair, F. S., & Leitner, M. (2002). Exercise training and heart failure: a systematic review of current evidence. *British Journal of General Practice*, *52*(474), 47-55.

Lourenço, A. P., Leite-Moreira, A. F., Balligand, J. L., Bauersachs, J., Dawson, D., de Boer, R. A., ... & Giacca, M. (2018). An integrative translational approach to study heart failure with preserved ejection fraction: a position paper from the Working Group on Myocardial Function of the European Society of Cardiology. *European Journal of Heart Failure*, *20*(2), 216-227.

Lund, L. H., Claggett, B., Liu, J., Lam, C. S., Jhund, P. S., Rosano, G. M., ... & McMurray, J. J. (2018). Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. *European Journal of Heart Failure*. https://doi-org.ezproxy.une.edu.au/10.1002/ejhf.1149

Mann, D. L. (2015). Innate immunity and the failing heart: the cytokine hypothesis revisited. *Circulation Research*, *116*(7), 1254-1268.

McKelvie, R. S., Teo, K. K., McCartney, N., Humen, D., Montague, T., & Yusuf, S. (1995). Effects of exercise training in patients with congestive heart failure: a critical review. *Journal of the American College of Cardiology*, *25*(3), 789-796.

Metra, M., & Teerlink, J, R. (2017). Heart Failure. *The Lancet, 390 (10106),* 1981-1995.

Miake-Lye, I. M., Hempel, S., Shanman, R., & Shekelle, P. G. (2016). What is an evidence map? A systematic review of published evidence maps and their definitions, methods, and products. *Systematic Reviews*, *5*(1), 28.

Montemezzo, D., Fregonezi, G. A., Pereira, D. A., Britto, R. R., & Reid, W. D. (2014). Influence of inspiratory muscle weakness on inspiratory muscle training responses in chronic heart failure patients: a systematic review and meta-analysis. *Archives of Physical Medicine and Rehabilitation*, *95*(7), 1398-1407.

Murad, M. H., Montori, V. M., Ioannidis, J. P., Jaeschke, R., Devereaux, P. J., Prasad, K., ... & Meade, M. O. (2014). How to read a systematic review and meta-analysis and apply the results to patient care: users' guides to the medical literature. *JAMA: Journal of the American Medical Association*, *312*(2), 171-179.

Nauta, J. F., Hummel, Y. M., van Melle, J. P., van der Meer, P., Lam, C. S., Ponikowski, P., & Voors, A. A. (2017). What have we learned about heart failure with mid-range ejection fraction one year after its introduction? *European Journal of Heart Failure, 19*, 1569-1573.

Neto, M., Rodrigues-Jr, E. S., Silva-Jr, W. M., & Carvalho, V. O. (2014)a. Effects of yoga in patients with chronic heart failure: a meta-analysis. *Arquivos Brasileiros de Cardiologia*, *103*(5), 433-439.

Neto, M., Menezes, M. A., & Carvalho, V. O. (2014)b. Dance therapy in patients with chronic heart failure: a systematic review and a meta-analysis. *Clinical Rehabilitation*, *28*(12), 1172-1179

Neto, M. G., Conceição, C. S., de Jesus, F. L. A., & Carvalho, V. O. (2015). Hydrotherapy on exercise capacity, muscle strength and quality of life in patients with heart failure: A meta-analysis. *International Journal of Cardiology*, *198*, 216-219.

Neto, M. G., Oliveira, F. A., Dos Reis, H. F. C., de Sousa Rodrigues, E., Bittencourt, H. S., & Carvalho, V. O. (2016)a. Effects of neuromuscular electrical stimulation on physiologic and functional measurements in patients with heart failure: a systematic review with meta-analysis. *Journal of Cardiopulmonary Rehabilitation and Prevention*, *36*(3), 157-166.

Neto, M. G., Martinez, B. P., Conceição, C. S., Silva, P. E., & Carvalho, V. O. (2016)b. Combined exercise and inspiratory muscle training in patients with heart failure: a systematic review and meta-analysis. *Journal of Cardiopulmonary Rehabilitation and Prevention*, *36*(6), 395-401.

Neves, L. M. T., Cahalin, L. P., Silva, V. Z. M., Silva, M. L., Arena, R., Spielholz, N. I., & Junior, G. C. (2014). Effect of chronic neuromuscular electrical stimulation on primary cardiopulmonary exercise test variables in heart failure patients: a systematic review and meta-analysis. *IJC Metabolic & Endocrine*, *5*, 28-35.

O'Connor, C. M., Whellan, D. J., Lee, K. L., Keteyian, S. J., Cooper, L. S., Ellis, S. J., ... & Rendall, D. S. (2009). Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA: Journal of the American Medical Association*, *301*(14), 1439-1450.

Palau, P., Núñez, E., Domínguez, E., Sanchis, J., & Núñez, J. (2016). Physical therapy in heart failure with preserved ejection fraction: a systematic review. *European Journal of Preventive Cardiology*, *23*(1), 4-13.

Pan, L., Yan, J., Guo, Y., & Yan, J. (2013). Effects of Tai Chi training on exercise capacity and quality of life in patients with chronic heart failure: a meta-analysis. *European Journal of Heart Failure*, *15*(3), 316-323.

Pandey, A., Parashar, A., Kumbhani, D., Agarwal, S., Garg, J., Kitzman, D., ... & Berry, J. D. (2014). Exercise training in patients with heart failure and preserved ejection fraction: a meta-analysis of randomized control trials. *Circulation: Heart Failure*, CIRCHEARTFAILURE-114.

Paulus, W. J., & Tschöpe, C. (2013). A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodelling through coronary microvascular endothelial inflammation. *Journal of the American College of Cardiology*, *62*(4), 263-271.

Piepoli, M. F., Flather, M., & Coats, A. J. S. (1998). Overview of studies of exercise training in chronic heart failure: the need for a prospective randomized multicentre European trial. *European Heart Journal*, *19*(6), 830-841.

Piepoli, M. F., & Coats, A. J. S. (2013). The 'skeletal muscle hypothesis in heart failure revised. *European Heart Journal, 34(7),* 48-488.

Plentz, R. D. M., Sbruzzi, G., Ribeiro, R. A., Ferreira, J. B., & Dal Lago, P. (2012). Inspiratory muscle training in patients with heart failure: meta-analysis of randomized trials. *Arquivos Brasileiros de Cardiologia*, *99*(2), 762-771.

Ponikowski, P., Voors, A. A., Anker, S. D., Bueno, H., Cleland, J. G., Coats, A. J., ... & Jessup, M. (2016). 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *European Heart Journal*, *37*(27), 2129-2200.

Price, K. J., Gordon, B. A., Bird, S. R., & Benson, A. C. (2016). A review of guidelines for cardiac rehabilitation exercise programmes: Is there an international consensus?. *European Journal of Preventive Cardiology*, *23*(16), 1715-1733.

Redfield, M. M. (2016). Heart failure with preserved ejection fraction. *New England Journal of Medicine*, *375*(19), 1868-1877.

Rees, K., Taylor, R. S., Singh, S., Coats, A. J., & Ebrahim, S. (2004). Exercise based rehabilitation for heart failure. *Cochrane Database Systematic Reviews*, (3), CD003331.

Reiter, B. D., & Arora, R. R. (2014). The role of exercise in heart failure: A Systematic Review. *American Journal of Therapeutics*, *21*(5), 403-411.

Rickenbacher, P., Kaufmann, B. A., Maeder, M. T., Bernheim, A., Goetschalckx, K., Pfister, O., ... & Rocca, B. L. (2017). Heart failure with mid-range ejection fraction: a distinct clinical entity? Insights from the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF). *European Journal of Heart Failure*, *19*(12), 1586-1596.

Sagar, V. A., Davies, E. J., Briscoe, S., Coats, A. J., Dalal, H. M., Lough, F., ... & Taylor, R. S. (2015). Exercise-based rehabilitation for heart failure: systematic review and meta-analysis. *Open Heart*, *2*(1), e000163.

Sahle, B. W., Owen, A. J., Mutowo, M. P., Krum, H., & Reid, C. M. (2016). Prevalence of heart failure in Australia: a systematic review. *BMC Cardiovascular Disorders*, *16*(1), 32.

Samson, R., Jaiswal, A., Ennezat, P. V., Cassidy, M., & Le Jemtel, T. H. (2016). Clinical phenotypes in heart failure with preserved ejection fraction. *Journal of the American Heart Association*, *5*(1), e002477.

Sanders-van Wijk, S., van Empel, V., Davarzani, N., Maeder, M. T., Handschin, R., Pfisterer, M. E., & Rocca, B. L. (2015). Circulating biomarkers of distinct pathophysiological pathways in heart failure with preserved vs. reduced left ventricular ejection fraction. *European Journal of Heart Failure*, *17*(10), 1006-1014.

Sbruzzi, G., Ribeiro, R. A., Schaan, B. D., Signori, L. U., Silva, A. M., Irigoyen, M. C., & Plentz, R. D. (2010). Functional electrical stimulation in the treatment of patients with chronic heart failure: a meta-analysis of randomized controlled trials. *European Journal of Cardiovascular Prevention & Rehabilitation*, *17*(3), 254-260.

Selig, S. E., Levinger, I., Williams, A. D., Smart, N., Holland, D. J., Maiorana, A., ... & Hare, D. L. (2010). Exercise & Sports Science Australia Position Statement on exercise training and chronic heart failure. *Journal of Science and Medicine in Sport*, *13*(3), 288-294.

Shah, S. J., Katz, D. H., & Deo, R. C. (2014). Phenotypic spectrum of heart failure with preserved ejection fraction. *Heart Failure Clinics*, *10*(3), 407-418.

Shah, S. J., Kitzman, D. W., Borlaug, B. A., Van Heerebeek, L., Zile, M. R., Kass, D. A., & Paulus, W. J. (2016). Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. *Circulation*, *134*(1), 73-90.

Shah, S. J. (2017). Precision medicine for heart failure with preserved ejection fraction: an overview. *Journal of Cardiovascular Translational Research*, *10*(3), 233-244.

Shamseer, L., Moher, D., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., ... & Stewart, L. A. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*, *349*, g7647.

Smart, N., & Marwick, T. H. (2004). Exercise training for patients with heart failure: a systematic review of factors that improve mortality and morbidity. *The American Journal of Medicine*, *116*(10), 693-706.

Smart, N. A., & Steele, M. (2010). Systematic review of the effect of aerobic and resistance exercise training on systemic brain natriuretic peptide (BNP) and N-terminal BNP expression in heart failure patients. *International Journal of Cardiology*, *140*(3), 260-265.

Smart, N. A., Larsen, A. I., Le Maitre, J. P., & Ferraz, A. S. (2011)a. Effect of exercise training on interleukin-6, tumour necrosis factor alpha and functional capacity in heart failure. *Cardiology Research and Practice*, *2011*.

Smart, N. A., & Steele, M. (2011)b. The effect of physical training on systemic proinflammatory cytokine expression in heart failure patients: a systematic review. *Congestive Heart Failure*, *17*(3), 110-114.

Smart, N. A., Meyer, T., Butterfield, J. A., Faddy, S. C., Passino, C., Malfatto, G., ... & Giallauria, F. (2012). Individual patient meta-analysis of exercise training effects on systemic brain natriuretic peptide expression in heart failure. *European Journal of Preventive Cardiology*, *19*(3), 428-435.

Smart, N. A., Dieberg, G., & Giallauria, F. (2013)a. Functional electrical stimulation for chronic heart failure: a meta-analysis. *International Journal of Cardiology*, *167*(1), 80-86.

Smart, N. A., Giallauria, F., & Dieberg, G. (2013)b. Efficacy of inspiratory muscle training in chronic heart failure patients: a systematic review and meta-analysis. *International Journal of Cardiology*, *167*(4), 1502-1507.

Smart, N. A., Dieberg, G., & Giallauria, F. (2013)c. Intermittent versus continuous exercise training in chronic heart failure: a meta-analysis. *International Journal of Cardiology*, *166*(2), 352-358.

Spruit, M. A., Eterman, R. M., Hellwig, V., Janssen, P., Wouters, E., & Uszko-Lencer, N. (2009). A systematic review on the effects of moderate-to-high intensity resistance training in patients with chronic heart failure. *Heart*, *95(17),* 1399-1408.

Sullivan, M. J., Higginbotham, M. B., & Cobb, F. R. (1988). Exercise training in patients with severe left ventricular dysfunction. Hemodynamic and metabolic effects. *Circulation*, *78*(3), 506-51

Tai, M. K., Meininger, J. C., & Frazier, L. Q. (2008). A systematic review of exercise interventions in patients with heart failure. *Biological Research for Nursing*, *10*(2), 156-182.

Taylor, R. S., Davies, E. J., Dalal, H. M., Davis, R., Doherty, P., Cooper, C., ... & Smart, N. A. (2012). Effects of exercise training for heart failure with preserved ejection fraction: a systematic review and meta-analysis of comparative studies. *International Journal of Cardiology*, *162*(1), 6-13.

Taylor, R. S., Sagar, V. A., Davies, E. J., Briscoe, S., Coats, A. J., Dalal, H., ... & Singh, S. (2014). Exercise-based rehabilitation for heart failure. *The Cochrane Library*. 4: CD003331.

Tromp, J., Khan, M. A., Klip, I. T., Meyer, S., de Boer, R. A., Jaarsma, T., ... & Voors, A. A. (2017). Biomarker Profiles in Heart Failure Patients With Preserved and Reduced Ejection Fraction. *Journal of the American Heart Association*, *6*(4), e003989.

Tschöpe, C., Birner, C., Böhm, M., Bruder, O., Frantz, S., Luchner, A., ... & Laufs, U. (2018). Heart failure with preserved ejection fraction: current management and future strategies. *Clinical Research in Cardiology*, 1-19.

Tucker, W. J., Lijauco, C. C., Hearon Jr, C. M., Angadi, S. S., Nelson, M. D., Sarma, S., ... & Haykowsky, M. J. (2018). Mechanisms of the Improvement in Peak VO2 with Exercise Training in Heart Failure with Reduced or Preserved Ejection Fraction. *Heart, Lung and Circulation*, *27*(1), 9-21.

Tu, R. H., Zeng, Z. Y., Zhong, G. Q., Wu, W. F., Lu, Y. J., Bo, Z. D., ... & Yao, L. M. (2014). Effects of exercise training on depression in patients with heart failure: a systematic review and meta-analysis of randomized controlled trials. *European Journal of Heart Failure*, *16*(7), 749-757.

Van der Meer, S., Zwerink, M., van Brussel, M., van der Valk, P., Wajon, E., & van der Palen, J. (2012). Effect of outpatient exercise training programmes in patients with chronic heart failure: a systematic review. *European Journal of Preventive Cardiology*, *19*(4), 795-803.

Van Heerebeek, L., & Paulus, W. J. (2016). Understanding heart failure with preserved ejection fraction: where are we today?. *Netherlands Heart Journal*, *24*(4), 227-236.

Van Linthout, S., & Tschöpe, C. (2017). Inflammation–Cause or Consequence of Heart Failure or Both? *Current Heart Failure Reports*, *14*(4), 251-265.

Van Tol, B. A., Huijsmans, R. J., Kroon, D. W., Schothorst, M., & Kwakkel, G. (2006). Effects of exercise training on cardiac performance, exercise capacity and quality of life in patients with heart failure: A meta-analysis. *European Journal of Heart Failure*, *8*(8), 841-850.

Verloop, W. L., Beeftink, M. M., Santema, B. T., Bots, M. L., Blankestijn, P. J., Cramer, M. J., ... & Voskuil, M. (2015). A systematic review concerning the relation between the sympathetic nervous system and heart failure with preserved left ventricular ejection fraction. *PloS ONE, 10(2*), e0117332.

Vromen, T., Kraal, J. J., Kuiper, J., Spee, R. F., Peek, N., & Kemps, H. M. (2016). The influence of training characteristics on the effect of aerobic exercise training in patients with chronic heart failure: a meta-regression analysis. *International Journal of Cardiology*, *208*, 120-127.

Whellan, D. J., O'Connor, C. M., Lee, K. L., Keteyian, S. J., Cooper, L. S., Ellis, S. J., ... & Rendall, D. S. (2007). Heart failure and a controlled trial investigating outcomes of exercise training (HF-ACTION): design and rationale. *American Heart Journal*, *153*(2), 201-211.

Yancy, C. W., Jessup, M., Bozkurt, B., Butler, J., Casey, D. E., Drazner, M. H., ... & Johnson, M. R. (2013). 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*, *62*(16), e147-e239

Yancy, C. W., Jessup, M., Bozkurt, B., Butler, J., Casey, D. E., Colvin, M. M., ... & Hollenberg, S. M. (2017). 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Journal of Cardiac Failure*, *23*(8), 628-651.

Zakeri, R., & Cowie, M. R. (2018). Heart failure with preserved ejection fraction: controversies, challenges and future directions. *Heart*, *104(5),* 377-384.

Zhang, Y., Xu, L., Yao, Y., Guo, X., Sun, Y., Zhang, J., & Fu, Q. (2016). Effect of short-term exercise intervention on cardiovascular functions and quality of life of chronic heart failure patients: A meta-analysis. *Journal of Exercise Science & Fitness*, *14*(2), 67-75

Zheng, S. L., Chan, F. T., Nabeebaccus, A. A., Shah, A. M., McDonagh, T., Okonko, D. O., & Ayis, S. (2018). Drug treatment effects on outcomes in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *Heart*, *104*(5), 407-415.

Ziaeian, B., & Fonarow, G. C. (2016). Epidemiology and aetiology of heart failure. *Nature Reviews Cardiology*, *13*(6), 368-378.

Zwisler, A. D., Norton, R. J., Dean, S. G., Dalal, H., Tang, L. H., Wingham, J., & Taylor, R. S. (2016). Home-based cardiac rehabilitation for people with heart failure: a systematic review and meta-analysis. *International Journal of Cardiology*, *221*, 963-969.

3 Chapter 3 - Peer reviewed publication: Effect of exercise training on endothelial function in heart failure patients: a systematic review meta-analysis

3.1 Manuscript Information

Pearson, M. J., & Smart, N. A. (2017). Effect of exercise training on endothelial function in heart failure patients: a systematic review meta-analysis. *International Journal of Cardiology*, *231*, 234-243, https://doi.org/10.1016/j.ijcard.2016.12.145

Submitted 20th September 2016, Submitted in revised form 23rd November 2016, Accepted 20th December 2016, Available online 28th December 2016

20th June 2018

Candidate

Principal Supervisor 20th June 2018

3.2 Statement of author's contribution

Higher Degree Research Thesis by Publication
University of New England

STATEMENT OF AUTHORS' CONTRIBUTION

We, the PhD candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated in the *Statement of Originality*.

	Author's Name (please print clearly)	**% of contribution**
Candidate	Melissa Pearson	80%
Other Authors	Neil Smart	20%

Name of Candidate: Melissa Jane Pearson

Name/title of Principal Supervisor: Professor Neil Smart

[redacted]

20th June 2018

Candidate Date

[redacted]

20th June 2018

Principal Supervisor Date

3.3 Statement of originality

Higher Degree Research Thesis by Publication
University of New England

STATEMENT OF ORIGINALITY

We, the PhD candidate and the candidate's Principal Supervisor, certify that the following text, figures and diagrams are the candidate's original work.

Type of work	Page number(s)
Systematic Review & Meta-analysis	58-78

Name of Candidate: Melissa Jane Pearson

Name/title of Principal Supervisor: Professor Neil Smart

20th June 2018

Candidate Date

20th June 2018

Principal Supervisor Date

3.4 Full manuscript as published

International Journal of Cardiology 231 (2017) 234–243

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Effect of exercise training on endothelial function in heart failure patients: A systematic review meta-analysis☆,☆☆

M.J. Pearson [1], N.A. Smart *,[1]

School of Science and Technology, University of New England, Armidale, NSW 2351, Australia

ARTICLE INFO

Article history:
Received 20 September 2016
Received in revised form 23 November 2016
Accepted 20 December 2016
Available online 28 December 2016

Keywords:
Heart failure
Exercise
Endothelial function
Flow-mediated dilation
Endothelial progenitor cells

ABSTRACT

Objective: Endothelial dysfunction contributes to the development and progression of cardiovascular disease and heart failure (HF) and is associated with an increased risk of mortality. Flow-mediated dilation (FMD) is widely utilised to assess endothelial function and is improved with exercise training in heart failure patients. The aim of this meta-analysis is to quantify the effect of exercise training in patients with heart failure.
Background: A large number of studies now exist that have examined endothelial function in patients with heart failure. We sought to add to the current literature by quantifying the effect of exercise training on endothelial function.
Methods: We conducted database searches (PubMed, EMBASE, PROQUEST and Cochrane Trials Register to June 2016) for exercise based rehabilitation trials in heart failure, using search terms exercise training, endothelial function, flow-mediated dilation (FMD) and endothelial progenitor cells (EPCs).
Results: The 16 included studies provided a total of 529 participants, 293 in an intervention and 236 in controls groups. FMD was improved with exercise training in exercise vs. control, SMD of 1.08 (95%CI 0.70 to 1.46, $p < 0.00001$).
Conclusion: Overall exercise training improved endothelial function, assessed via FMD, and endothelial progenitor cells in heart failure patients.

1. Introduction

Heart failure (HF) is a complex syndrome caused by structural and/or functional cardiac abnormalities [1], a leading cause of morbidity and mortality and a significant financial and social burden. Exercise intolerance is a hallmark characteristic of HF, interfering with activities of daily living and consequently having a negative effect on a patient's quality of life [2]. Exercise training is now considered an effective adjunct treatment in heart failure and the consistent benefits of exercise training on a range of outcomes [3–8] have led to a class IA level recommendation in stable HF patients [1]. While the mechanisms underlying exercise intolerance are complex [2,9,10], they are generally considered multifactorial, of which endothelial dysfunction (ED) is one factor [9]. In patients with HF, improved endothelial-dependant dilation as a result exercise training has been shown to be associated with improved exercise capacity [11–13].

Endothelial dysfunction is associated with the pathogenesis and progression of HF [14], and predicts mortality risk [15]. The vascular endothelium, a monolayer of cells representing a barrier between the blood and vascular wall is critical in maintaining vascular homeostasis [14]. Not only forming a physical barrier, endothelial cells synthesize vasodilators and vasoconstrictors, regulating vascular tone [14,16], with Nitric Oxide (NO) considered to be the most important mediator of vascular function [16] .

Flow-mediated dilation (FMD) is currently the most common and widely utilised method in the assessment of endothelial function [17], and in HF, FMD has been shown to be predictive of deterioration and death [18]. FMD is a non-invasive assessment that measures the arterial response to shear stress, induced by reactive hyperemia as a result of temporary arterial occlusion [19,20]. Most commonly measured in the brachial artery, it is also assessed in the radial artery and arteries of the lower limbs [19] and correlates with endothelial function of the coronary arteries [21].

Analyses [22–24] of studies across diverse populations indicate exercise training improves FMD. Primarily shear stress mediates endothelial adaptation to exercise by increasing NO bioavailaibility [25]; a result of the upregulation of endothelial NO synthase (eNOS) expression and phosphorylation [26] and an increase in antioxidant enzymes [27]. More recently, evidence indicates that exercise also promotes endothelial repair

☆ This work received no financial support and has no relationship to industry.
☆☆ The authors report no relationships that could be construed as a conflict of interest.
* Corresponding author.
E-mail address: nsmart2@une.edu.au (N.A. Smart).
[1] The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

http://dx.doi.org/10.1016/j.ijcard.2016.12.145
0167-5273/

mechanisms in HF patients; specifically the mobilisation of bone-marrow derived endothelial progenitor cells (EPCs) [28], further making the endothelium a valid target for exercise therapy [29].

A 2013 review paper [30] included studies up until December 2011 that measured endothelial function via ultrasound or plethysmography. However, data was not pooled for analysis. Two [22,24] recent analyses investigating vascular function in diverse populations, including HF patients, reported the favourable effects of exercise on FMD. The primary aim of our paper was to conduct a systematic review and meta-analysis to quantify the effect of exercise training on endothelial function, assessed by FMD, in heart failure patients. A secondary aim was to examine the possible effects of exercise training on EPCs in this population.

2. Methods

2.1. Search strategy

Potential studies were identified by conducting systematic searches of PubMed, EMBASE, PROQUEST and the Cochrane Library of Controlled Trials up until 30th June 2016. Searches included a mix of MeSH and free text terms related to the key concepts of heart failure, exercise training, endothelial function, flow-mediated dilation and endothelial progenitor cells. Additionally, systematic reviews, meta-analyses and reference lists of papers were hand searched for additional studies. One reviewer (MJP) conducted the search and full articles were assessed for eligibility by two reviewers (MJP and NAS). Two authors were contacted to provide additional information; one author did not respond and the second responded but was unable to provide any further information.

2.2. Study selection

Randomised controlled trials and clinically controlled trials of exercise training in heart failure patients with reduced ejection fractions (HFrEF) were included. Exercise training was defined to allow for inclusion of a broad range of physical activities, and included aerobic, resistance, combined training (aerobic and resistance), Yoga, Pilates, Tai Chi, and hydrotherapy. Additionally, the physical therapies of Functional Electrical Stimulation (FES) and Inspiratory Muscle Training (IMT) were included in the definition of exercise training for the purpose of this review. Studies included in the review compare an exercise intervention to a no exercise or usual care control group. Only studies that measured endothelial function by FMD, measured via ultrasound, as a result of reactive hyperaemia (RH), reported as FMD% or absolute FMD (mm or μm) in either the Brachial or Radial Artery were included.

2.3. Data extraction and outcome measures

Data were extracted by one reviewer (MJP). The primary outcome measure was flow-mediated dilation (FMD % or FMD absolute (mm)). Where FMD was reported as both FMD% and FMD (mm), FMD% was utilised in the analysis. Where the unit of measurement of FMD absolute was reported in micrometres (μm), data were converted to millimetres (mm), using 1 μm equals 0.001 mm.

2.4. Data synthesis

Statistical analyses were performed using Revman 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark). The individual meta-analyses were completed for continuous data by using the change in the mean and standard deviation. The primary outcome measure was FMD (FMD% or FMD mm). Where the change in mean and SD were not reported, the change in mean was calculated by subtracting the pre-intervention mean from the post-intervention mean, and Revman 5.3 enabled calculations of SD using number of participants in each group, within or between group p values or 95% CI. In cases were exact p values were not provided, we used default values e.g., $P < 0.05$ becomes $P = 0.049$, $p < 0.01$ becomes $p = 0.0099$ and $p =$ not significant becomes $p = 0.051$. Data not provided in main text or tables were extracted from figs. A random effects inverse variance was used with the effects measure of standardised mean difference (SMD). We utilised the widely accepted guideline for SMD interpretation [31], with 0.2 defined as small, 0.5 medium and 0.8 as large. Where a study included multiple intervention groups and a control group, the sample size of the control group was divided by the number of intervention groups to eliminate over inflation of the sample size. We used a 5% level of significance and a 95% CI to report change in outcome measures.

2.5. Heterogeneity and publication bias

Heterogeneity was quantified using the I^2 test [32]. Values range from 0% (homogeneity) to 100% (highly heterogeneity) [32]. Funnel plots [33] assessed risk of publication bias.

2.6. Study quality

Study quality was assessed by using the TESTEX; the Tool for assessment of study quality and reporting, designed specifically for use in exercise training studies [34]. This is a 15-point scale that assesses study quality (maximum 5 points) and reporting (maximum 10 points). Two reviewers (MJP and NAS) conducted quality assessment.

3. Results

The initial search identified 485 manuscripts. After removal of duplicates and exclusion of articles based on abstract and title, 48 full-text articles remained for screening. Full screening resulted in 16 articles meeting the stated inclusion criteria (fig. 1 PRISMA statement). The characteristics of the studies in the meta-analysis are included in Table 1. Details of full-text articles reviewed but excluded are provided, with reasons, in Supplementary Table S1.

3.1. Study characteristics

Sixteen studies [12,35–49] provided a total of 529 participants diagnosed with HF; 293 exercising participants and 236 control subjects. Thirteen studies [12,36–42,44–47,49] randomised participants, two were non-randomised controlled trials [43,48] and one [35] study randomised participants between two exercise interventions but the control group was non-randomised. The average age of participants ranged between 49 ± 5 yrs. and 75.5 ± 13 yrs. Sex distribution was predominantly male. Baseline Brachial FMD% ranged from approximately 3% to >8% and reported baseline Radial FMD% ranged from approximately 6% to >12% (Supplementary Table S2). Additional participant characteristics are detailed in Supplementary Table S2.

3.2. Intervention details

Of the 16 [12,35–49] included studies, 13 [12,35–41,43,45,47–49] predominantly involved aerobic training, one [42] investigated resistance training and two studies [44,46] examined FES. Intervention duration ranged from 4 weeks to 6 months, the weekly frequency of sessions from 2 to 7 sessions per week and the duration of exercise sessions ranged from 10 to 60 min. The intensity of aerobic training ranged from moderate to high. Seven [35,36,38,39,43,47,49] studies reported specific session attendance percentages and 13 [35–39,41–47,49] studies reported on occurrence of any adverse events (Supplementary Table S3).

3.3. FMD assessment

Detailed specifics of the method of FMD assessment were not provided by all studies, with some studies simply referencing a particular FMD guideline (Supplementary table S4). In studies that provided specific details of assessment, variation existed between studies in regard to cuff position, cuff pressure and occlusion duration. Eleven [35–38,41,43–46,48,49] studies assessed FMD in the Brachial Artery (BA), with the Radial Artery (RA) utilised in five [12,39,40,42,47] studies. Ten [35–38,41,43,45,47–49] studies reported FMD as FMD%, while three [40,42,46] studies reported absolute FMD (mm or μm) and three [12,39,44] studies reported both FMD% and absolute FMD. Only one study [35] reported on shear rate (SR_{AUC}).

3.4. Endothelial-independent dilation assessment

This measure is usually evaluated in conjunction with FMD as a measure of the responsiveness of vascular smooth muscle cells. Commonly also referred to as nitrate mediated dilation (NMD), it is measured via the administration of an exogenous source of NO (e.g., Nitroglycerine - NTG). The evaluation of the vasodilator responses to NTG may explain changes in smooth muscle function or arterial compliance that might be playing a role in any observed

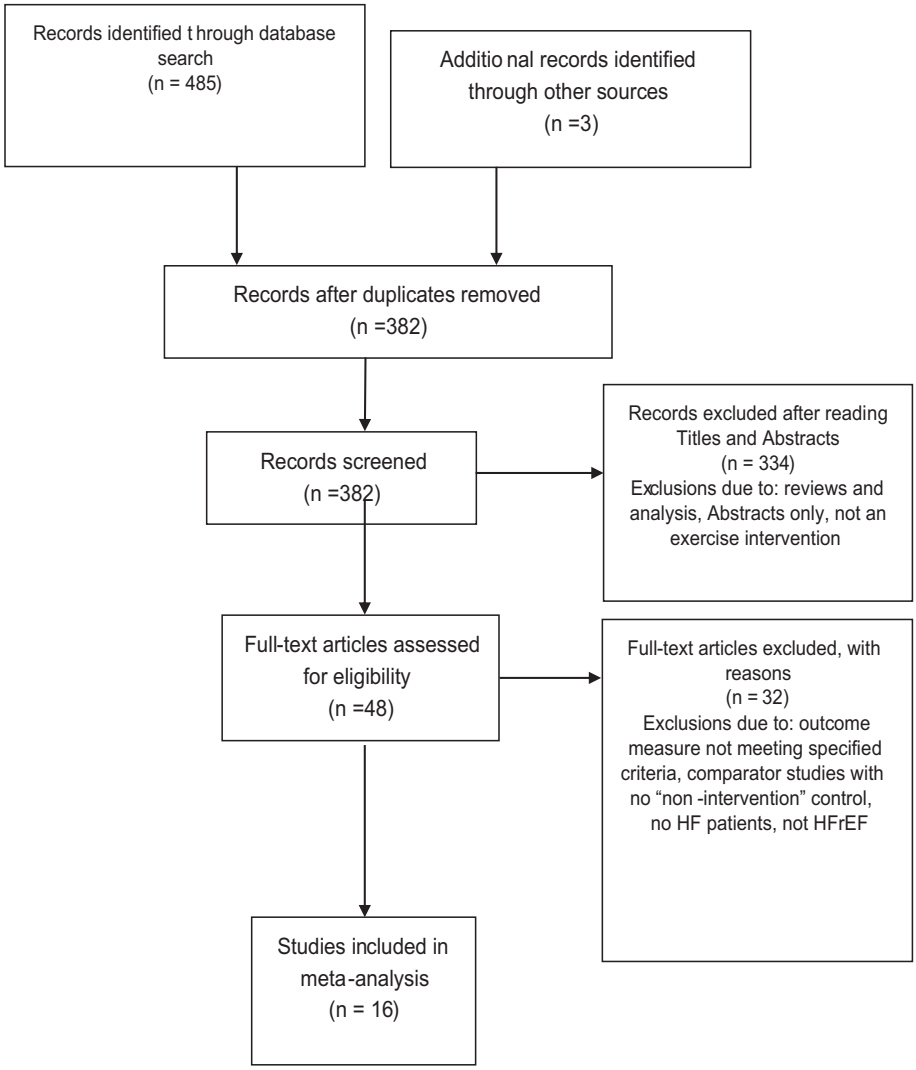


Fig. 1. PRISMA Statement

changes in FMD. Only nine [12,35–37,40–44] studies noted the assessment of endothelial-independent vasodilation. Seven studies [35–37,40,41,43,44] assessed NMD via sublingual administration of NTG and two studies [12,42] utilised intra-arterial infusion of NTG.

3.5. EPC assessment

Four studies [38,39,47,48] measured EPCs by flow cytometry before and after an exercise intervention. Several different EPCs were measured and three studies [39,47,48] measured the same EPC phenotype ($CD34^+/KDR^+$), with two [39,47] studies reporting data as cells/ml blood and one study [48] reporting units as cells per 10^6 events. The fourth study [38] measured a different EPC ($CD^{45dim}CD34^+/KDR^+$ Cells) and hence this study's data was not pooled.

4. Outcome measures

4.1. Flow-mediated dilation (FMD)

4.1.1. Exercise vs. control

Pooled data from 16 [12,35–49] studies showed a significant improvement in FMD as a result of exercise training, SMD 1.08 (95% CI 0.70 to 1.46, $P < 0.00001$) (fig. 2). Sensitivity analysis to remove three non-RCTs [35,43,48] did not significantly alter the result; SMD 1.30 (95%CI 0.88 to 1.71, $p < 0.00001$). Individually, both FMD% and FMD (mm) were significant; FMD% SMD 1.11 (95%CI 0.65 to 1.56, $p < 0.00001$) and FMD (mm) SMD 0.98 (95%CI 0.48 to 1.48, $p = 0.0001$) (fig. 2). Sensitivity analysis to examine the effects of brachial artery FMD from 11 studies [35–38,41,43–46,48,49] and radial artery FMD from five studies [12,39,40,42,47] indicated significant improvement in both, SMD 0.80 (95% CI 0.36 to 1.23, $p = 0.0003$) (Supplementary Fig. S1) and SMD 1.65 (95% CI 1.06 to 2.23 $P < 0.00001$) in brachial and radial artery respectively (Supplementary Fig. S2).

4.2. Endothelial-independent dilation

In each of the studies that administered NTG, a similar degree of vasodilation occurred in exercise and controls and pooled data of nine studies [12,35–37,40–44] indicated that exercise training did not have a significant effect on the endothelial-independent response, SMD -0.15 (95%CI -0.79 to 0.49, $p = 0.64$) (Supplementary Fig. S3).

4.3. EPCs

Pooled data from three studies [39,47,48] showed a significant improvement in $CD34^+/KDR^+$ as a result of exercise training, SMD 0.91 (95% CI 0.30 to 1.52, $p = 0.003$) (fig. 3). When sensitivity analysis was

performed to remove the non-RCT [48] the effect size and significance of the result increased; SMD 1.20 (95%CI 0.76 to 1.65, $p < 0.00001$).

4.4. Study quality assessment

The median TESTEX score was 9 (maximum 15) (Supplementary Table S5). While studies noted participant randomisation, details of the specific procedure were only provided in four studies. The majority of studies lost points in the areas of allocation concealment, activity monitoring in the control group, review of relative exercise intensity and energy expenditure characteristics.

4.5. Heterogeneity and publication bias

The main analysis showed moderate heterogeneity (<75%), with only the analysis of endothelial-independent dilation demonstrating high heterogeneity (>75%). Funnel plots demonstrated some evidence of publication bias.

5. Discussion

This work analysed the effects of exercise training on FMD in patients with chronic heart failure. Our primary finding shows that exercise training significantly improves endothelial function, assessed via FMD, in patients with HF. Our findings in HF patients are consistent with those of improved FMD from exercise training demonstrated in CAD patients [50,51] and type II diabetics [23].

Our pooled data demonstrated that exercise training did not have a significant effect on endothelial-independent vasodilation, indicating that the FMD improvement occurred primarily at the level of the endothelium [52]. This finding is consistent with studies in patients with CAD [50], post MI [51] and in Type II diabetics [23]. In the HF population vascular smooth muscle (VSM) responsiveness may not be severely impaired [11,13,40] or where VSM cell impairment exists, training interventions may need to be greater in duration and/or more intense to elicit adaptations [12,23,50].

Several mechanisms may explain the beneficial effects of exercise training on endothelial function. Exercise increases blood flow resulting in repetitive shear stress, the main stimulus for NO synthesis [25]. It increases antioxidant status and decreases the production of pro-inflammatory molecules [53]. We did not conduct an analysis of change in antioxidant or inflammatory status that may be associated with improved endothelial function. However, reduced levels of TNF-α [39,44], IL-10[44] and trends for a reduction in IL-6 [38,44] observed in studies included in the review provides support for the antioxidant and anti-inflammatory effects of exercise. Additionally, Wisloff and colleagues (2007) [49] demonstrated a significant 15% increase in antioxidant status from high intensity aerobic training, which correlated with FMD. The improved antioxidant status and reduction of pro-inflammatory cytokines as a result of exercise training is consistent with analyses of HF exercise studies [6,54] and studies [55] across diverse populations.

The final mechanism via which exercise may improve endothelial function is its ability to mobilise and recruit EPCs, an important player in endothelial repair [9,28]. HF patients demonstrate a reduced ability to recruit EPCs [28] and our analysis indicated that exercise training enhances EPCs, promoting endothelial repair and therefore likely improves endothelial function, as evidenced by the accompanied improvement in FMD [39,47,48]. Our pooled results support those from one of the first HF and exercise studies [56] to examine EPCs, which found a 251% increase in EPCs after an 8 week aerobic exercise program [56]. Both acute and chronic exercise have the potential to mobilise EPCs from the bone marrow of both healthy and diseased individuals [57] and our findings of enhanced EPCs from exercise training in HF patients are in agreement with those reported in other clinical conditions [58,59].

In the early 1990's endothelial dysfunction was noted in patients with reduced ejection fractions and in the period since the early exercise training studies of Horning et al. (1996) [13] and Hambrecht et al. (1998) [11] indicated improved endothelial function, a growing body of studies have now utilised FMD to assess endothelial function in HFrEF patients. Our analysis of HFrEF patients now quantifies the positive effect of exercise training on endothelial function, as assessed via FMD. All but two of the studies [35,45] in our analysis reported improved brachial or radial artery FMD in their exercise training groups. Higher baseline FMD values, a factor differentiating FMD responders from non-responders [60] and the possibility that the intervention protocol delivered a sub-optimal shear rate stimulus in one study [35] are noted as possible explanations. Importantly, however, improvements in FMD were demonstrated to occur in advanced (NYHA Class IIIb) HF patients as shown by Erbs et al. (2010) [39] as well as being equally evident in younger and older HFrEF patients, as demonstrated in the age stratified LEICA study [47], with improvements evident in as little as 4 weeks.

While approximately half of all patients have a preserved ejection fraction our analysis only included patients with reduced ejection fractions and therefore our findings cannot be generalised to patients with preserved ejection fractions (HFpEF). Only two [61,62] exercise training studies to date have reported on FMD in HFpEF patients, reflective of the minimal number of exercise studies addressing this phenotype. The two studies [61,62] utilised different exercise modalities, differed in duration and reported contrasting results. Kitzman and colleagues (2013) [62] reported no change in endothelial function after 16 weeks of endurance training, suggesting improved functional capacity in this population is not related to large artery function, and that impaired microvascular function may limit exercise performance in these patients. While HFpEF patients experience reduced exercise tolerance, the degree to which impaired endothelial function contributes is uncertain [63], with both normal [64] and impaired [65] FMD reported in these patients when compared to age-matched non-HF patients.

Exercise intolerance and reduced quality of life are primary symptoms in HF and exercise training has demonstrated improvements in both parameters [3,4,8]. Endothelial dysfunction is one of several underlying mechanisms that may contribute to these improvements and a large number of studies now exist that have utilised FMD to measure the effect of exercise interventions on endothelial function in the HF population. This current analysis adds to the literature by quantifying the effects of exercise training on endothelial function.

5.1. Strengths and Limitations in the systematic review and meta-analysis

To our knowledge this is the first systematic review and meta-analysis that examines endothelial function in heart failure patients. The major limitation of the review is the moderate to high level of heterogeneity among studies. Differences in the methodological assessment of FMD may have contributed to the level of heterogeneity. Despite the presence of general guidelines on FMD assessment [19,20], we found variation among studies in the application of these guidelines. A number of methodological issues, such as cuff position [66], time of measurement of peak diameter after cuff release and user experience [17] can all increase measurement error and reproductibility [17], and these differences may impact between study comparisons [20]. Future studies should aim to strongly adhere to FMD assessment guidelines. The severity of heart failure and medication use may have also contributed to the high heterogeneity.

In regard to data pooling, we measured the difference between pre-intervention and post-intervention means, however, in cases where exact p values within or between groups, or 95% CI were not available, default values for p were utilised and this may introduce errors. Additionally, data from some studies was extracted

Table 1
Characteristics of included studies

Study	Study Duration	Design	Participant Characteristics	Exercise Intervention				Major Findings
				Type	Frequency (per wk.)	Session Duration	Intensity	FMD & EPCs
Benda (2015)	12	Non-RCT [1]	$n = 33$ randomised, $n = 29$ completed ExT1: HIIT n = 10, 63 ± 8 yrs, 90% male LVEF 37 ± 6% ExT2: CT n = 10, 64 ± 8 yrs, 100% male, LVEF 38 ± 6% Con: n = 9, 67 ± 7 yrs, 56%male, LVEF 40 ± 11% All participants NYHA Class II & III HF Aetiology: Ischemic and non-Ischemic	A (C)	2	35 min (HIIT) 30 min (CT) (+10 min warm-up, 5 min cool-down each group)	HIIT: 10 x 1 min @ 90%max. WL (RPE 15–17) separated by 2.5 min @ 30%max. WL CT: @60–75%max. WL (RPE 12–14) Warm-up @ 40% max. WL & cool-down @ 30% max WL	↔FMD%
Belardinelli (2006)	8	RCT	$n = 52$ randomised, $n = 52$ completed ExT: n = 30, 55 ± 14 yrs, 100%male, LVEF 30.2 ± 7% Con: n = 22, 53 ± 15 yrs, 100% male, LVEF 33.6 ± 8% All participants NYHA Class II & III HF Aetiology: previous MI, previous stenting, previous CABG	A (C)	3	40 min (+ 15 min warm-up stretch, 5 min cool-down)	60% VO_{2peak}	↑ FMD% trained group Good correlation between Δpeak VO_2 & ΔFMD response in trained group
Belardinelli (2005)	8	RCT	$n = 59$ randomised, $n = 59$ completed ExT: n = 30, 56 ± 15 yrs, 100% male, LVEF 29.3 ± 6% Con: n = 29, 58 ± 12 yrs, 100% male, LVEF 28.1 ± 5% All participants NYHA Class II & III HF Aetiology: IHD and Idiopathic	A (C)	3	40 min (+ 15 min warm-up stretch, 5 min cool-down)	60% VO_{2peak}	↑FMD% trained group
Eleuteri (2013)	12	RCT	$n = 21$randomised, $n = 21$ completed ExT: n = 11, 66 ± 2 yrs, 100% male, LVEF 28 ± 2.1% Con: n = 10, 63 ± 2 yrs, 100% male, LVEF 30 ± 1.8% All participants NYHA Class II HF Aetiology: IHD and Idiopathic CM	A (C)	5	30 min (+5 min warm-up, 5 min cool-down)	HR & power @ VAT (cycle @ 60RPM)	↑FMD% Training group ↑EPC ($CD^{45dim}CD34^+/KDR^+$, p = 0.025)
Erbs (2010)	12	RCT	$n = 37$ randomised, $n = 34$ completed ExT: n = 17, 60 ± 11 yrs, 100% male, LVEF 24 ± 5% Con: n = 17, 62 ± 10 yrs, 100% male, LVEF 25 ± 4% *NB: age, LVEF based on n = 37* All participants NYHA Class III(b) HF Aetiology: IHD and DCM	A (C) + 1 x GS *	Daily + 1 GS wk.	20–30 min (+60 min GS)	60%VO_{2max}	↑FMD% training group ↑EPCs ($CD34^+/KDR^+$ cells/ml, p = 0.014 vs. control), ↑No. $CD34^+$ (p = 0.032 vs. control)
Giannattasio (2001)	8	RCT	$n = 22$ randomised, $n = 22$ completed ExT: n = 11, 61 ± 5 yrs, 82% male, LVEF 32.9 ± 3.4% Con: n = 11, 61 ± 5 yrs, 82% male, LVEF 32.2 ± 0.7 *NB: age, % male based on n = 44* All participants NYHA Class I, II & III HF Aetiology: Ischemic and non-ischemic	A(C)	3	30 min	NR	↑FMD(mm) (ΔDiameter) in training group

Guazzi (2004)	8	RCT	$n = 38$ randomised, $n = 31$ completed ExT: n = 16, 52 ± 5 yrs, 100% male, LVEF 34.3 ± 3.3% Con: n = 15, 54 ± 4 yrs, 100% male, LVEF 35.5 ± 3.7% All participants NYHA Class II & III HF Aetiology: IHD and DCM	A(C)	4	30 min (+5 min warm-up, 5 min cool-down)	60% HRR wk.1–2,↑ 80% HRR @ wk. 3	↑FMD% in training group
Hambrecht (2000)	4	RCT	$n = 20$ randomised, $n = 18$ completed ExT: n = 10, 55 ± 4 yrs, 100% male, LVEF 18 ± 3% C: n = 8, 56 ± 3 yrs, 100% male, LVEF 19 ± 3% All participants NYHA Class II & III HF Aetiology: DCM & ischemic CM	R (DHG)	Daily (6 x day)	Time determined in Ex. test	70% (60 N) of maximal capacity	↑FMD(μm) (ΔDiameter) in training group
Isaksen (2015)	12	Non-RCT	$n = 38$ started, $n = 35$ completed ExT: n = 24, 65 ± 9 yrs, 88% male, LVEF 37.6 ± 10.9% Con: n = 11, 69 ± 9 yrs, 100% male, LVEF 30.0 ± 8.1% All participants NYHA Class I, II & III HF Aetiology: IHD and DCM	A (C/T)	3	30 min (+15 min warm-up, 15 min strength/stretch)	4x4 HIIT @ 85% HR_{max} (~RPE 15–17) separated by 3 min recovery @60–70% HR_{max}, warm-up @60–70%HR_{max}	↑ FMD% Training Groups
Karavidas (2006)	6	RCT	$n = 24$ randomised, $n = 24$ completed ExT: n = 16, 57.4 ± 15.3 yrs, 88% male, LVEF 22.7 ± 6.5% Con: n = 8, 63.8 ± 8.1 yrs, 88% male, LVEF 27.2 ± 4.5% All participants NYHA Class II & III HF Aetiology: Ischemic and IDCM	FES (lower limb)	5	30 min	Intensity for visible muscle contraction - 25 Hz for 5 s than 5 s rest	↑FMD% in FES group
Kobayashi (2003)	12	RCT	$n = 28$ randomised, $n = 28$ completed ExT: n = 14, 55 ± 2 yrs, 86% male, LVEF 29 ± 2% Con: n = 14, 62 ± 2 yrs, 57% male, LVEF 33 ± 2% All participants NYHA Class II & III HF Aetiology: IHD and DCM	A (C)	2–3 (2 x day)	2 x15 min session/day (30 min/day total)	HR @ Ventilatory threshold (~60–70% VO_{2max})	↔FMD% Brachial Artery (↑FMD% posterior tibial artery)
Linke (2001)	4	RCT	$n = 22$ randomised, $n = 22$ completed ExT: n = 11, 58 ± 2 yrs, 100% male, LVEF 26 ± 3% Con: n = 11, 59 ± 3 yrs, 100% male, LVEF 24 ± 2 yrs All participants NYHA Class II & III HF Aetiology: IHD and DCM	A (C)	daily (6 x per day)	10 min/session (60 min/day total)	70% VO_{2peak}	↑ FMD% training group
Parissis (2015)	6	RCT	$n = 30$ randomised, $n = 30$ completed ExT: n = 15, 75.2 ± 3.69 yrs, 63% male, LVEF 27.3 ± 3.2% Con: n = 15, 75.2 ± 3.32%, 60% male, LVEF 28 ± 2.5% All participants NYHA Class II & III HF Aetiology: NR	FES (lower limb)	5	30 min	Intensity for visible muscle contraction - 25 Hz for 5 s than 5 s rest	↑FMD(mm) in FES group
Sandri (2015)	4	RCT	$n = 60$ randomised, $n = 60$ completed ExT1: n = 15, 50 ± 5 yrs, 80% male, LVEF 27 ± 6% Con1: n = 15, 49 ± 5 yrs, 87% male, LVEF 28 ± 5% ExT2: n = 15, 72 ± 4 yrs, 80% male, LVEF 29 ± 6% Con2: n = 15, 72 ± 3 yrs, 80% male, LVEF 28 ± 6%. All participants NYHA Class II & III HF Aetiology: IHD and DCM	A (C)+ 1 x GS*	5 (4 x per weekday)	15–20 min/session (~60 min/day total) (+ 1 x 60 min GS per/wk.)	70% of symptom limited VO_{2max}.	↑ FMD% in both HF training groups ↑EPCs ($CD34^+/KDR^+$ & $CD\ 133^+/KDR^+$ cells/ml)

(continued on next page)

Table 1 (*continued*)

Study	Study Duration	Design	Participant Characteristics	Exercise Intervention				Major Findings
				Type	Frequency (per wk.)	Session Duration	Intensity	FMD & EPCs
Van Craenenbroeck (2010)	26	Non-RCT	$n = 38$ started, $n = 38$ completed ExT: n = 21, 61.3 ± 2.2 yrs, 86% male, LVEF 27.0 ± 1.9% Con: n = 17, 63.4 ± 3 yrs, 71% male, LVEF 31.3 ± 1.7% All participants NYHA Class II HF Aetiology: Ischemic and DCM	A	3	60 min	90% HR @ respiratory compensation point	↑FMD% Exercise group Trend for ↑EPCs ($CD34^+/KDR^+$ cells per 10^6events) but not significant compared to control group. ↔ $CD34^+$ cells compared to control.
Wisloff (2007)	12	RCT	$n = 27$ randomised, $n = 26$ completed ExT1: AIT n = 9, 76.5 ± 9ys, 78% male, LVEF 28.0 ± 7.3% ExT2: MICT n = 8, 74.4 ± 12 yrs, 78% male, LVEF 32.8 ± 4.8% Con: n = 9, 75.5 ± 13 yrs, 67% male, LVEF 26.2 ± 8% HF Aetiology: Ischemic post infarct on β-Blockers	A (W)	3	HIIT: 38 min (includes 10 min warm-up) MICT: 47 min	HIIT: 4 min X 4 @90–95% HR_{max}, separated by 3 min @ 50–70%HR_{max} MICT: @ 70–75%HR_{max}	↑FMD% AIT & MCT, but greater in AIT Relationship between improved aerobic capacity and FMD

A: aerobic, AERG: arm ergometer, AIT: aerobic interval training, CABG: coronary artery bypass surgery, Con: control, C: cycle, CM: cardiomyopathy, CT: continuous, DCM: dilated cardiomyopathy, DHG: dynamic handgrip, EPC: endothelial progenitor cell, ExT: exercise training , GS: group session, , FES: functional electrical stimulation , FMD: flow-mediated dilation, HIIT: high intensity interval training, HR: heart rate, HR_{max}: maximum heart rate, HR_{peak}: peak heart rate , HRR: heart rate reserve , IHD: Ischemic heart disease, LVEF: left ventricular ejection fraction, MIACT: moderate intensity aerobic training, MICT: moderate continuous training, NYHA: New York Heart Association, non-RCT: non-randomised controlled trial, RCT: Randomised controlled trial, R: resistance, RPE: rating of perceived exertion, RPM: revolutions per minute, T: treadmill, VAT: ventilatory anaerobic threshold, VO_{2peak}: peak oxygen uptake, VO_{2max}: maximal oxygen uptake, W: walking, WL: workload. (1) ExT 1 and ExT2 randomised, but control group not randomised, (2) n = 53 for FMD, n = 24 analysed for other outcomes.

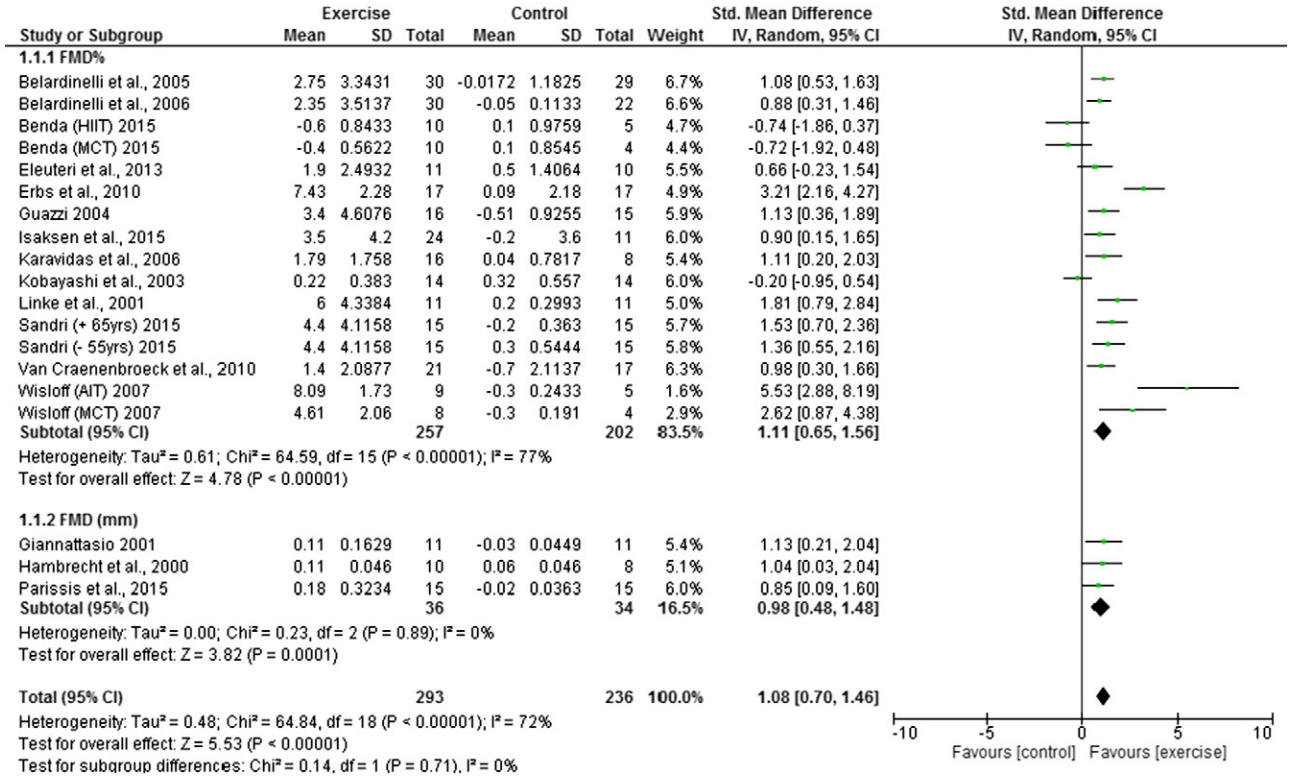


Fig. 2. Change in Flow-mediated dilation in HF patients - exercise vs. control

from figures. This in itself has the potential to introduce errors. Meta-analyses have a key role in evidenced based medicine and in order to provide evidence of the highest quality, data reporting by researchers needs to be consistent across studies to aid in elimination of potential errors.

6. Conclusion

This meta-analysis found that exercise training improves endothelial function, assessed by FMD, in heart failure patients with reduced ejection fractions. This result is consistent with findings of analyses in a range of populations. However, whether or not the same effects occur in both HF phenotypes is unclear given the small number of trials to date assessing FMD in HFpEF patients. Future exercise studies should look to examine endothelial function in HFpEF patients and also consider inclusion of HFmrEF, the latest classification for HF patients as noted in the updated ESC guidelines [1].

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2016.12.145.

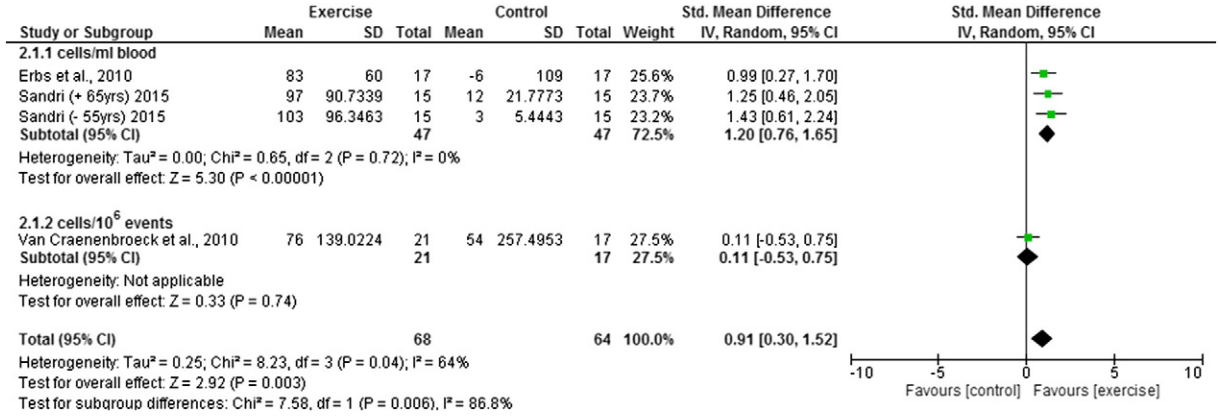


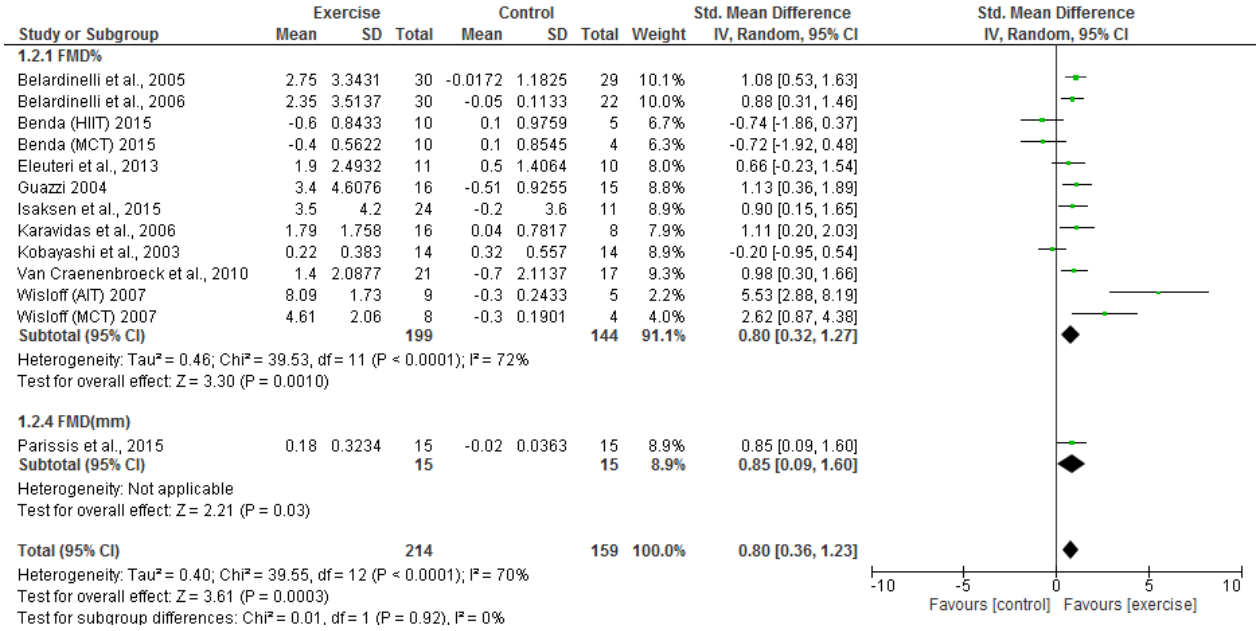
Fig. 3. Change in EPCs in HF patients - exercise vs. control.

References

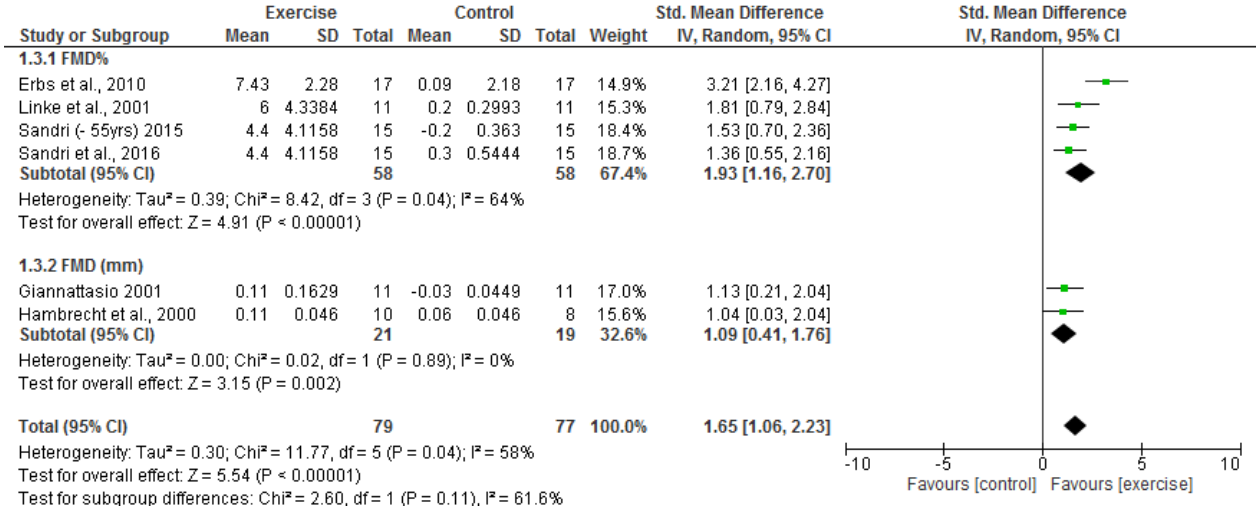
[1] J.J. Atherton, J. Bauersachs, S. Carerj, et al., 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, Eur. Heart J. 18 (8) (2016) 891–975.
[2] J.L. Fleg, L.S. Cooper, B.A. Borlaug, et al., Exercise training as therapy for heart failure current status and future directions, Circ. Heart Fail. 8 (1) (2015) 209–220.
[3] R.S. Taylor, V.A. Sagar, E.J. Davies, et al., Exercise-based rehabilitation for heart failure, The Cochrane Library, 2014.
[4] G. Dieberg, H. Ismail, F. Giallauria, N.A. Smart, Clinical Outcomes and Cardiovascular Responses to Exercise Training in Preserved Ejection Fraction Heart Failure Patients: Systematic Review & Meta-Analysis, J. Appl. Physiol. (2015) (jap. 00904.02014).
[5] M.J. Haykowsky, Y. Liang, D. Pechter, L.W. Jones, F.A. McAlister, A.M. Clark, A meta-analysis of the effect of exercise training on left ventricular remodeling in heart failure patients: the benefit depends on the type of training performed, J. Am. Coll. Cardiol. 49 (24) (2007) 2329–2336.
[6] N.A. Smart, M. Steele, The effect of physical training on systemic proinflammatory cytokine expression in heart failure patients: a systematic review, Congest. Heart Fail. 17 (3) (2011) 110–114.
[7] N. Smart, M. Steele, Systematic review of the effect of aerobic and resistance exercise training on systemic brain natriuretic peptide (BNP) and N-terminal BNP expression in heart failure patients, Int. J. Cardiol. 140 (3) (2010) 260–265.
[8] N. Smart, T.H. Marwick, Exercise training for patients with heart failure: a systematic review of factors that improve mortality and morbidity, Am. J. Med. 116 (10) (2004) 693–706.
[9] V.M. Conraads, E.M. Van Craenenbroeck, C. De Maeyer, A.M. Van Berendoncks, P.J. Beckers, C.J. Vrints, Unraveling new mechanisms of exercise intolerance in chronic heart failure. Role of exercise training, Heart Fail. Rev. 18 (1) (2013) 65–77.
[10] M.J. Haykowsky, C.R. Tomczak, J.M. Scott, D.I. Paterson, D.W. Kitzman, Determinants of exercise intolerance in patients with heart failure and reduced or preserved ejection fraction, J. Appl. Physiol. 119 (6) (2015) 739–744.
[11] R. Hambrecht, E. Fiehn, C. Weigl, et al., Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure, Circulation 98 (24) (1998) 2709–2715.
[12] A. Linke, N. Schoene, S. Gielen, et al., Endothelial dysfunction in patients with chronic heart failure: systemic effects of lower-limb exercise training, J. Am. Coll. Cardiol. 37 (2) (2001) 392–397.
[13] B. Hornig, V. Maier, H. Drexler, Physical training improves endothelial function in patients with chronic heart failure, Circulation 93 (2) (1996) 210–214.
[14] C.N. Marti, M. Gheorghiade, A.P. Kalogeropoulos, V.V. Georgiopoulou, A.A. Quyyumi, J. Butler, Endothelial dysfunction, arterial stiffness, and heart failure, J. Am. Coll. Cardiol. 60 (16) (2012) 1455–1469.
[15] M. Shechter, S. Matetzky, M. Arad, M.S. Feinberg, D. Freimark, Vascular endothelial function predicts mortality risk in patients with advanced ischaemic chronic heart failure†, Eur. J. Heart Fail. 11 (6) (2009) 588–593.
[16] A.J. Flammer, T. Anderson, D.S. Celermajer, et al., The assessment of endothelial function from research into clinical practice, Circulation 126 (6) (2012) 753–767.
[17] A. Greyling, A.C. van Mil, P.L. Zock, D.J. Green, L. Ghiadoni, D.H. Thijssen, Adherence to guidelines strongly improves reproducibility of brachial artery flow-mediated dilation, Atherosclerosis 248 (2016) 196–202.
[18] B. Meyer, D. Mörtl, K. Strecker, et al., Flow-mediated vasodilation predicts outcome in patients with chronic heart failure: comparison with B-type natriuretic peptide, J. Am. Coll. Cardiol. 46 (6) (2005) 1011–1018.
[19] M.C. Corretti, T.J. Anderson, E.J. Benjamin, et al., Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force, J. Am. Coll. Cardiol. 39 (2) (2002) 257–265.
[20] D.H. Thijssen, M.A. Black, K.E. Pyke, et al., Assessment of flow-mediated dilation in humans: a methodological and physiological guideline, Am. J. Phys. Heart Circ. Phys. 300 (1) (2011) H2–H12.
[21] T.J. Anderson, A. Uehata, M.D. Gerhard, et al., Close relation of endothelial function in the human coronary and peripheral circulations, J. Am. Coll. Cardiol. 26 (5) (1995) 1235–1241.
[22] A.W. Ashor, J. Lara, M. Siervo, et al., Exercise modalities and endothelial function: a systematic review and dose–response meta-analysis of randomized controlled trials, Sports Med. 45 (2) (2015) 279–296.
[23] D. Montero, G. Walther, E. Benamo, A. Perez-Martin, A. Vinet, Effects of Exercise Training on Arterial Function in Type 2 Diabetes Mellitus, Sports Med. 43 (11) (2013) 1191–1199.
[24] J.S. Ramos, L.C. Dalleck, A.E. Tjonna, K.S. Beetham, J.S. Coombes, The impact of high-intensity interval training versus moderate-intensity continuous training on vascular function: a systematic review and meta-analysis, Sports Med. 45 (5) (2015) 679–692.
[25] D.J. Green, A. Maiorana, G. O'Driscoll, R. Taylor, Effect of exercise training on endothelium-derived nitric oxide function in humans, J. Physiol. 561 (1) (2004) 1–25.
[26] R. Hambrecht, V. Adams, S. Erbs, et al., Regular physical activity improves endothelial function in patients with coronary artery disease by increasing phosphorylation of endothelial nitric oxide synthase, Circulation 107 (25) (2003) 3152–3158.
[27] A. Linke, V. Adams, P.C. Schulze, et al., Antioxidative effects of exercise training in patients with chronic heart failure increase in radical scavenger enzyme activity in skeletal muscle, Circulation 111 (14) (2005) 1763–1770.
[28] R. Recchioni, F. Marcheselli, R. Antonicelli, et al., Physical activity and progenitor cell-mediated endothelial repair in chronic heart failure: Is there a role for epigenetics? Mech. Ageing Dev. (2016).
[29] E.M. Van Craenenbroeck, V.M. Conraads, Mending injured endothelium in chronic heart failure: a new target for exercise training, Int. J. Cardiol. 166 (2) (2013) 310–314.
[30] K.M. Vuckovic, M.R. Piano, S.A. Phillips, Effects of exercise interventions on peripheral vascular endothelial vasoreactivity in patients with heart failure with reduced ejection fraction, Heart Lung Circ. 22 (5) (2013) 328–340.
[31] J. Cohen, Statistical power analysis for the behavioural sciences, Lawrence Earlbaum Associates, Hillside. NJ, 1988.
[32] J.P. Higgins, S.G. Thompson, J.J. Deeks, D.G. Altman, Measuring inconsistency in meta-analyses, BMJ 327 (7414) (2003) 557–560.
[33] M. Egger, G.D. Smith, M. Schneider, C. Minder, Bias in meta-analysis detected by a simple, graphical test, BMJ 315 (7109) (1997) 629–634.
[34] N.A. Smart, M. Waldron, H. Ismail, et al., Validation of a new tool for the assessment of study quality and reporting in exercise training studies: TESTEX, Int. J. Evid. Based Healthc. 13 (1) (2015) 9–18.
[35] N.M. Benda, J.P. Seeger, G.G. Stevens, et al., Effects of High-Intensity Interval Training versus Continuous Training on Physical Fitness, Cardiovascular Function and Quality of Life in Heart Failure Patients, PLoS One 10 (10) (2015), e0141256.
[36] R. Belardinelli, F. Lacalaprice, E. Faccenda, A. Purcaro, G. Perna, Effects of short-term moderate exercise training on sexual function in male patients with chronic stable heart failure, Int. J. Cardiol. 101 (1) (2005) 83–90.
[37] R. Belardinelli, F. Capestro, A. Misiani, P. Scipione, D. Georgiou, Moderate exercise training improves functional capacity, quality of life, and endothelium-dependent vasodilation in chronic heart failure patients with implantable cardioverter defibrillators and cardiac resynchronization therapy, Eur. J. Cardiovasc. Prev. Rehabil. 13 (5) (2006) 818–825.
[38] E. Eleuteri, A. Mezzani, A. Di Stefano, et al., Aerobic training and angiogenesis activation in patients with stable chronic heart failure: a preliminary report, Biomarkers 18 (5) (2013) 418–424.
[39] S. Erbs, R. Höllriegel, A. Linke, et al., Exercise training in patients with advanced chronic heart failure (NYHA IIIb) promotes restoration of peripheral vasomotor function, induction of endogenous regeneration, and improvement of left ventricular function, Circ. Heart Fail. 3 (4) (2010) 486–494.
[40] C. Giannattasio, F. Achilli, A. Grappiolo, et al., Radial Artery Flow-Mediated Dilatation in Heart Failure Patients Effects of Pharmacological and Nonpharmacological Treatment, Hypertension 38 (6) (2001) 1451–1455.
[41] M. Guazzi, G. Reina, G. Tumminello, M.D. Guazzi, Improvement of alveolar-capillary membrane diffusing capacity with exercise training in chronic heart failure, J. Appl. Physiol. 97 (5) (2004) 1866–1873.
[42] R. Hambrecht, L. Hilbrich, S. Erbs, et al., Correction of endothelial dysfunction in chronic heart failure: additional effects of exercise training and oral L-arginine supplementation, J. Am. Coll. Cardiol. 35 (3) (2000) 706–713.
[43] K. Isaksen, P.S. Munk, T. Valborgland, A.I. Larsen, Aerobic interval training in patients with heart failure and an implantable cardioverter defibrillator: a controlled study evaluating feasibility and effect, Eur. J. Prev. Cardiol. 22 (3) (2015) 296–303.
[44] A.I. Karavidas, K.G. Raisakis, J.T. Parissis, et al., Functional electrical stimulation improves endothelial function and reduces peripheral immune responses in patients with chronic heart failure, Eur. J. Cardiovasc. Prev. Rehabil. 13 (4) (2006) 592–597.
[45] N. Kobayashi, Y. Tsuruya, T. Iwasawa, et al., Exercise training in patients with chronic heart failure improves endothelial function predominantly in the trained extremities, Circ. J. 67 (6) (2003) 505–510.
[46] J. Parissis, A. Karavidas, D. Farmakis, et al., Efficacy and safety of functional electrical stimulation of lower limb muscles in elderly patients with chronic heart failure: A pilot study, Eur. J. Prev. Cardiol. 22 (7) (2015) 831–836.
[47] M. Sandri, M. Viehmann, V. Adams, et al., Chronic heart failure and aging–effects of exercise training on endothelial function and mechanisms of endothelial regeneration: Results from the Leipzig Exercise Intervention in Chronic heart failure and Aging (LEICA) study, Eur. J. Prev. Cardiol. (2015) (2047487315588391).
[48] E.M. Van Craenenbroeck, V.Y. Hoymans, P.J. Beckers, et al., Exercise training improves function of circulating angiogenic cells in patients with chronic heart failure, Basic Res. Cardiol. 105 (5) (2010) 665–676.
[49] U. Wisløff, A. Støylen, J.P. Loennechen, et al., Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients a randomized study, Circulation 115 (24) (2007) 3086–3094.
[50] T.-H. Luk, Y.-L. Dai, C.-W. Siu, et al., Effect of exercise training on vascular endothelial function in patients with stable coronary artery disease: a randomized controlled trial, Eur. J. Prev. Cardiol. 19 (4) (2012) 830–839.
[51] M. Vona, G. Codeluppi, T. Iannino, E. Ferrari, J. Bogousslavsky, L. Von Segesser, Effects of different types of exercise training followed by detraining on endothelium-dependent dilation in patients with recent myocardial infarction, Circulation 119 (12) (2009) 1601–1608.
[52] A. Barac, U. Campia, J.A. Panza, Methods for evaluating endothelial function in humans, Hypertension 49 (4) (2007) 748–760.
[53] M. Piepoli, Exercise training in chronic heart failure: mechanisms and therapies, Neth. Hear. J. 21 (2) (2013) 85.
[54] N.A. Smart, A.I. Larsen, J.P. Le Maitre, A.S. Ferraz, Effect of exercise training on interleukin-6, tumour necrosis factor alpha and functional capacity in heart failure, Cardiol. Res. Pract. 2011 (2011).
[55] C.V. de Sousa, M.M. Sales, T.S. Rosa, J.E. Lewis, R.V. de Andrade, H.G. Simoes, The Antioxidant Effect of Exercise: A Systematic Review and Meta-Analysis, Sports Med. 1-17 (2016).
[56] P. Sarto, E. Balducci, G. Balconi, et al., Effects of exercise training on endothelial progenitor cells in patients with chronic heart failure, J. Card. Fail. 13 (9) (2007) 701–708.

[57] K.A. Volaklis, S.P. Tokmakidis, M. Halle, Acute and chronic effects of exercise on circulating endothelial progenitor cells in healthy and diseased patients, Clin. Res. Cardiol. 102 (4) (2013) 249–257.
[58] O. Schlager, A. Giurgea, O. Schuhfried, et al., Exercise training increases endothelial progenitor cells and decreases asymmetric dimethylarginine in peripheral arterial disease: a randomized controlled trial, Atherosclerosis 217 (1) (2011) 240–248.
[59] S. Steiner, A. Niessner, S. Ziegler, et al., Endurance training increases the number of endothelial progenitor cells in patients with cardiovascular risk and coronary artery disease, Atherosclerosis 181 (2) (2005) 305–310.
[60] D.J. Green, T. Eijsvogels, Y.M. Bouts, et al., Exercise training and artery function in humans: nonresponse and its relationship to cardiovascular risk factors, J. Appl. Physiol. 117 (4) (2014) 345–352.
[61] A. Karavidas, M. Driva, J.T. Parissis, et al., Functional electrical stimulation of peripheral muscles improves endothelial function and clinical and emotional status in heart failure patients with preserved left ventricular ejection fraction, Am. Heart J. 166 (4) (2013) 760–767.
[62] D.W. Kitzman, P.H. Brubaker, D.M. Herrington, et al., Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial, J. Am. Coll. Cardiol. 62 (7) (2013) 584–592.
[63] D.W. Kitzman, M.J. Haykowsky, Vascular dysfunction in heart failure with preserved ejection fraction, J. Card. Fail. 22 (1) (2016) 12–16.
[64] M.J. Haykowsky, D.M. Herrington, P.H. Brubaker, T.M. Morgan, W.G. Hundley, D.W. Kitzman, Relationship of flow-mediated arterial dilation and exercise capacity in older patients with heart failure and preserved ejection fraction, J. Gerontol. Ser. A Biol. Med. Sci. 68 (2) (2013) 161–167.
[65] S. Maréchaux, R. Samson, E. Van Belle, et al., Vascular and microvascular endothelial function in heart failure with preserved ejection fraction, J. Card. Fail. 22 (1) (2016) 3–11.
[66] L. Ghiadoni, M. Salvetti, M.L. Muiesan, S. Taddei, Evaluation of endothelial function by flow mediated dilation: Methodological issues and clinical importance, High Blood Press. Cardiovasc. Prev. 22 (1) (2015) 17–22.

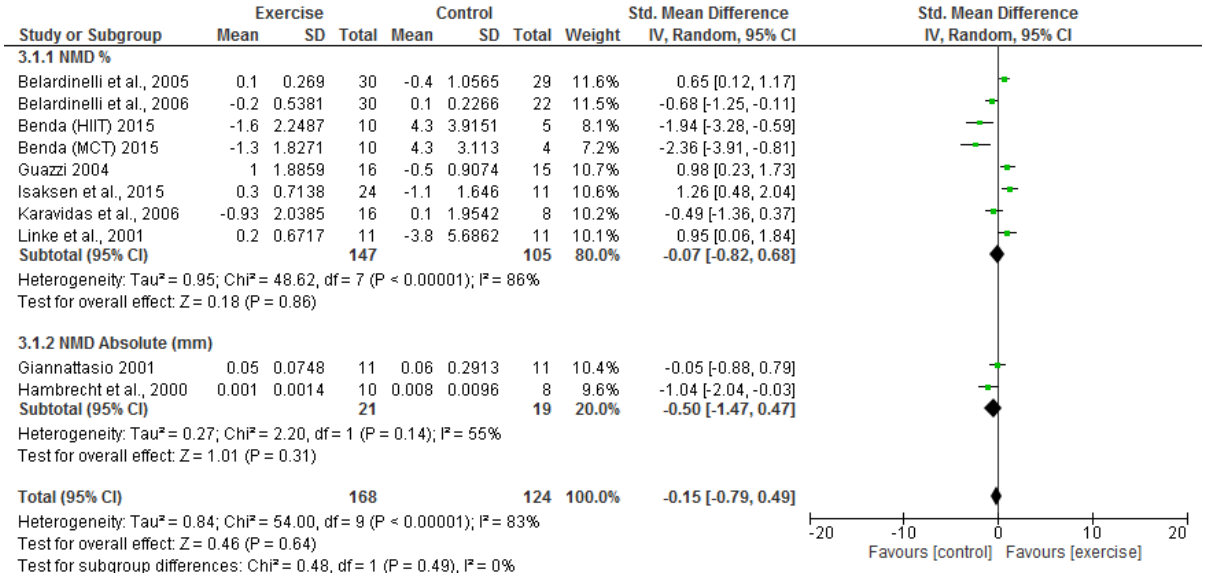
Supplementary Material Online http://dx.doi.org/10.1016/j.ijcard.2016.12.145



Supplementary Fig. S1 Change in Flow-mediated dilation in Brachial Artery - exercise vs. control



Supplementary Fig S2. Change in Flow-mediated dilation in Radial Artery - exercise vs. control



Supplementary Fig S3. Change in Endothelial Independent Dilation - exercise vs. control

Supplementary Table 1

Studies reviewed but excluded with reason

Study	Reason for Exclusion
Aksoy (2015)	No ultrasound FMD measurement, endothelial damage assessed via endothelial biomarkers (e.g., VCAM)
Anagnostakou (2011)	Comparison of Combined trained to interval training, no non-exercise control group
Angadi (2015)	No non-exercise control group
Bank (1998)	Healthy control group, no CHF control group.
Belardinelli (2008)	Possible data crossover from already included studies. Unable to confirm with Author.
Braith (2008)	Heart Transplant patients only
Dean (2011)	Single group study only, no control group
Deftereos (2010)	Comparison of FES to conventional cycling, no control group.
Katz (1997)	Single group study, and endothelial dilation assessed via venous occlusion Plethysmography
Gatta (2012)	No HF control group, single group study
Green (2003)	Pooled analysis of diverse population including CHF from Maiorana et al. 2000 study, and CHF endothelial function assessed by Plethysmography
Hambrecht (1998)	Assessment of Femoral Artery and via Intra-arterial infusion to assess endothelial dilation
Haykowsky (2009)	Post Heart Transplant Patients only
Hornig (1996)	Healthy Controls, no CHF control group
Karavidas (2013)	Participants had Preserved ejection fraction
Kitzman (2013)	Participants had Preserved ejection fraction
Laoutaris (2008)	No Ultrasound FMD, endothelial assessment via venous occlusion plethysmography
Legallois (2016)	Single group study, no Control group, no ultrasound FMD assessment. Coronary Endothelial Function assessed via (15)-O water positron emission tomography at rest and during a cold pressor test
Ozasa (2011)	Comparison of two modes or cycling, no non-exercise control group and endothelial function assessed via RH-PAT (Plethysmography technique)
Parnell (2002)	No measure of Ultrasound FMD to RH, only FBF to ACh
Laurent (2009)	No Ultrasound FMD measurement, assessment of NO metabolites only in Land vs. Water exercise.
Maiorana (2011)	No measure of FMD noted in study, only BA diameter
Maiorana (2000)	No Ultrasound FMD measure, strain-gauge Plethysmography for FBF measure
Mezzani (2013)	Same Study as Eleuteri (already include)
Miche (2006)	Two CHF groups performing same intervention (diabetic vs. non diabetic group), no non-exercise control group.
Sabelis (2004)	No Ultrasound FMD assessment, measurement of endothelial markers
Sarto (2007)	Single group study, participants acted as their own control
Smart (2012)	Comparison of Intermittent and Continuous, No non-exercise control group
Suchy (2014)	Study Protocol only
Tsarouhas (2011)	Only assessed serum markers of endothelial function as a result of exercise training, no FMD assessment
Vona (2009)	All recent post Myocardial Infarction Patients, no CHF
Vona (2004)	All recent post Myocardial Infarction Patients, no CHF

Supplementary Table 2

Additional participant characteristics

Author		Baseline VO_{2max}	BMI	SBP	DBP	Baseline FMD (% or mm)
Benda (2015)	ExT 1: HIIT	19.1±4.1	28.1±7.5	132±18	79±10	5.3±2.6%
	ExT 2: CT	21.0±3.4	28.9±4.7	132±23	83±11	5.2±2.5%
	Con	17.4±5.8	25.4±2.7	130±25	78±14	5.3±2%
Belardinelli (2006)	ExT	14.8±2.5	NR	NR	NR	~4%
	Con	14.7±2.5				~4%
Belardinelli (2005)	ExT	16.8±3.7	NR	NR	NR	2.29±1.13%
	Con	15.9±1.5				~3%
Eleuteri (2013)	ExT	14.8±0.7	NR	NR	NR	5.1±0.7%
	Con	16.7±0.4				7.7±1.4%
Erbs (2010)	ExT	15.3±3.3	26.5±2.3	111±15	73±13	6.1±2.5% (RA)
	Con	15.4±3.8	25.8±3.2	117±16	77±11	5.9±2.5% (RA)
Giannattasio (2001)	ExT	NR	NR	127±6.5	77±2.8	NR (RA)
	Con			118±5.4	76±2.3	
Guazzi (2004)	ExT	~17	26±3	133±13	83±9	4.8±0.4%
	Con	~16.3	25±2	136±16	81±11	~4.5%
Hambrecht (2000)	ExT	NR	NR	116±6	76±3	NR (RA)
	Con			118±4	74±2	
Isaksen (2015)	ExT	17.4±4.6	27.8±4.0	NR	NR	6.41±3.44%
	Con	16.9±2.8	27.3±4.2			7.15±4.5%
Karavidas (2006)	ExT	19.52±6.58	26.57±4.80	NR	NR	5.77±2.58%
	Con	18.36±4.98	28.07±3.68			5.73±2.18%
Kobayashi (2013)	ExT	18.0±1.3	NR	NR	NR	4.34±0.45%
	Con	13.7±0.9				4.19±0.45%
Linke (2001)	ExT	NR	NR	128±3	83±2	11.3±2% (RA)
	Con			123±5	78±2	11.7±1% (RA)
Parissis (2015)	ExT	NR	>25 (n=5)	NR	NR	NR
	Con		>25 (n=7)			

Sandri (2015)	ExT 1	13.3±1.6	29±2	118±3	66±2	11.3±2.5% (RA)
	Con 1	13.6±1.3	30±3	116±3	71±3	11.7±2.0% (RA)
	ExT 2	12.9±1.4	28±3	113±3	65±2	10.5±1.5% (RA)
	Con 2	13.1±1.5	28±2	113±3	66±2	11.2±1.4% (RA)
Van Craenenbroeck (2010)	ExT	18.3±1.4	27.5±0.9	107±4	69±2	5.1±0.3%
	Con	21.3±2.1	27.8±1.1	118±5	69±2	5.9±0.6%
Wisloff (2007)	ExT: AIT	13.0±1.6	24.5±3	119±9	72±10	~3.5%
	ExT: MICT	13.0±1.1	24.7±3	124±11	73±8	~3.7%
	Con	13.2±1.9	25.5±2	121±7	76±11	~3.8%
		(n=26)	(n=27)	(n=27)	(n=27)	

* Initial randomised not the analysed, AIT: aerobic interval training, BMI=body mass index, DBP=diastolic blood pressure, ExT: exercise training, Con: control, CT: continuous training, FMD: low-mediated dilation, HIIT: high intensity interval training, MICT: moderate intensity continuous training, NR= not reported, RA= radial artery, SBP=systolic blood pressure.

Supplementary Table 3

Intervention Adherence and Adverse Events

Study	Intervention Attendance	Adverse Events
Benda (2015)	100% (missed sessions rescheduled)	1 dropout each training group due to Progression HF 1 dropout each group due to musculoskeletal complaints Nil other training related events
Belardinelli (2005)	88%	Nil Adverse Events
Belardinelli (2006)		Nil Adverse Events
Eleuteri (2013)	Non-adherence <1%	Nil Adverse Events
Erbs (2010)	~90%	1 Sudden Cardiac Death (Control)
Giannattasio (2001)		
Guazzi (2004)		Nil Adverse Events
Hambrecht (2000)		1 Death - sudden arrhythmogenic complication (Control)
Isaksen (2015)	98% (average) (n=20 100%) No patient completed <75%	No symptomatic arrhythmias during AIT 1 patient in control and 1 in training group experienced one episode of anti-tachycardia pacing (ATP), but not during or after the session I patient complained of dizziness during two AIT sessions due to hypotension 1 patient in AIT group has a non-sustained supraventricular tachycardia during initial ergospirometry test No other adverse events during intervention period
Karavidas (2006)		Nil Adverse Events
Kobayashi (2003)		Nil Adverse Events
Linke (2001)		
Parissis (2015)		Nil Adverse Events
Sandri (2015)	100%*	Nil Adverse Events*
Van Craenenbroeck (2010)		
Wisloff (2007)	AIT = 92±2% MCT =95±3%	Nil Adverse Events related to training 1 cardiac death in MCT group - unrelated to training

* Reported in Sandri M, Kozarez I, Adams V, et al. Age-related effects of exercise training on diastolic function in heart failure with reduced ejection fraction: The Leipzig Exercise Intervention in Chronic Heart Failure and Aging (LEICA) diastolic dysfunction study. Eur Heart J 2012, 33: 1758–176

Supplementary Table 4

Summary of Flow-mediated dilation (FMD) assessment via Reactive Hyperaemia (RH)

Author	Instrument	Artery	Cuff Position (upper limb)	Cuff Pressure (mmHg)	Occlusion duration (minutes)	Notes on Guidelines, measurements
Benda (2015)	Ultrasound (Terason T3000, Burlington, MA, USA) 10 MHz linear array probe	BA				According to Guidelines Thijssen at al. 2011
Belardinelli (2006)	Ultrasound (ESAOTE, Challenge, Florence, Italy) 7.5 MHz probe	BA	Wrist	240	4.5	According to Guidelines - Corretti et al.
Belardinelli (2005)	Ultrasound (ESAOTE, Challenge, Florence, Italy) 7.5 MHz probe	BA	Wrist	240	4.5	Guidelines - Corretti et al.
Erbs (2010)	Ultrasound (NIUS 02 Asulab Research laboratory, Neuchatel, Switzerland)	RA		50 above systolic	5	
Eleuteri (2013)	Ultrasound	BA	Forearm		5	Guidelines - Corretti et al.
Giannattasio (2001)	B-M mode Ultrasound (WTS, Pie Medical) 7.5 MHz	RA	Wrist	Suprasystolic	4	
Guazzi (2004)	Ultrasound 11 MHz linear array transducer	BA	Forearm	50 above systolic	5	Guidelines - BARTF (Corretti et al.)
Hambrecht (2000)	Ultrasound (NIUS 02 Asulab Research laboratory, Neuchatel, Switzerland)	RA		50 above systolic	5	
Isaksen (2015)	Ultrasound (Vivid 7 System, GE Vingmed Ultrasound, Horten, Norway) 12 MHz Doppler probe	BA				Guidelines BARTF (Corretti et al.)
Karavidas (2006)	Ultrasound (Philips HDI 5000 Sonos CT) 8 MHz linear array transducer	BA				Guidelines Corretti et al.
Kobayashi (2003)	Ultrasound (SONOS 5500, Philips Medical Systems, Best, The Netherlands) 15 MHz	BA	Forearm	200	5	
Linke (2001)	A-mode Ultrasound (NIUS-02, Asulan Research laboratories, Switzerland) 10 MHz transducer	RA		50 above systolic	5	
Parissis (2015)	Ultrasound (Philips HDI 5000 Sonos CT) 8 MHz linear array transducer	BA				FMD determined as described by Arnold et al. (1991) & Corretti et al.
Sandri (2015)	Ultrasound (NIUS-02, Asulan Research laboratories, Switzerland) 10 MHz transducer	RA		50 above systolic	5	As described in Linke et al.
Van Craenenbroeck (2010)	Ultrasound (AU5 Ultrasound System, Esaote, Biomedia, Genova, Italy) 10 MHz	BA	Forearm	200 (or 50 above systolic)	4	Guidelines - Corretti et al.
Wisloff (2007)	Ultrasound (Vivid 7 System, GE Vingmed Ultrasound, Horten, Norway) 14 MHz Doppler probe	BA	Upper Arm	250	5	Guidelines - Corretti et al.

Supplementary Table S5

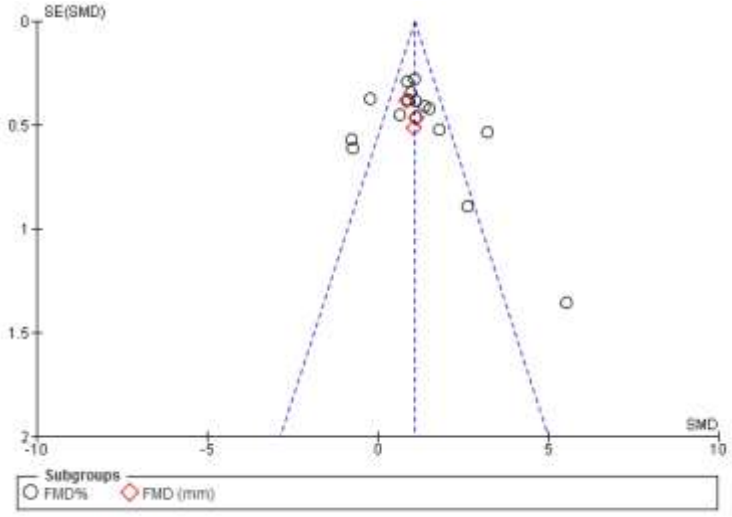
Assessment of study quality and reporting using TESTEX

Study	Eligibility Criteria specified	Randomisation	Allocation concealed	Groups similar at baseline	Assessors blinded	Outcomes measures assessed >85% participants #	Intention to treat analysis	Reporting between group statistical comparison *	Point measures & measures of variability	Activity monitoring in control group	Relative exercise intensity constant	Exercise volume & Energy expenditure	Overall TESTEX (/15)
RCTs													
Belardinelli (2006)	1	0	0	1	0	2	1	2	1	0	0	0	8
Belardinelli (2005)	1	0	0	1	0	3	1	2	1	0	0	0	9
Eleuteri (2013)	1	0	0	1	1	3	1	0	1	0	1	1	10
Erbs (2010)	1	1	1	1	1	3	0	2	1	0	0	0	11
Giannattasio (2001)	1	0	0	1	1	1	1	0	1	0	0	0	6
Guazzi (2004)	1	1	0	1	1	1	0	2	1	1	0	0	9
Hambrecht (2000)	1	0	0	1	0	2	0	2	1	0	1	0	8
Karavidas (2006)	1	0	0	1	1	2	1	2	1	0	1	0	10
Kobayashi (2003)	1	0	0	1	1	2	1	1	1	0	0	0	8
Linke (2001)	1	0	0	1	0	1	1	2	1	0	0	0	7
Parissis (2015)	1	0	0	1	0	2	1	2	1	0	1	0	9
Sandri (2015)	1	1	1	1	1	3	1	2	1	0	0	0	12
Wisloff (2007	1	1	0	1	1	3	0	2	1	0	1	0	12
Non- Randomised													
Benda (2015)	1	0	0	1	0	2	0	1	1	0	1	1	8
Isaksen (2015)	1	0	0	1	1	3	0	2	1	0	0	0	9
Van Craenenbroeck (2011)	1	0	0	1	1	1	1	2	1	0	0	0	8

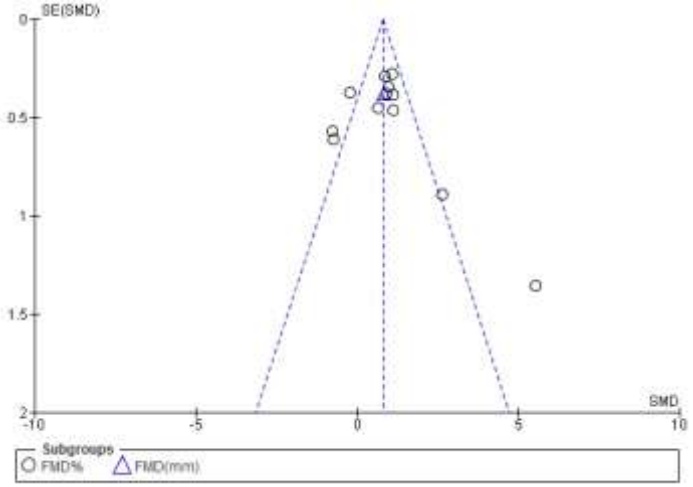
Key: total out of 15 points. Legend: #three points possible—one point if adherence >85%, one point if adverse events reported, one point if exercise attendance is reported. *Two points possible—one point if primary outcome is reported, one point if all other outcomes reported. TESTEX, Tool for the assEssment of Study qualiTy and reporting in Exercise. 0 awarded if no mention was made of this criteria or if it was unclear

Funnel Plots

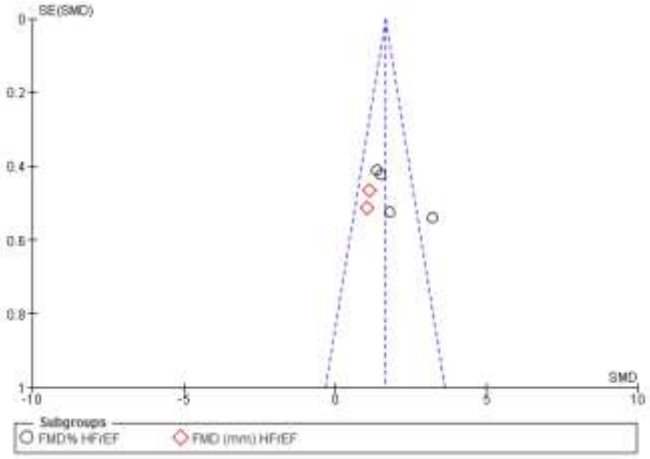
FMD – Exercise vs. Control



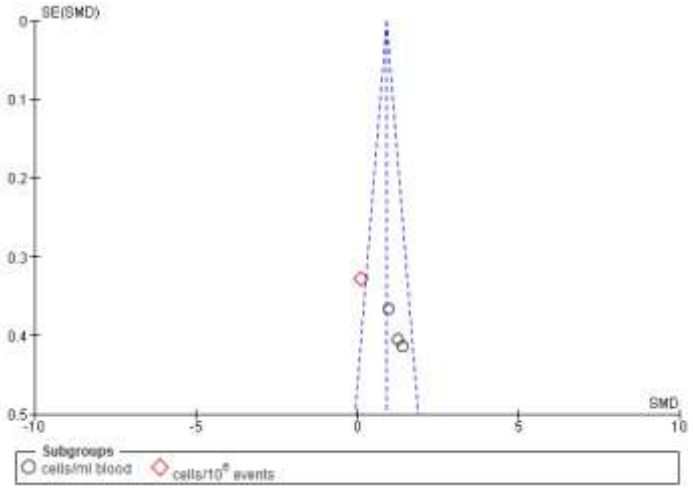
FMD Brachial Artery - Exercise vs. Control



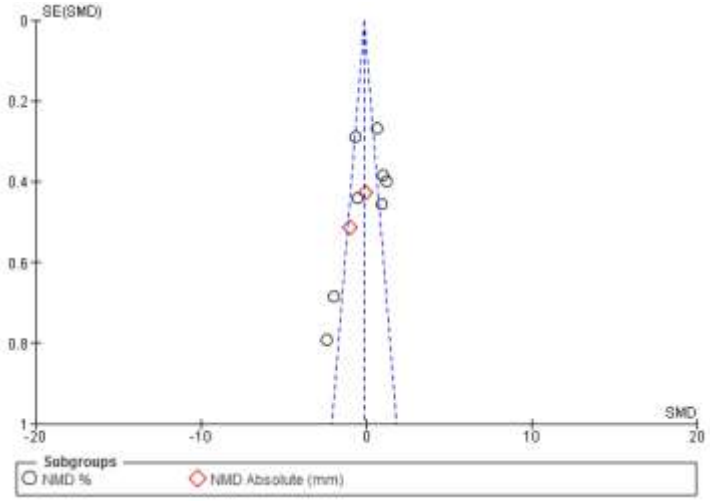
FMD Radial Artery - Exercise vs. Control



EPCs – Exercise vs. Control



NMD – Exercise vs. Control



4 Chapter 4 - Peer reviewed publication: Aerobic Training Intensity for Improved Endothelial Function in Heart Failure Patients: A Systematic Review and Meta-Analysis.

4.1 Manuscript Information

Pearson, M. J., & Smart, N. A. (2017). Aerobic Training Intensity for Improved Endothelial Function in Heart Failure Patients: A Systematic Review and Meta-Analysis. *Cardiology Research and Practice*, *2017*. Article ID 2450202. https://doi.org/10.1155/2017/2450202

Submitted 9th December 2016, Accepted 7th February 2017, Published 27th February 2017

20th June 2018

Candidate

Principal Supervisor 20th June 2018

4.2 Statement of author's contribution

Higher Degree Research Thesis by Publication
University of New England

STATEMENT OF AUTHORS' CONTRIBUTION

We, the PhD candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated in the *Statement of Originality*.

	Author's Name (please print clearly)	**% of contribution**
Candidate	Melissa Pearson	80%
Other Authors	Neil Smart	20%

Name of Candidate: Melissa Jane Pearson

Name/title of Principal Supervisor: Professor Neil Smart

[redacted]

20th June 2018

Candidate Date

[redacted]

20th June 2018

Principal Supervisor Date

4.3 Statement of originality

Higher Degree Research Thesis by Publication
University of New England

STATEMENT OF ORIGINALITY

We, the PhD candidate and the candidate's Principal Supervisor, certify that the following text, figures and diagrams are the candidate's original work.

Type of work	Page number(s)
Systematic Review & Meta-analysis	83-101

Name of Candidate: Melissa Jane Pearson

Name/title of Principal Supervisor: Professor Neil Smart

Candidate

20th June 2018

Date

Principal Supervisor

20th June 2018

Date

4.4 Full manuscript as published

Hindawi
Cardiology Research and Practice
Volume 2017, Article ID 2450202, 10 pages
https://doi.org/10.1155/2017/2450202

Research Article

Aerobic Training Intensity for Improved Endothelial Function in Heart Failure Patients: A Systematic Review and Meta-Analysis

M. J. Pearson and N. A. Smart

School of Science and Technology, University of New England, Armidale, NSW 2351, Australia

Correspondence should be addressed to N. A. Smart; nsmart2@une.edu.au

Received 9 December 2016; Accepted 7 February 2017; Published 27 February 2017

Academic Editor: Stephan von Haehling

Objective. Flow-mediated dilation (FMD) is widely utilised to assess endothelial function and aerobic exercise improves FMD in heart failure patients. The aim of this meta-analysis is to quantify the effect of aerobic training intensity on FMD in patients with heart failure. *Background*. A large number of studies now exist that examine endothelial function in patients with heart failure. We sought to add to the current literature by quantifying the effect of the aerobic training intensity on endothelial function. *Methods*. We conducted database searches (PubMed, Embase, ProQuest, and Cochrane Trials Register to June 30, 2016) for exercise based rehabilitation trials in heart failure, using search terms exercise training, endothelial function, and flow-mediated dilation (FMD). *Results*. The 13 included studies provided a total of 458 participants, 264 in intervention groups, and 194 in nonexercising control groups. Both vigorous and moderate intensity aerobic training significantly improved FMD. *Conclusion*. Overall both vigorous and moderate aerobic exercise training improved FMD in patients with heart failure.

1. Introduction

Results of numerous studies and meta-analyses have now shown that exercise training is not only safe but is associated with a range of physiological, functional, and clinical benefits in patients with heart failure (HF) [1–3]. While exercise interventions in HF patients have utilised a range of training modalities, aerobic or endurance training is the most investigated and has been shown to improve a range of parameters in HF patients [1, 4], including endothelial function [5]. Endothelial dysfunction is associated with the pathogenesis and progression of HF [6] and flow-mediated dilation (FMD), a noninvasive assessment of endothelial function, has been shown to be predictive of deterioration and death [7] in HF patients. Aerobic exercise training improves endothelial dependent vasodilation primarily by improving nitic oxide (NO) bioavailability [8].

Despite a large number of exercise training studies it was not until 2011 that a consensus document by the Heart Failure Association (HFA) and European Association for Cardiovascular Prevention and Rehabilitation (EACPR) provided a detailed and comprehensive guideline for exercise training in HF patients [9]. However, while aerobic exercise is now a feature of cardiac rehabilitation guidelines around the world, training program characteristics still vary considerably and the focus of current and emerging research is on identifying the exercise modality, dose, and intensity that will deliver optimal benefits [10–13]. While all training characteristics will likely influence results to some degree, the role of exercise intensity in cardiac rehabilitation is considered a key issue [14]. As the pattern of blood flow and amount of shear stress [8] that occur during exercise may be related to the specific training characteristics, including training intensity, ascertaining an optimal training protocol is important.

A meta-analysis in HF patients by Ismail and colleagues (2013) [12] demonstrated that as exercise intensity increases the magnitude of change in $VO_{2\,peak}$ also increases. In addition, a considerable body of evidence is mounting in relation to aerobic intermittent or interval training in clinical populations including HF patients [15, 16], and more specifically in relation to high-intensity interval training (HIIT) [15] for improving a range of physiological, functional and clinical parameters, including vascular function [5].

While exercise intensity is associated with the magnitude of change in $VO_{2\,peak}$ in HF patients [12], the relationship

between aerobic intensity and endothelial function is not clear. In healthy men, high-intensity exercise has been shown to increase oxidative stress reducing the bioavailability of NO and possibly negating the positive effect of exercise induced shear stress on endothelial function [17]. However, increases in antioxidant levels and greater improvements in FMD from HIIT compared to moderate intensity continuous training (MICT) in heart failure patients [5] suggest that intensity may have a role in the endothelial response to exercise in this population.

In a range of clinical populations both moderate [18] and high-intensity [19, 20] aerobic training have significantly improved FMD. A recent meta-analysis [21] across a diverse population reported a significant improvement in FMD from aerobic exercise and a significant dose-response relationship between intensity and FMD. In addition, Ramos and colleagues (2015) [22] examined the effects of high-intensity training, specifically HIIT compared to MICT across a diverse population, demonstrating HIIT to be more effective for improving FMD [22].

A number of aerobic exercise training studies have now investigated FMD in HF patients and therefore the primary aim of our paper was to conduct a systematic review and meta-analysis to investigate if training intensity reflects the magnitude of change in FMD.

2. Methods

2.1. Search Strategy. Potential studies were identified by conducting systematic searches of PubMed, Embase, CINAHL, SPORTDiscus, and the Cochrane Library of Controlled Trials up until 30 June 30, 2016. Searches included a mix of MeSH and free text terms related to the key concepts of heart failure, exercise training, endothelial function, and flow-mediated dilation. Additionally, systematic reviews, meta-analyses, and reference lists of papers were hand searched for additional studies. One reviewer (MJP) conducted the search; and full articles were assessed for eligibility by two reviewers (MJP and NAS). Two authors were contacted to provide additional information; one author did not respond and the second responded but was unable to provide any further details.

2.2. Study Selection. Randomised controlled trials and controlled trials of aerobic exercise training in heart failure patients with reduced ejection fractions (HFrEF) were included. Studies included in the review compare an aerobic training intervention to a no exercise or usual care control group or compared continuous aerobic training with interval or intermittent aerobic training. Only studies that measured endothelial function by flow-mediated dilation (FMD) measured via ultrasound reported as relative FMD% or absolute FMD (mm or μm) in either the brachial or radial artery were included.

2.3. Data Extraction and Outcome Measures. Data were extracted by one reviewer (MJP). The primary outcome measure was flow-mediated dilation (FMD% or FMD absolute (mm)). Where FMD was reported as FMD% and FMD (mm), FMD% was utilised in the analysis.

2.4. Data Synthesis. Statistical analyses were performed using Revman 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark). The individual meta-analyses were completed for continuous data by using the change in the mean and standard deviation (SD). The primary outcome measure was FMD%. Where the change in mean and SD were not reported, the change in mean was calculated by subtracting the preintervention mean form the postintervention mean, and Revman 5.3 enabled calculations of SD using number of participants in each group, within or between group p values or 95% CI. In cases where exact p values were not provided, we used default values; for example, $p < 0.05$ becomes $p = 0.049$, $p < 0.01$ becomes $p = 0.0099$, and $p =$ not significant becomes $p = 0.051$. Data not provided in main text or tables were extracted from figures. A random effects inverse variance was used with the effects measure of standardised mean difference (SMD). We utilised the widely accepted guideline for SMD interpretation [23], with 0.2 defined as small, 0.5 medium, and 0.8 as large. Where a study included multiple intervention groups and a control group, the sample size of the control group was divided by the number of intervention groups to eliminate over inflation of the sample size. We used a 5% level of significance and a 95% CI to report change in outcome measures. Aerobic intensity was defined and classified according to the ACSM (2011) [24]. Where prescribed intensity overlapped between two intensity classifications an additional analysis was conducted by reallocation of the studies to the alternative classification.

2.5. Heterogeneity and Publication Bias. Heterogeneity was quantified using the I^2 test [25]. Values range from 0% (homogeneity) to 100% (highly heterogeneity) [25]. Egger tests and funnel plots [26] were provided to assess risk of publication bias.

2.6. Study Quality. Study quality was assessed by using the TESTEX, the tool for assessment of study quality and reporting, designed specifically for use in exercise training studies [27]. This is a 15-point scale that assesses study quality (maximum 5 points) and reporting (maximum 10 points). Two reviewers (MJP and NAS) conducted quality assessment.

3. Results

The initial search identified 485 manuscripts. After removal of duplicates and exclusion of articles based on abstract and title, 26 full-text articles remained for screening. Full screening resulted in 13 articles meeting the stated inclusion criteria (Figure 1 PRISMA statement). The aerobic exercise intervention characteristics of the 13 studies in the meta-analysis are included in Table 1. Details of full-text articles reviewed but excluded are provided in Supplementary Table S1 in Supplementary Material available online at https://doi.org/10.1155/2017/2450202. Full participant details are provided in Supplementary Table S2.

3.1. Study Characteristics. Thirteen [5, 28–39] studies provided a total of 458 participants diagnosed with HFrEF, 264 exercising participants, and 194 nonexercising control

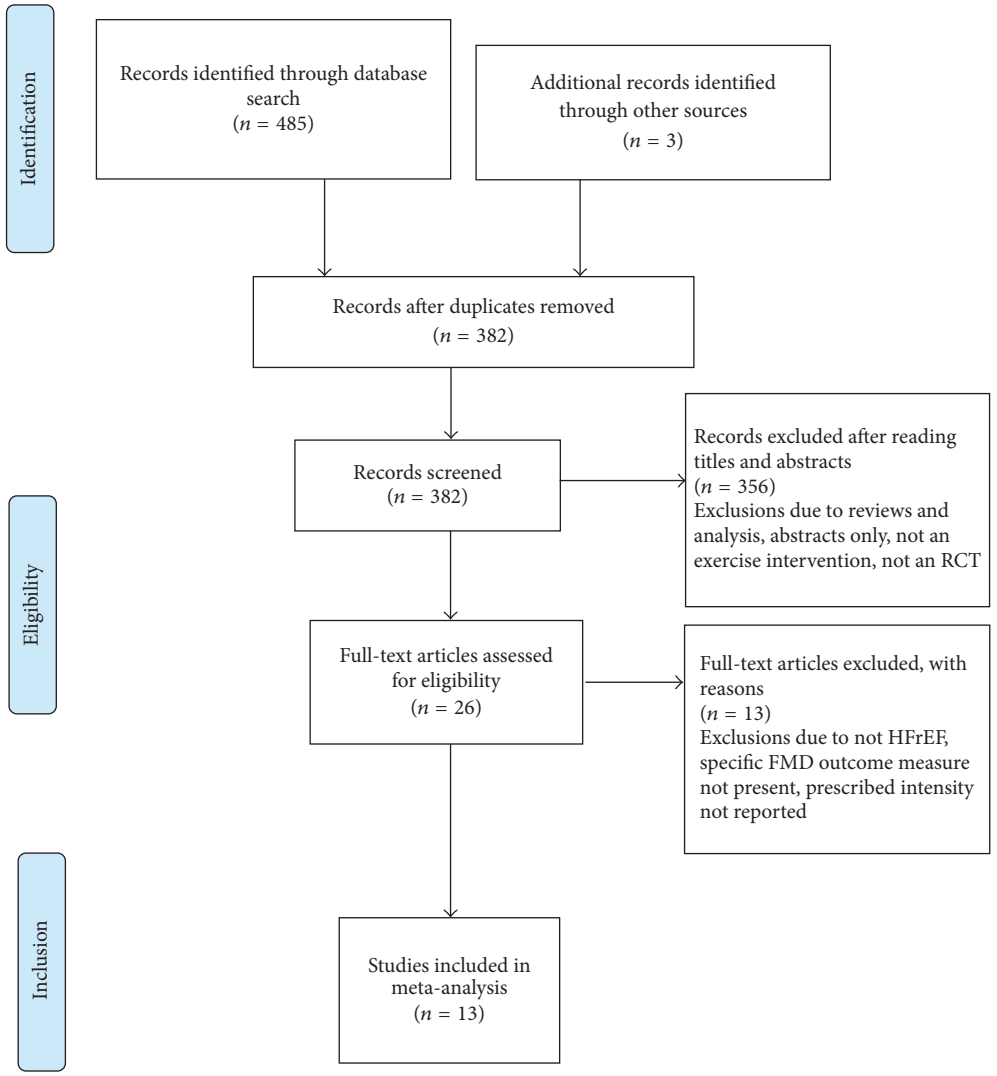


Figure 1: PRISMA flow diagram.

subjects. Twelve studies [5, 28–37, 39] included a usual care control group, of these, two studies [5, 28] included two different aerobic intervention groups. One study [38] did not include a control group and only compared intervention groups undertaking different aerobic exercise protocols. Ten studies [5, 29–33, 35–38] randomised participants, two studies were nonrandomised controlled trials [34, 39], and one study randomised participants between two exercise interventions but the control group was nonrandomised [28]. The average age of participants ranged between 49 ± 5 yrs and 76 ± 13 yrs and sex distribution was predominantly male. Brachial baseline FMD% ranged from ~3% to >7% and reported that baseline radial FMD% ranged from ~6% to >12% (Supplementary Table S2).

3.2. Intervention Details. Intervention duration ranged from 4 weeks to 6 months, the frequency of sessions ranged from 2 days per week to daily, and the duration of exercise sessions ranged from 10 to 60 minutes. All studies performed an exercise test from which training intensity was prescribed and cycling was the most common mode of aerobic exercise. For pooled analysis, aerobic training intensity was classified according to ACSM (2011) [24]. The training protocol of four studies [5, 28, 34, 38] utilised interval/intermittent training and of these, three [5, 28, 34] utilised a training intensity deemed as high-intensity interval training (HIIT). Two [28, 38] studies employed short to moderate length intervals [40] and two [5, 34] utilised long length [40] intervals classified as a 4 × 4 HIIT protocol, but with different intensities. Seven [5, 28, 31, 34, 35, 37, 38] studies reported on how intensity was monitored, but only four [5, 28, 31, 34] studies reported actual or perceived (RPE) training intensity of participants and only one [32] reported actual energy expenditure (Supplementary Table S3). Seven [5, 28, 30–32, 34, 37] studies reported session attendance percentages and 11 studies [5, 28–35, 37, 38] reported on the occurrence of any adverse events (Supplementary Table S4). The assessment of FMD varied between studies (Supplementary Table S5) and

Table 1: Aerobic exercise characteristics of studies included in meta-analysis.

Study	Study design	Sample size (completed/analysed)	Intervention duration (weeks)	Training modality	Frequency (per wk.)	Session duration	Prescribed exercise intensity
Benda et al. (2015) [28]	Non-RCT(1)	29	12	Cycle	2	35 min (HIIT) 30 min (CT) *plus* 10 min warm-up, 5 min cooldown each group	*HIIT*: 10 × 1 min @ 90% max. workload (RPE 15–17) separated by 2.5 min @ 30% max. workload *CT*: @60–75% max. workload (RPE 12–14) warm-up @ 40% max. Workload & cooldown @ 30% max. workload
Belardinelli et al. (2006) [29]	RCT	52	8	Cycle	3	40 min *plus* 15 min warm-up stretch, 5 min cooldown	60% $VO_{2\,peak}$
Belardinelli et al. (2005) [30]	RCT	59	8	Cycle	3	40 min *plus* 15 min warm-up stretch, 5 min cooldown	60% $VO_{2\,peak}$
Eleuteri et al. (2013) [31]	RCT	21	12	Cycle	5	30 min *plus* 5 min warm-up, 5 min cooldown	HR & power @ VAT (cycle @ 60 RPM) (VAT ~ 60% $VO_{2\,max}$)[1]
Erbs et al. (2010) [32]	RCT	34	12	Cycle 1 × GS*	Daily +1 GS wk.	20–30 min (*plus* 1 × 60 min GS/wk.)	HR @ 60% $VO_{2\,max}$
Guazzi et al. (2004) [33]	RCT	31	8	Cycle	4	30 min *plus* 5 min warm-up, 5 min cooldown	60% HRR wk. 1-2, ↑ 80% HRR @ wk. 3
Isaksen et al. (2015) [34]	Non-RCT	35	12	Cycle or treadmill	3	25 min *plus* 15 min warm-up, 5 min cooldown, 15 min strength/stretch	4 × 4 HIIT @ 85% HR_{max} (~RPE 15–17) separated by 3 min recovery @ 60–70% HR_{max}, warm-up @ 60–70% HR_{max}
Kobayashi et al. (2003) [35]	RCT	28	12	Cycle	2-3 (2x day)	2 × 15 min session/day (30 min/day total)	HR @ VAT (~60–70% $VO_{2\,max}$)
Linke et al. (2001) [36]	RCT	22	4	Cycle	daily (6x per day)	10 min (60 min/day total)	70% $VO_{2\,peak}$
Sandri et al. (2015) [37]	RCT	60	4	Cycle 1 × GS*	5 (4x per weekday)	15–20 min (~60 min/day total) *plus* 5 min warm-up and cooldown (*plus* 1 × 60 min GS per/wk.)	70% of symptom limited $VO_{2\,max}$
Smart and Steele (2012) [38]	RCT	23	16	Cycle	3	60 min (INT) 30 min (CONT)	*INT*: work : rest (60 s : 60 s) @ 60–70% $VO_{2\,peak}$ *CT*: 60–70% $VO_{2\,peak}$ (cycle @ 60 RPM)
Van Craenenbroeck et al. (2010) [39]	Non-RCT	38	26	Ambulatory base	3	60 min	90% HR @ respiratory compensation point
Wisløff et al. (2007) [5]	RCT	26	12	Treadmill/ home walking	3	28 min (AIT) *plus* 10 min warm-up 47 min (MICT)	*AIT*: 4 min × 4 @ 90–95% HR_{max}, separated by 3 min @ 50–70% HR_{max}, *MICT*: @ 70–75% HR_{max}

AIT: aerobic interval training, Con: control, CT: continuous training, GS: group session, HIIT: high intensity interval training, HR: heart rate, HR_{max}: maximum heart rate, HR_{peak}: peak heart rate, HRR: heart rate reserve, MIACT: moderate intensity aerobic training, MICT: moderate continuous training, non-RCT: nonrandomised controlled trial, RCT: randomised controlled trial, RPE: rating of perceived exertion, RPM: revolutions per minute, VAT: ventilatory anaerobic threshold, $VO_{2\,peak}$: peak oxygen uptake, and $VO_{2\,max}$: maximal oxygen uptake. (1)Two exercise groups randomised, but control group not randomised. [1]VO_2 @ $VT/VO_{2\,peak}$ = 8.8/14.8 = 59.5% of $VO_{2\,peak}$. *1 group session per week composed of walking, calisthenics, and ball games.

Study or subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. mean difference IV, random, 95% CI
Belardinelli et al., 2005	2.75	3.3431	30	−0.0172	1.1825	29	16.6%	1.08 [0.53, 1.63]
Belardinelli et al., 2006	2.35	3.5137	30	−0.05	0.1133	22	16.5%	0.88 [0.31, 1.46]
Benda et al. (MCT), 2015	−0.4	0.5622	10	0.1	0.8545	4	12.9%	−0.72 [−1.92, 0.48]
Eleuteri et al., 2013	1.9	2.4932	11	0.5	1.4064	10	14.8%	0.66 [−0.23, 1.54]
Erbs et al., 2010	7.43	2.28	17	0.09	2.18	17	13.8%	3.21 [2.16, 4.27]
Kobayashi et al., 2003	0.22	0.383	14	0.32	0.557	14	15.6%	−0.20 [−0.95, 0.54]
Wisløff et al. (MCT), 2007	4.61	2.06	8	−0.3	0.1901	4	9.7%	2.62 [0.87, 4.38]
Total (95% CI)			*120*			*100*	*100.0%*	*1.00 [0.19, 1.80]*

Heterogeneity: $\tau^2 = 0.94$; $\chi^2 = 38.37$, df = 6 ($p < 0.00001$); $I^2 = 84\%$
Test for overall effect: $Z = 2.42$ ($p = 0.02$)

Std. mean difference IV, random, 95% CI

−20 −10 0 10 20
Favours [control] Favours [moderate]

(a)

Study or subgroup	Moderate Mean	Moderate SD	Moderate Total	Control Mean	Control SD	Control Total	Weight	Std. mean difference IV, random, 95% CI
Belardinelli et al., 2005	2.75	3.3431	30	−0.0172	1.1825	29	19.9%	1.08 [0.53, 1.63]
Belardinelli et al., 2006	2.35	3.5137	30	−0.05	0.1133	22	19.7%	0.88 [0.31, 1.46]
Benda et al. (MCT), 2015	−0.4	0.5622	10	0.1	0.8545	4	15.2%	−0.72 [−1.92, 0.48]
Eleuteri et al., 2013	1.9	2.4932	11	0.5	1.40646	10	17.6%	0.66 [−0.23, 1.54]
Erbs et al., 2010	7.43	2.28	17	0.09	2.18	17	16.3%	3.21 [2.16, 4.27]
Wisløff et al. (MCT), 2007	4.61	2.06	8	−0.3	0.1901	4	11.3%	2.62 [0.87, 4.38]
Total (95% CI)			*106*			*86*	*100.0%*	*1.22 [0.36, 2.07]*

Heterogeneity: $\tau^2 = 0.87$; $\chi^2 = 28.67$, df = 5 ($p < 0.0001$); $I^2 = 83\%$
Test for overall effect: $Z = 2.80$ ($p = 0.005$)

Std. mean difference IV, random, 95% CI

−10 −5 0 5 10
Favours [control] Favours [moderate]

(b)

Figure 2: (a) FMD: moderate aerobic training versus control. (b) FMD: moderate aerobic training versus control (removal of Kobayashi study from moderate intensity).

10 studies [5, 28–31, 33–35, 38, 39] assessed FMD in the Brachial Artery (BA), with the Radial Artery utilised in three studies [32, 36, 37].

4. Outcome Measures

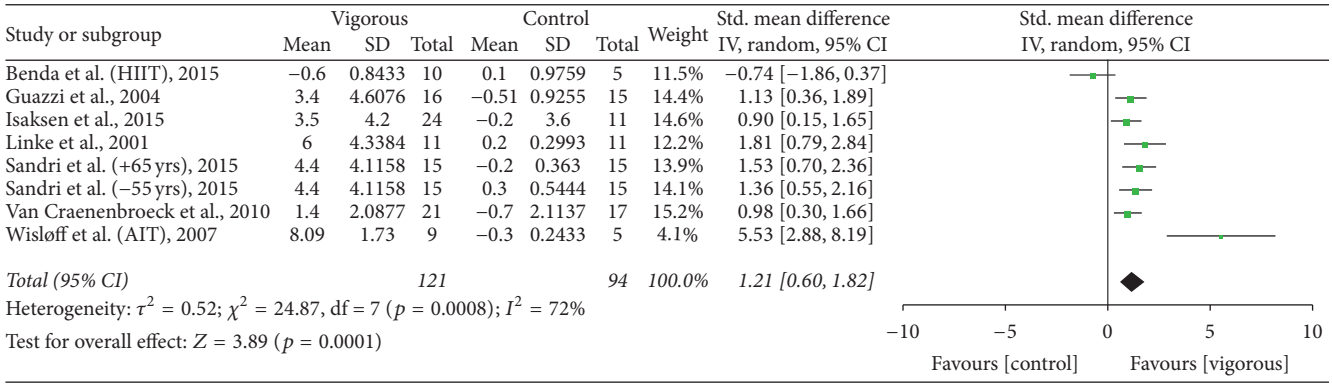
4.1. Flow-Mediated Dilation (FMD)

4.1.1. Moderate Aerobic Intensity versus Control. Pooled data from seven studies [5, 28–32, 35] that utilised moderate intensity demonstrated a significant improvement in FMD, exercise versus control, SMD of 1.00 (95% CI 0.19 to 1.80, $p = 0.02$) (Figure 2(a)). The significance level increased with removal of the one non-RCT [28], SMD of 1.24 (95% CI 0.42 to 2.06, $p = 0.003$). One [35] study prescribed an intensity range that incorporates both the moderate and vigorous intensity definition, and removal of the study resulted in an increased SMD of 1.22 (95% CI 0.36 to 2.07, $p = 0.005$) (Figure 2(b)), which increased further with removal of the one non-RCT [28] [SMD of 1.53 (95% CI 0.72 to 2.35, $p = 0.0002$)].

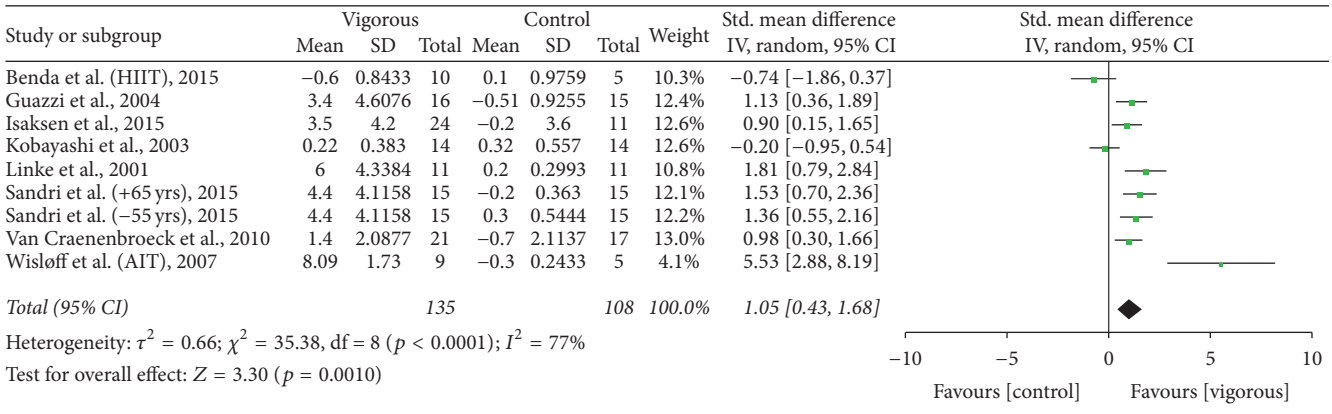
4.1.2. Vigorous Aerobic Intensity versus Control. Pooled data from seven studies [5, 28, 33, 34, 36, 37, 39] utilising vigorous intensity demonstrated a significant improvement in FMD, SMD of 1.21 (95% CI 0.60 to 1.82, $p = 0.0001$) (Figure 3(a)). Removal of the three non-RCTs [28, 34, 39] increased the significance, SMD of 1.69 (95% CI 0.97 to 2.40, $p < 0.00001$). Reclassification of the one [35] study that straddled both moderate and vigorous intensity decreased SMD to 1.05 (95% CI 0.43 to 1.68, $p = 0.001$) (Figure 3(b)); however with removal of the three non-RCTs [28, 34, 39] SMD increased to 1.43 (95% CI 0.56 to 2.30, $p = 0.001$).

4.1.3. Aerobic Interval/Intermittent versus Continuous. Pooled data from three studies [5, 28, 38] demonstrated a nonsignificant change in FMD with interval training versus control; SMD of 0.56 (95% CI −0.49 to 1.61, $p = 0.30$) (Supplementary Figure S1). With removal of the one non-RCT [28] the change in FMD increased but remained nonsignificant [SMD of 1.00 (95% CI −0.33 to 2.33, $p = 0.14$)]. One [38] study utilised a moderate intensity, with the remaining two studies [5, 28] utilising a high intensity. With removal of the one [38] moderate intensity study the result remained nonsignificant for HIIT versus continuous [SMD of 0.70 (95% CI −1.27 to 2.69, $p = 0.49$)].

4.1.4. HIIT versus Control. Pooled data from three studies [5, 28, 34] that included a HIIT and control group, indicated a trend toward improvement with HIIT in FMD; however this was not significant, SMD of 1.80 (95% CI −0.69 to 4.29, $p = 0.16$) (Supplementary Figure S2). Two [28, 34] of the three studies were however non-RCTs.



(a)



(b)

Figure 3: (a) FMD: vigorous aerobic training versus control. (b) FMD: vigorous aerobic training versus control (reallocation of Kobayashi from moderate to vigorous intensity).

4.2. Endothelial-Independent Dilation. Six [28–30, 33, 34, 36] of the included studies noted the assessment of endothelial-independent vasodilation. Five studies [28–30, 33, 34] provided relative% change in arterial diameter, while one study [36] provided both absolute and relative% change. The endothelial-independent response did not differ significantly between exercise and control, SMD of −0.02 (95% CI −0.85 to 0.82, $p = 0.97$) (Supplementary Figure S3).

4.3. Study Quality Assessment. The median TESTEX score was 9 (Supplementary Table S6). While RCTs noted participant randomisation, specific details were lacking from the majority of studies. The majority of studies lost points in the areas of allocation concealment and activity monitoring in the control group.

4.4. Heterogeneity and Publication Bias. All analyses demonstrated moderate to high heterogeneity. Funnel plots demonstrated some evidence of publication bias.

5. Discussion

This work analysed the effects of aerobic training intensity on FMD in patients with chronic heart failure. Our primary finding shows that aerobic exercise training significantly improves endothelial function, assessed via FMD, in patients with heart failure. Our pooled data failed to find a significant change in endothelial-independent vasodilation, indicating that the improvement occurred at the level of the endothelium [41]. All but two [28, 35] of the studies included in our analysis found improvements in brachial or radial artery FMD. Interestingly, while Kobayashi et al. (2003) [35] failed to find any improvement in upper limb FMD they did report a significant improvement in lower limb artery FMD (posterior tibial artery).

Training intensity is considered a key component in determining optimal outcomes in cardiac rehabilitation [14] and our analysis demonstrated that both moderate and vigorous intensity, defined according to ACSM (2011) [24], significantly improved FMD of the brachial or radial artery. However, whether or not the magnitude of improvement increased with intensity remains unclear. As only four studies reported actual training intensities, our analysis of intensity was based on the prescribed training intensity for the exercise intervention. Whether or not vigorous or moderate intensity provided greater improvements in FMD was dependent upon the allocation of one [35] study, which prescribed a training intensity range that fell within both moderate and vigorous

categories. Two analyses were therefore conducted to ascertain the effect of this study, and due to the nonsignificant finding of the study, reallocation demonstrated contrasting results. Based on the analysis we therefore cannot conclude that the magnitude of the improvement in FMD increases with intensity as was recently reported in the case of $VO_{2\,peak}$ by Ismail and colleagues [12]. Additionally, it is likely that the result would also vary depending on the actual definition or range of a particular intensity adopted, which varies between organization [24, 42], and whether or not the actual training intensities were as prescribed.

Since the impressive findings of Wisløff et al. (2007) [5] there has been an increased interest in aerobic intermittent/interval training and some guidelines [9] now advocate for this as a form of aerobic training in stable HF patients, although the actual prescribed intensity of the intervals still vary. We therefore conducted an analysis of HIIT compared to MICT. Our analysis of FMD indicated a trend toward interval or HIIT providing a greater improvement than MICT; however, the pooled results were not significant. Only the study of Wisløff et al. [5] demonstrated HIIT as significantly superior to MICT. However, only two [5, 38] of the three studies included in our analysis were RCTs and while the RCT of Smart and Steele (2012) [38] utilised interval training, the intensity of the intervals did not fall within the definition of HIIT [40]. Interval or intermittent training can be performed at any intensity; however, HIIT has been shown to invoke more significant improvements in $VO_{2\,peak}$ compared to MICT in HF patients [15, 16].

The broad definition of HIIT also means that a range of protocols are employed in both research and practice and a large number of variables can be manipulated in prescribing HIIT [43]. All three studies in our analysis of HIIT versus MICT utilised different protocols, with only Wisløff et al. (2007) [5] employing a long interval (4 × 4) protocol, which may account for some of the contrasting results between studies. Different interval/HIIT protocols may have different physiological responses and may impact the amount of shear stress [5, 22, 28]. For this reason a long HIIT protocol may be more effective [22]. Interestingly the participants in the Wisløff et al. [5] study also had lower baseline FMD% (<4%) than participants in the other two studies [28, 38] and therefore could provide a further explanation of the contrasting results, as lower baseline FMD% is one factor suggested as differentiating FMD responders from nonresponders [44]. Our nonsignificant finding is in contrast to the significant and superior improvement in FMD after HIIT compared to MICT in studies across a diverse population [22], although in CAD patients the recent SAINTEX-CAD study [45] reported significant improvements in FMD from HIIT and MICT with no difference between groups. Recently it was demonstrated in obese adults that HIIT and MICT may result in different vascular adaptations with HIIT improving FMD and MICT improving resting brachial diameter [46]. However, no studies in our review reported a significant change in resting arterial diameter after MICT. Interestingly, a recent meta-analysis that compared HIIT to MICT to investigate other clinical parameters in heart failure patients (not FMD) revealed mixed findings [13], while data from previous meta-analyses have shown HIIT more effective than MICT in improving $VO_{2\,peak}$ [12, 15].

In our pooled analysis of HIIT compared to no training, despite a trend toward HIIT, we failed to find a significant change in FMD. However, two of the three studies were non-RCTs [28, 34]. Of the three included studies, the non-RCT of Isaksen et al. (2015) [34] and RCT of Wisløff et al. (2007) [5] both reported a significant change in FMD in training groups after intervention with no change in controls, and interestingly both studies utilised a 4×4 HIIT protocol, which may be a more optimal protocol to improve vascular function [22]. Interestingly, a short duration HIIT interval (30 seconds work; 60 seconds rest) utilised by Anagnostakou et al. [47] in a comparison of HIIT to combined HIIT and resistance training failed to elicit a significant improvement in FMD in a HIIT only training group. However, FMD improved in a combined HIIT and resistance training group. Of particular interest is that, in the Isaksen et al. [34] study, while HR data was not stored for intensity analysis on any variables, they do note that, in a separate analysis on $VO_{2\,peak}$, the improvement in $VO_{2\,peak}$ was almost doubled in patients who reported an average RPE ≥ 16, and while no details are provided on FMD, one can question whether this may have occurred with FMD, indicating the role of intensity.

As there are still unanswered questions in relation to the role of endothelial dysfunction in the development and symptoms of HF patients with preserved ejection fractions [48] our analysis only included patients with reduced ejection fractions. Therefore our analysis cannot be generalised to HFpEF patients. Additionally, only minimal studies to date exist that have utilised aerobic training and investigated FMD. Kitzman and colleagues (2013) [49] failed to find any significant change in FMD following 16 weeks of high-intensity aerobic training (70% $VO_{2\,max}$), while more recently Angadi et al. (2015) [50] in a relatively small, short duration (4 weeks) study compared HIIT and MICT and failed to find a significant change in FMD in either group.

Strengths and Limitations in the Systematic Review and Meta-Analysis. To the best of our knowledge this is the first meta-analysis that provides analysis on aerobic training intensity and endothelial function in heart failure patients. The major limitation of the review is the high level of heterogeneity among studies. Differences in the methodological assessment of FMD and medication use may have contributed to the level of heterogeneity. Another limitation of the review is the classification of exercise intensity. We classified aerobic intensity according to the ACSM (2011) guidelines [24], which provides intensity ranges based on % HRR or VO_2 reserve (VO_2R), $VO_{2\,max}$, HR_{max}, RPE, or Metabolic Equivalent of Task (METS). Over the years these ranges have changed which would change the classification of studies. Additionally, intensity ranges defined by other organizations [42] differ from the ACSM [24]. As the majority of studies did not report on the actual training intensities of the sessions, whether or not the mean training intensity was firstly within the prescribed intensity range for the duration of the intervention and secondly whether the mean training intensity was closer to the upper or lower end of the prescribed ranges could

not be ascertained. We were unable to conduct an analysis according to different intensity domains and thresholds, as opposed to ranges, as suggested by Mezzani et al. (2012) [14], as the relevant information could not be extracted from all studies. In regard to data pooling, we measured the difference between preintervention and postintervention means; however, in cases where exact p values, within groups or between groups, or 95% CI were not available, default values for p were utilised and this may introduce errors. Additionally, data from some studies was extracted from figures; this in itself has the potential to introduce errors.

6. Conclusion

This meta-analysis found that both vigorous and moderate aerobic exercise training improves endothelial function, assessed by FMD, in heart failure patients with reduced ejection fractions. Future studies investigating FMD responses to different training intensities including high-intensity training protocols will further assist in providing more evidence as to optimal aerobic training intensity prescription to elicit superior improvements in endothelial function as well as other physiological and clinically relevant endpoints.

Disclosure

This work received no financial support and has no relationship to industry. The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Competing Interests

The authors report no relationships that could be construed as a conflict of interests.

References

[1] M. J. Haykowsky, Y. Liang, D. Pechter, L. W. Jones, F. A. McAlister, and A. M. Clark, "A meta-analysis of the effect of exercise training on left ventricular remodeling in heart failure patients: the benefit depends on the type of training performed," *Journal of the American College of Cardiology*, vol. 49, no. 24, pp. 2329–2336, 2007.

[2] N. A. Smart, T. Meyer, J. A. Butterfield et al., "Individual patient meta-analysis of exercise training effects on systemic brain natriuretic peptide expression in heart failure," *European Journal of Preventive Cardiology*, vol. 19, no. 3, pp. 428–435, 2012.

[3] G. Dieberg, H. Ismail, F. Giallauria, and N. A. Smart, "Clinical outcomes and cardiovascular responses to exercise training in heart failure patients with preserved ejection fraction: a systematic review and meta-analysis," *Journal of Applied Physiology*, vol. 119, no. 6, pp. 726–733, 2015.

[4] G. Cipriano Jr., V. T. F. Cipriano, V. Z. Maldaner Da Silva et al., "Aerobic exercise effect on prognostic markers for systolic heart failure patients: a systematic review and meta-analysis," *Heart Failure Reviews*, vol. 19, no. 5, pp. 655–667, 2014.

[5] U. Wisløff, A. Støylen, J. P. Loennechen et al., "Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study," *Circulation*, vol. 115, no. 24, pp. 3086–3094, 2007.

[6] C. N. Marti, M. Gheorghiade, A. P. Kalogeropoulos, V. V. Georgiopoulou, A. A. Quyyumi, and J. Butler, "Endothelial dysfunction, arterial stiffness, and heart failure," *Journal of the American College of Cardiology*, vol. 60, no. 16, pp. 1455–1469, 2012.

[7] B. Meyer, D. Mörtl, K. Strecker et al., "Flow-mediated vasodilation predicts outcome in patients with chronic heart failure: comparison with B-type natriuretic peptide," *Journal of the American College of Cardiology*, vol. 46, no. 6, pp. 1011–1018, 2005.

[8] D. J. Green, "Exercise training as vascular medicine: direct impacts on the vasculature in humans," *Exercise and Sport Sciences Reviews*, vol. 37, no. 4, pp. 196–202, 2009.

[9] M. F. Piepoli, V. Conraads, U. CorrÁ et al., "Exercise training in heart failure: From theory to practice. A consensus document of the heart failure association and the european association for cardiovascular prevention and rehabilitation," *European Journal of Heart Failure*, vol. 13, no. 4, pp. 347–357, 2011.

[10] T. Vromen, J. J. Kraal, J. Kuiper, R. F. Spee, N. Peek, and H. M. Kemps, "The influence of training characteristics on the effect of aerobic exercise training in patients with chronic heart failure: a meta-regression analysis," *International Journal of Cardiology*, vol. 208, pp. 120–127, 2016.

[11] H. Ismail, J. R. McFarlane, G. Dieberg, and N. A. Smart, "Exercise training program characteristics and magnitude of change in functional capacity of heart failure patients," *International Journal of Cardiology*, vol. 171, no. 1, pp. 62–65, 2014.

[12] H. Ismail, J. R. McFarlane, A. H. Nojoumian, G. Dieberg, and N. A. Smart, "Clinical Outcomes and cardiovascular responses to different exercise training intensities in patients with heart failure. A systematic review and meta-analysis," *JACC: Heart Failure*, vol. 1, no. 6, pp. 514–522, 2013.

[13] J. Cornelis, P. Beckers, J. Taeymans, C. Vrints, and D. Vissers, "Comparing exercise training modalities in heart failure: a systematic review and meta-analysis," *International Journal of Cardiology*, vol. 221, pp. 867–876, 2016.

[14] A. Mezzani, L. F. Hamm, A. M. Jones et al., "Aerobic exercise intensity assessment and prescription in cardiac rehabilitation: a joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation and the Canadian Association of Cardiac Rehabilitation," *European Journal of Preventive Cardiology*, vol. 20, no. 3, pp. 442–467, 2013.

[15] M. J. Haykowsky, M. P. Timmons, C. Kruger, M. McNeely, D. A. Taylor, and A. M. Clark, "Meta-analysis of aerobic interval training on exercise capacity and systolic function in patients with heart failure and reduced ejection fractions," *The American Journal of Cardiology*, vol. 111, no. 10, pp. 1466–1469, 2013.

[16] N. A. Smart, G. Dieberg, and F. Giallauria, "Intermittent versus continuous exercise training in chronic heart failure: a meta-analysis," *International Journal of Cardiology*, vol. 166, no. 2, pp. 352–358, 2013.

[17] C. Goto, Y. Higashi, M. Kimura et al., "Effect of different intensities of exercise on endothelium-dependent vasodilation in humans: role of endothelium-dependent nitric oxide and oxidative stress," *Circulation*, vol. 108, no. 5, pp. 530–535, 2003.

[18] M. Vona, G. M. Codeluppi, T. Iannino, E. Ferrari, J. Bogousslavsky, and L. K. Von Segesser, "Effects of different types of exercise training followed by detraining on endothelium-dependent dilation in patients with recent myocardial infarction," *Circulation*, vol. 119, no. 12, pp. 1601–1608, 2009.

[19] T. S. Hermann, C. H. Dall, S. B. Christensen, J. P. Goetze, E. Prescott, and F. Gustafsson, "Effect of high intensity exercise on peak oxygen uptake and endothelial function in long-term heart transplant recipients," *American Journal of Transplantation*, vol. 11, no. 3, pp. 536–541, 2011.

[20] P. S. Munk, E. M. Staal, N. Butt, K. Isaksen, and A. I. Larsen, "High-intensity interval training may reduce in-stent restenosis following percutaneous coronary intervention with stent implantation: a randomized controlled trial evaluating the relationship to endothelial function and inflammation," *American Heart Journal*, vol. 158, no. 5, pp. 734–741, 2009.

[21] A. W. Ashor, J. Lara, M. Siervo et al., "Exercise modalities and endothelial function: a systematic review and dose-response meta-analysis of randomized controlled trials," *Sports Medicine*, vol. 45, no. 2, pp. 279–296, 2015.

[22] J. S. Ramos, L. C. Dalleck, A. E. Tjonna, K. S. Beetham, and J. S. Coombes, "The impact of high-intensity interval training versus moderate-intensity continuous training on vascular function: a systematic review and meta-analysis," *Sports Medicine*, vol. 45, no. 5, pp. 679–692, 2015.

[23] J. Cohen, *Statistical Power Analysis for the Behavioral Sciences*, Lawrence Erlbaum Associates, Hillside, NJ, USA, 1988.

[24] C. E. Garber, B. Blissmer, M. R. Deschenes et al., "Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise," *Medicine and Science in Sports and Exercise*, vol. 43, no. 7, pp. 1334–1359, 2011.

[25] J. P. T. Higgins, S. G. Thompson, J. J. Deeks, and D. G. Altman, "Measuring inconsistency in meta-analyses," *British Medical Journal*, vol. 327, no. 7414, pp. 557–560, 2003.

[26] M. Egger, G. D. Smith, M. Schneider, and C. Minder, "Bias in meta-analysis detected by a simple, graphical test," *British Medical Journal*, vol. 315, no. 7109, pp. 629–634, 1997.

[27] N. A. Smart, M. Waldron, H. Ismail et al., "Validation of a new tool for the assessment of study quality and reporting in exercise training studies: TESTEX," *International Journal of Evidence-Based Healthcare*, vol. 13, no. 1, pp. 9–18, 2015.

[28] N. M. M. Benda, J. P. H. Seeger, G. G. C. F. Stevens et al., "Effects of high-intensity interval training versus continuous training on physical fitness, cardiovascular function and quality of life in heart failure patients," *PLoS ONE*, vol. 10, no. 10, Article ID e0141256, 2015.

[29] R. Belardinelli, F. Capestro, A. Misiani, P. Scipione, and D. Georgiou, "Moderate exercise training improves functional capacity, quality of life, and endothelium-dependent vasodilation in chronic heart failure patients with implantable cardioverter defibrillators and cardiac resynchronization therapy," *European Journal of Cardiovascular Prevention and Rehabilitation*, vol. 13, no. 5, pp. 818–825, 2006.

[30] R. Belardinelli, F. Lacalaprice, E. Faccenda, A. Purcaro, and G. Perna, "Effects of short-term moderate exercise training on sexual function in male patients with chronic stable heart failure," *International Journal of Cardiology*, vol. 101, no. 1, pp. 83–90, 2005.

[31] E. Eleuteri, A. Mezzani, A. Di Stefano et al., "Aerobic training and angiogenesis activation in patients with stable chronic heart failure: a preliminary report," *Biomarkers*, vol. 18, no. 5, pp. 418–424, 2013.

[32] S. Erbs, R. Höllriegel, A. Linke et al., "Exercise training in patients with advanced chronic heart failure (NYHA IIIb) promotes restoration of peripheral vasomotor function, induction of endogenous regeneration, and improvement of left ventricular function," *Circulation: Heart Failure*, vol. 3, no. 4, pp. 486–494, 2010.

[33] M. Guazzi, G. Reina, G. Tumminello, and M. D. Guazzi, "Improvement of alveolar-capillary membrane diffusing capacity with exercise training in chronic heart failure," *Journal of Applied Physiology*, vol. 97, no. 5, pp. 1866–1873, 2004.

[34] K. Isaksen, P. S. Munk, T. Valborgland, and A. I. Larsen, "Aerobic interval training in patients with heart failure and an implantable cardioverter defibrillator: a controlled study evaluating feasibility and effect," *European Journal of Preventive Cardiology*, vol. 22, no. 3, pp. 296–303, 2015.

[35] N. Kobayashi, Y. Tsuruya, T. Iwasawa et al., "Exercise training in patients with chronic heart failure improves endothelial function predominantly in the trained extremities," *Circulation Journal*, vol. 67, no. 6, pp. 505–510, 2003.

[36] A. Linke, N. Schoene, S. Gielen et al., "Endothelial dysfunction in patients with chronic heart failure: systemic effects of lower-limb exercise training," *Journal of the American College of Cardiology*, vol. 37, no. 2, pp. 392–397, 2001.

[37] M. Sandri, M. Viehmann, V. Adams et al., "Chronic heart failure and aging—effects of exercise training on endothelial function and mechanisms of endothelial regeneration: results from the Leipzig Exercise Intervention in Chronic heart failure and Aging (LEICA) study," *European Journal of Preventive Cardiology*, vol. 23, no. 4, pp. 349–358, 2016.

[38] N. A. Smart and M. Steele, "A Comparison of 16 weeks of continuous vs intermittent exercise training in chronic heart failure patients," *Congestive Heart Failure*, vol. 18, no. 4, pp. 205–211, 2012.

[39] E. M. Van Craenenbroeck, V. Y. Hoymans, P. J. Beckers et al., "Exercise training improves function of circulating angiogenic cells in patients with chronic heart failure," *Basic Research in Cardiology*, vol. 105, no. 5, pp. 665–676, 2010.

[40] T. Guiraud, A. Nigam, V. Gremeaux, P. Meyer, M. Juneau, and L. Bosquet, "High-intensity interval training in cardiac rehabilitation," *Sports Medicine*, vol. 42, no. 7, pp. 587–605, 2012.

[41] A. Barac, U. Campia, and J. A. Panza, "Methods for evaluating endothelial function in humans," *Hypertension*, vol. 49, no. 4, pp. 748–760, 2007.

[42] K. Norton, L. Norton, and D. Sadgrove, "Position statement on physical activity and exercise intensity terminology," *Journal of Science and Medicine in Sport*, vol. 13, no. 5, pp. 496–502, 2010.

[43] M. Buchheit and P. B. Laursen, "High-intensity interval training, solutions to the programming puzzle: part I: cardiopulmonary emphasis," *Sports Medicine*, vol. 43, no. 5, pp. 313–338, 2013.

[44] D. J. Green, T. Eijsvogels, Y. M. Bouts et al., "Exercise training and artery function in humans: nonresponse and its relationship to cardiovascular risk factors," *Journal of Applied Physiology*, vol. 117, no. 4, pp. 345–352, 2014.

[45] V. M. Conraads, N. Pattyn, C. De Maeyer et al., "Aerobic interval training and continuous training equally improve aerobic exercise capacity in patients with coronary artery disease: The SAINTEX-CAD Study," *International Journal of Cardiology*, vol. 179, pp. 203–210, 2015.

[46] B. J. Sawyer, W. J. Tucker, D. M. Bhammar, J. R. Ryder, K. L. Sweazea, and G. A. Gaesser, "Effects of high-intensity interval training and moderate-intensity continuous training on endothelial function and cardiometabolic risk markers in obese adults," *Journal of Applied Physiology*, vol. 121, no. 1, pp. 279–288, 2016.

[47] V. Anagnostakou, K. Chatzimichail, S. Dimopoulos et al., "Effects of interval cycle training with or without strength training on vascular reactivity in heart failure patients," *Journal of Cardiac Failure*, vol. 17, no. 7, pp. 585–591, 2011.

[48] D. W. Kitzman and M. J. Haykowsky, "Vascular dysfunction in heart failure with preserved ejection fraction," *Journal of Cardiac Failure*, vol. 22, no. 1, pp. 12–16, 2016.

[49] D. W. Kitzman, P. H. Brubaker, D. M. Herrington et al., "Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial," *Journal of the American College of Cardiology*, vol. 62, no. 7, pp. 584–592, 2013.

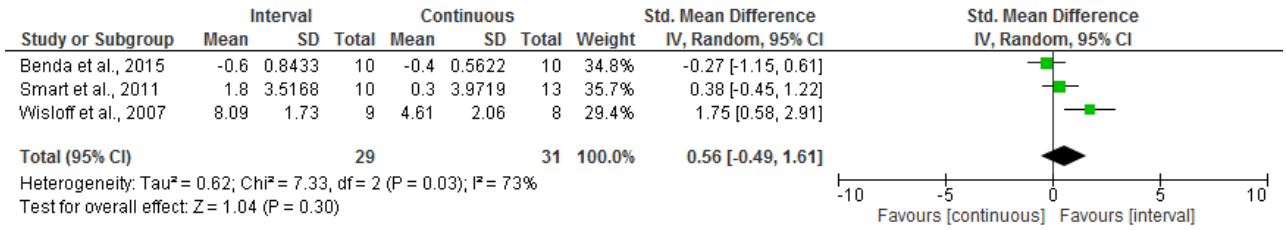
[50] S. S. Angadi, F. Mookadam, C. D. Lee, W. J. Tucker, M. J. Haykowsky, and G. A. Gaesser, "High-intensity interval training vs. moderate-intensity continuous exercise training in heart failure with preserved ejection fraction: a pilot study," *Journal of Applied Physiology*, vol. 119, no. 6, pp. 753–758, 2015.

Supplementary Material

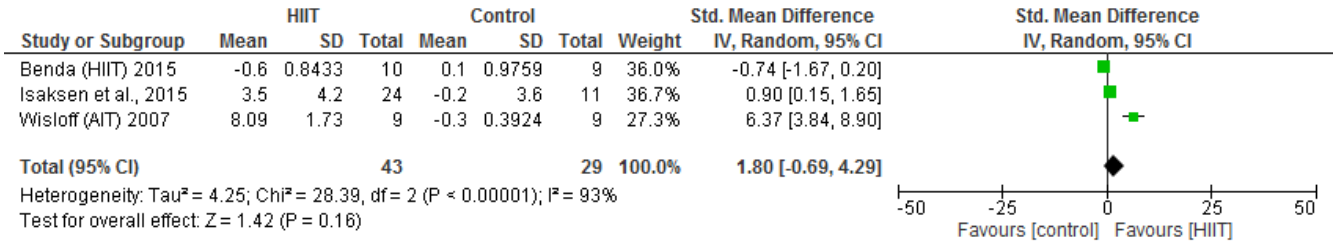
Online supplementary material contains supplementary figures S1, S2 and S3 as referred to in section 4.1.3, 4.1.4 and 4.2 of the review. Supplementary material also contains details of excluded studies, additional participant and intervention characteristics and a table of assessment of study quality.

Supplementary Data File – Figures and Tables

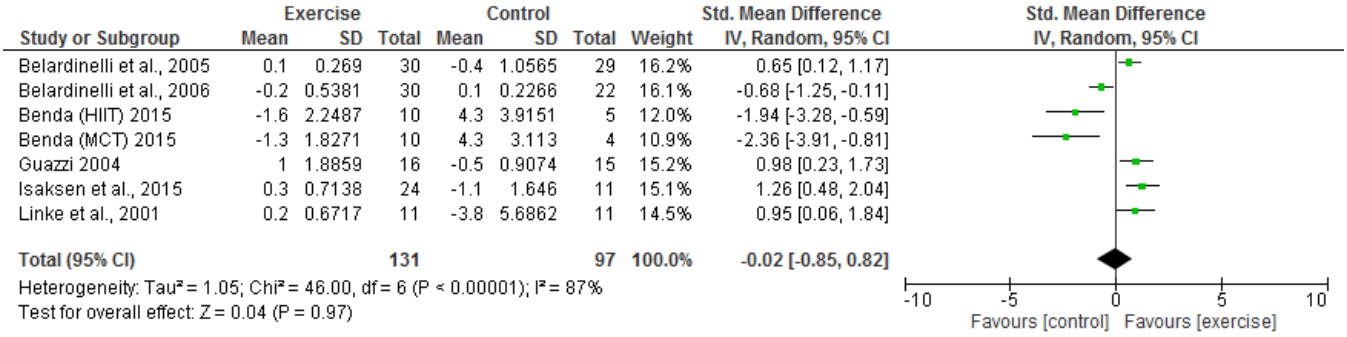
Supplementary Fig. S1 FMD Interval vs. continuous



Supplementary Fig. S2 FMD HIIT vs. control



Supplementary Fig. S3 NMD Aerobic vs. Control



Supplementary Table S1. Studies reviewed but excluded with reason

Study	Reason for Exclusion
Aksoy (2015)	No ultrasound FMD measurement, endothelial damage assessed via endothelial biomarkers (e.g., VCAM)
Anagnostakou (2011)	Comparison of Combined trained to interval training, no non-exercise control group
Angadi (2015)	Heart Failure preserved ejection fraction patients
Belardinelli (2008)	Possible data crossover from already included studies. Unable to confirm with Author.
Deftereos (2010)	Comparison of FES to conventional cycling, no control group.
Giannattasio (2001)	No details of prescribed exercise intensity
Hambrecht (1998)	Assessment of Femoral Artery and via Intra-arterial infusion to assess endothelial dilation
Kitzman (2013)	Heart Failure preserved ejection fraction patients
Ozasa (2011)	Endothelial function assessed via RH-PAT (Plethysmography technique)
Parnell (2002)	No measure of Ultrasound FMD to RH, only FBF to ACh
Laurent (2009)	No FMD measurement, assessment of NO metabolites only in Land vs. Water exercise.
Maiorana (2011)	No measure of FMD noted in study, only BA diameter
Mezzani (2013)	Same Study as Eleuteri (already include)

Supplementary Table S2. Additional participant characteristics

Author	Group	*n=*	Age (yrs.)	% Male	LVEF%	Baseline VO_{2max}	*Baseline FMD%*	Aetiology	*NYHA Class*
Benda (2015)	Ex 1: HIIT	10	63±8	90%	37±6	19.1±4.1	5.3±2.6%	Ischemic & non-ischemic	II & III
	Ex 2: MICT	10	64±8	100%	38±6	21.0±3.4	5.2±2.5%		
	C	9	67±7	56%	40±11	17.4±5.8	5.3±2%		
Belardinelli (2006)	Ex	30	55±14	100%	30±7	14.8±2.5	~4%	Previous MI, stenting & CABG	II & III
	C	22	53±15	100%	34±8	14.7±2.5	~4%		
Belardinelli (2005)	Ex	30	56±15	100%	39±6	16.8±3.7	2.29±1.13%	Ischemic & idiopathic	II & III
	C	29	58±15	100%	28±5	15.9±1.5	~3%		
Eleuteri (2013)	Ex	11	66±2	100%	28±2	14.8±0.7	5.1±0.7%	Ischemic & idiopathic CM	II
	C	10	63±2	100%	30±2	16.7±0.4	7.7±1.4%		
Erbs (2010)	Ex	17	60±11	100%	24±5	15.3±3.3	6.1±2.5% (RA)	Ischemic & DCM	III(b)
	C	17	62±10	100%	25±4	15.4±3.8	5.9±2.5% (RA)		
Guazzi (2004)	Ex	16	52±5	100%	34±3	~17.0	4.8±0.4%	Ischemic & DCM	II & III
	C	15	54±4	100%	36±4	~16.3	~4.5%		
Isaksen (2015)	Ex	24	65±9	88%	38±11	17.4±4.6	6.41±3.44%	Ischemic & DCM	I, II & III
	C	11	69±9	100%	30±8	16.9±2.8	7.15±4.5%		
Kobayashi (2013)	Ex	14	55±2	86%	29±2	18.0±1.3	4.34±0.45%	Ischemic & DCM	II & III
	C	14	62±2	57%	33±2	13.7±0.9	4.19±0.45%		
Linke (2001)	Ex	11	58±2	100%	26±3	NR	11.3±2% (RA)	Ischemic & DCM	II & III
	C	11	59±3	100%	24±2		11.7±1% (RA)		
Sandri (2015)	Ex 1 (<55yrs)	15	50±5	80%	27±6	13.3±1.6	11.3±2.5% (RA)	Ischemic & DCM	II & III
	C 1 (<55yrs)	15	49±5	87%	28±5	13.6±1.3	11.7±2.0% (RA)		
	Ex 2 (>65yrs)	15	72±4	80%	29±6	12.9±1.4	10.5±1.5% (RA)		
	C 2 (>65yrs)	15	72±3	80%	28±6	13.1±1.5	11.2±1.4% (RA)		
Smart (2012)	Ex 1: INT	10	59±11	80%	27±8	12.6±6.5	7.4±5.5%		II & III
	Ex 2: MICT	13	63±9	100%	30±8	12.4±2.5	8.0±5.2%		
Van Craenenbroeck (2010)	Ex	21	61±2	86%	27±2	18.3±1.4	5.1±0.3%	Ischemic & DCM	II
	C	17	63±3	71%	31±2	21.3±2.1	5.9±0.6%		
Wisloff (2007)	Ex: AIT	9	77±9	78%	28±7	13.0±1.6	~3.5%	Ischemic post infarct on β-blockers	
	Ex: MICT	8	74±12	78%	33±5	13.0±1.1	~3.7%		
	C	9	76±13	67%	26±8	13.2±1.9	~3.8%		

AIT: aerobic interval training, DCM: dilated cardiomyopathy, CABG: coronary artery bypass graft, Ex: exercise training, C: control, CT: continuous training, FMD: flow-mediated dilation, HIIT: high intensity interval training, INT: intermittent training, LVEF: left ventricular ejection fraction, MI: myocardial infarction, MICT: moderate intensity continuous training, NR: not reported, NYHA: New York Heart Association, RA: radial artery

Supplementary Table S3. Intensity Characteristics of Included Studies

Study	Intensity Prescribed	Monitoring of Intensity	Actual Training Intensity Reported	Energy Expenditure recorded or calculated
Belardinelli (2005)	60% VO_{2peak}	Not Reported	Not Reported	Not Reported
Belardinelli (2005)	60% VO_{2peak}	Not Reported	Not Reported	Not Reported
Benda (2015)	MICT – 60-75% max workload (RPE 12-14) HIIT – 90% max workload (RPE 15-17)	Intensity monitored using RPE - 12-14 for MICT - 15-17 for HIIT	MICT: - Actual WL 66±5% of max WL - Actual HR 81±7% HR_{max} - Reported RPE 13±1 HIIT: - Actual WL 102±7% of max WL - Actual HR 83±9% HR_{max} - Reported RPE 14±1	Not Reported
Eleuteri (2013)	HR @ VT (mean VT~60% VO_{2peak})[1]	Intensity monitored using portable electrocardiograph CPET repeated after 6 weeks to adjust training intensity.	Actual Heart rate achieved = 102±4% of prescribed	Not Reported
Erbs (2010)	HR @ 60% VO_{2max}	Not Reported	Not Reported	650kCal/week
Guazzi (2004)	60-80% HRR	Not Reported	Not Reported	Not Reported
Isaksen (2015)	85% HR_{max} (RPE 15-17)	Intensity monitored using HR monitors	HR data not stored for intensity analysis Mean RPE 15.3±1.4 (50% patients RPE ≥16)	Not Reported
Kobayashi (2003)	HR @ VT (60-70% VO_{2max}) (mean VT~67%VO_{2max})[2]	Intensity monitored using telemetry to monitor HR. Exercise speed was adjusted in each to maintain the HR equivalent to the VT. RPE used when difficult to assess HR- exercise speed regulated within the rating of 13 RPE	Not Reported	Not Reported
Linke (2001)	70% VO_{2peak}	Not Reported	Not Reported	Not Reported
Sandri (2015)	70% $VO_{2max\ (Symptom\ limited)}$	Workloads were adjusted to a HR so that 70% of the symptom-limited VO_{2max} was reached No adjustment to intensity as was a 4 week training period.	Not Reported	Not Reported
Smart (2012)	60-70% VO_{2peak}	Exercise intensity was uptitrated by 2 to5 W⁄ week. In patients in paced rhythm or experiencing	Not Reported	Not Reported

		frequent ectopy RPE was used with a target RPE of 3 to 5 (moderate to hard) on the modified Borg scale.		
Van Craenenbroeck (2010)	90% HR @ RCP	Not Reported	Not Reported	Not Reported
Wisloff (2007)	AIT - 90-95% HR_{max} MICT - 70-85% HR_{max}	Intensity monitored using HR monitor and RPE during and after sessions. Speed and incline of the treadmill adjusted to ensure training carried out at the assigned HR.	Intensity recorded as km/hr on treadmill, inclination and RPE: - AIT= RPE 17±1 & MICT =RPE 12±1	Not Reported

1. $\dot{V}O_2$ @ VT/VO_{2peak} = 8.8/14.8 =59.5% of VO_{2peak}, 2. VO_2 @ VT/VO_{2peak} = 12.0/18.0 = 66.7% of VO_{2peak}, AIT: Aerobic interval training CPET: cardiopulmonary exercise test, HIIT: high intensity interval training, HR: heart rate, HRR: heart rate reserve, HR_{max}: maximum heart rate, INT: intermittent training, MICT: moderate-intensity continuous training, RCP: respiratory compensation threshold, RPE: ratings of perceived exertion, VO_{2peak}: peak oxygen uptake, VT: ventilatory threshold, WL: workload

Supplementary Table S4. Intervention Adherence and Adverse Events

Study	Intervention Attendance	Adverse Events
Benda (2015)	100% (missed sessions rescheduled)	1 dropout each training group due to Progression HF 1 dropout each group due to musculoskeletal complaints Nil other training related events
Belardinelli (2005)	88%	Nil Adverse Events
Belardinelli (2006)		Nil Adverse Events
Eleuteri (2013)	Non-adherence <1%	Nil Adverse Events
Erbs (2010)	~90% compliance	1 Sudden Cardiac Death (Control)
Guazzi (2004)		Nil Adverse Events
Isaksen (2015)	98% (average) (n=20 100%) No patient completed <75%	No symptomatic arrhythmias during AIT 1 patient in control and 1 in training group experienced one episode of anti-tachycardia pacing (ATP), but not during or after the session I patient complained of dizziness during two AIT sessions due to hypotension 1 patient in AIT group has a non-sustained supraventricular tachycardia during initial ergospirometry test No other adverse events during intervention period
Kobayashi (2003)		Nil Adverse Events
Linke (2001)		
Sandri (2015)	100%*	Nil Adverse Events*
Smart (2012)	NR – Good adherence noted	Nil Adverse Event
Van Craenenbroeck (2010)		
Wisloff (2007)	AIT = 92±2% MCT =95±3%	Nil Adverse Events related to training 1 cardiac death in MCT group - unrelated to training

* Reported in Sandri M, Kozarez I, Adams V, et al. Age-related effects of exercise training on diastolic function in heart failure with reduced ejection fraction: The Leipzig Exercise Intervention in Chronic Heart Failure and Aging (LEICA) diastolic dysfunction study. Eur Heart J 2012, 33: 1758–176

Supplementary Table S5. Summary of Flow-mediated dilation (FMD) assessment via Reactive Hyperaemia (RH)

Author	Artery	Cuff Position (upper limb)	Cuff Pressure (mmHg)	Occlusion duration (minutes)	Notes on Guidelines, measurements
Belardinelli (2006)	BA	Wrist	240	4.5	According to Guidelines (Corretti 2002)
Belardinelli (2005)	BA	Wrist	240	4.5	According to Guidelines (Corretti 2002)
Benda (2015)	BA				According to Guidelines (Thijssen 2011)
Erbs (2010)	RA		50 above systolic	5	
Eleuteri (2013)	BA	Forearm		5	According to Guidelines (Corretti 2002)
Guazzi (2004)	BA	Forearm	50 above systolic	5	Guidelines - BARTF (Corretti 2002)
Isaksen (2015)	BA				Guidelines BARTF (Corretti 2002)
Kobayashi (2003)	BA	Forearm	200	5	
Linke (2001)	RA		50 above systolic	5	
Sandri (2015)	RA		50 above systolic	5	As described in Linke (2001)
Smart (2012)	BA	Forearm	250	4.5	
Van Craenenbroeck (2010)	BA	Forearm	200 (or 50 above systolic)	4	According to Guidelines (Corretti 2002)
Wisloff (2007)	BA	Upper Arm	250	5	According to Guidelines (Corretti 2002)

Supplementary Table S6. Assessment of study quality and reporting using TESTEX

Study	Eligibility Criteria specified	Randomisation Details Specified	Allocation concealed	Groups similar at baseline	Assessors blinded	Outcomes measures assessed >85% participants #	Intention to treat analysis	Reporting between group statistical comparison *	Point measures & measures of variability	Activity monitoring in control group	Relative exercise intensity constant	Exercise volume & Energy expenditure	Overall TESTEX (/15)
RCTs													
Belardinelli (2006)	1	0	0	1	0	2	1	2	1	0	0	0	8
Belardinelli (2005)	1	0	0	1	0	3	1	2	1	0	0	0	9
Eleuteri (2013)	1	0	0	1	1	3	1	0	1	0	1	1	10
Erbs (2010)	1	1	1	1	1	3	0	2	1	0	0	0	11
Guazzi (2004)	1	1	0	1	1	1	0	2	1	1	0	0	9
Kobayashi (2003)	1	0	0	1	1	2	1	1	1	0	0	0	8
Linke (2001)	1	0	0	1	0	1	1	2	1	0	0	0	7
Sandri (2015)	1	1	1	1	1	3	1	2	1	0	0	0	12
Smart (2012)	1	0	0	1	0	2	1	2	1	0	1	0	9
Wisloff (2007	1	1	0	1	1	3	0	2	1	0	1	0	12
Non- Randomised													
Benda (2015)	1	0	0	1	0	2	0	1	1	0	1	1	8
Isaksen (2015)	1	0	0	1	1	3	0	2	1	0	0	0	9
Van Craenenbroeck (2010)	1	0	0	1	1	1	1	2	1	0	0	0	8

Key: total out of 15 points. Legend: #three points possible—one point if adherence >85%, one point if adverse events reported, one point if exercise attendance is reported. *Two points possible—one point if primary outcome is reported, one point if all other outcomes reported. TESTEX, Tool for the assessment of Study quality and reporting in Exercise. 0 awarded if no mention was made of this criteria or if it was unclear

5 Chapter 5 - Peer reviewed publication: Exercise therapy and autonomic function in heart failure patients: a systematic review and meta-analysis

5.1 Manuscript Information

Pearson, M. J., & Smart, N. A. (2018). Exercise therapy and autonomic function in heart failure patients: a systematic review and meta-analysis. *Heart Failure Reviews*, *23*(1), 91-108. https://doi.org/10.1007/s10741-017-9662-z

Submitted 8th September 2017, Submitted in revised form 13th November 2017, Accepted 16th November 2017, Available online 29th November 2017

20th June 2018

Candidate

Principal Supervisor 20th June 2018

5.2 Statement of author's contribution

Higher Degree Research Thesis by Publication

University of New England

STATEMENT OF AUTHORS' CONTRIBUTION

We, the PhD candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated in the *Statement of Originality*.

	Author's Name (please print clearly)	**% of contribution**
Candidate	Melissa Pearson	80%
Other Authors	Neil Smart	20%

Name of Candidate: Melissa Jane Pearson

Name/title of Principal Supervisor: Professor Neil Smart

[redacted]

Candidate

20th June 2018
Date

[redacted]

Principal Supervisor

20th June 2018
Date

5.3 Statement of originality

Higher Degree Research Thesis by Publication

University of New England

STATEMENT OF ORIGINALITY

We, the PhD candidate and the candidate's Principal Supervisor, certify that the following text, figures and diagrams are the candidate's original work.

Type of work	Page number(s)
Systematic Review & Meta-analysis	106-134

Name of Candidate: Melissa Jane Pearson

Name/title of Principal Supervisor: Professor Neil Smart

20th June 2018

Candidate Date

20th June 2018

Principal Supervisor Date

5.4 Full manuscript as published

Heart Failure Reviews (2018) 23:91–108
https://doi.org/10.1007/s10741-017-9662-z

Exercise therapy and autonomic function in heart failure patients: a systematic review and meta-analysis

M. J. Pearson[1] · N. A. Smart[1]

Published online: 29 November 2017

Abstract

A large body of evidence exists indicating that autonomic imbalance is characteristic of heart failure, with several parameters of autonomic function associated with adverse clinical outcomes. The aim of this systematic review and meta-analysis was to investigate the effects of exercise training on parameters of autonomic function in patients with heart failure and where possible quantify the size of the effect. We conducted database searches (PubMed, EMBASE and Cochrane Trials Register to 31 March 2017) for exercise-based rehabilitation trials in heart failure; using search terms, exercise training, autonomic function, heart rate recovery, heart rate variability and muscle sympathetic nerve activity. Pooled data indicated a statistically significant increase in heart rate recovery at 1 min (HRR_1) in exercise compared to control groups, mean difference 5.90 bpm (95%CI 5.12, 6.69; $p < 0.00001$). Pooled data also indicated that exercise training improved the short-term heart rate variability (HRV) parameters of root mean square of successive differences between normal heart beats (RMSSD (ms)) [mean difference 10.44 (95%CI 0.60, 20.28, $p = 0.04$)] and high-frequency normalised units (HF_{nu}) [mean difference 7.72 (95%CI 3.32, 12.12, $p = 0.0006$), which are predominantly reflective of parasympathetic activity. Analyses also indicated a statistically significant decrease in muscle sympathetic nerve activity (MSNA) bursts/minute (mean difference − 11.09 (95%CI − 16.18, − 6.00; $p < 0.0001$) and MSNA bursts/100 heart beats (mean difference − 15.44 (95%CI − 20.95, −9.92; $p < 0.00001$) in exercise groups compared to controls. With improvements in HRR, HRV and MSNA, exercise training appears to facilitate an improvement in parasympathetic tone and reduction in sympathetic activity.

Keywords Heart failure · Exercise · Autonomic function · Heart rate variability · Heart rate recovery · Muscle sympathetic nerve activity

Introduction

Heart failure is a complex syndrome associated with a range of cardiac and non-cardiac abnormalities and remains a leading cause of morbidity and mortality. Autonomic imbalance is a characteristic of cardiovascular disease, including heart failure, irrespective of heart failure phenotype [1–4]. This imbalance is reflected by increased sympathetic nervous system (SNS) activity and withdrawal of parasympathetic nervous system (PNS) (vagal) activity and is associated with adverse outcomes [1]. Therefore therapies, pharmacological or otherwise, which improve autonomic balance, are of interest in heart failure management. Exercise training is an adjunct therapy in heart failure with consistent benefits for a range of outcomes [5–8] including improved autonomic function [9–11].

Several methods are utilised to assess autonomic function in both research and clinical settings [1], each with advantages and limitations [3]. In heart failure patients accumulating evidence suggests that several parameters of autonomic function have prognostic significance [12–16]. Heart rate recovery (HRR) is simple and is commonly utilised to assess autonomic function. In individuals referred for exercise testing, irrespective of cardiovascular history [17], HRR has been identified as having prognostic value, and in heart failure patients, a lower HRR is associated with adverse cardiovascular events and mortality [12, 18–20]. Exercise capacity and physical activity

The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10741-017-9662-z) contains supplementary material, which is available to authorized users.

✉ M. J. Pearson
mpears23@myune.edu.au

[1] School of Science and Technology, University of New England, Armidale, NSW 2351, Australia

[21] have been linked to HRR with a faster HRR observed in trained and athletic populations [22, 23] and an abnormal HRR associated with reduced exercise capacity [24, 25]. Simply, HRR is assessed as the difference between peak heart rate and heart rate at a particular time post-exercise. Depending on the post-exercise time frame measured, HRR is taken to be reflective of parasympathetic reactivation [24, 26] or a combination of parasympathetic reactivation and sympathetic withdrawal [24].

Heart rate variability (HRV), also commonly utilised in the assessment of autonomic function, is the degree of variability in the length of intervals between heart beats, i.e. variation in successive RR intervals [27]. A depressed HRV suggests deregulation of cardiac autonomic control [28] and predicts death in heart failure patients [16, 29]. Exercise training results in improvements in HRV in healthy subjects [30], and in heart failure patients [31], including a relationship to survival [32]. HRV can be assessed in the time domain, frequency domain from spectral analysis [27], or using non-linear methods [33], providing parameters that reflect the action of the PNS and SNS at the sinus node [24]. Specific components of HRV are considered to indirectly denote the relative input of different branches of the autonomic nervous system (ANS) [27], with the high-frequency band (HF) and the root mean square of successive differences between intervals (RMSSD) both considered to be primarily reflective of vagal activity [24, 34]. However, the exact contributions of the PNS and SNS to different HRV parameters remain debatable [34, 35].

While HRR and HRV are both simple non-invasive tools, they do not directly measure autonomic activity. However, the invasive technique of microneurography directly assesses sympathetic nerve activity to muscle and peripheral nerves (MSNA) and is considered the gold standard assessment of sympathetic nerve activity [36]. While microneurography cannot be applied to internal organs [37] such as the heart, studies have shown it a reliable marker of sympathetic response in some internal organs [36]. Compared to healthy individuals, MSNA is increased in heart failure patients [38] and associated with reduced exercise capacity in this population [39] predicting mortality [15]. A growing number of published human studies of varying design have examined exercise training effects on MSNA across healthy and clinical populations [36], and accumulating evidence suggests unaltered MSNA in healthy populations and a reduction in certain at risk populations [36].

A systematic review [40] of studies up until March 2015 reported HRR and HRV parameters in heart failure patients; however, MSNA was not an included outcome and there was limited data pooling. The primary aim of our paper was to conduct a systematic review and meta-analysis to update the previous review and quantify where possible the effect of exercise training on autonomic function, assessed by both indirect (HRR and HRV) and direct (MSNA) methods, in heart failure patients.

Methods

Search strategy

Potential studies were identified by conducting systematic searches of PubMed, EMBASE and the Cochrane Library of Controlled Trials up until 31 March 2017. Searches included a mix of MeSH and free text terms related to the key concepts of heart failure, exercise training, autonomic function, heart rate recovery, heart rate variability and muscle sympathetic nerve activity. Additionally, systematic reviews, meta-analyses and reference lists of papers were hand searched for additional studies. One reviewer (MJP) conducted the search, and full articles were assessed for eligibility by two reviewers (MJP and NAS). One author was contacted and provided clarification of study information.

Study selection

Study type and participants Randomised controlled trials, quasi-randomised controlled trials and controlled trials of exercise training in adult heart failure patients were included. Only studies in which the authors' note a diagnosis of heart failure were considered for inclusion. Heart failure type (i.e. preserved, moderately reduced and reduced ejection fraction) or comorbidities were not considered as inclusion or exclusion criteria.

Intervention Exercise training was defined to allow for inclusion of a broad range of physical activities and included aerobic, resistance training, combined training (aerobic and resistance), Yoga, Pilates, Tai Chi and hydrotherapy. Additionally, the physical therapies of Functional Electrical Stimulation and Inspiratory Muscle Training were included in the definition of exercise training for the purpose of this review. To be included in the review, studies must have compared an exercise intervention to a no exercise or usual care control group and the duration of the exercise training must have been for a minimum of 4 weeks.

Outcomes Studies were included if they reported one or more of the following parameters of HRR, HRV or MSNA criteria:

1. *HRR:* Studies must have reported on HRR at 1 min (HRR_1) or HRR at 2 min (HRR_2) post-exercise. Post-recovery protocol was not considered as an inclusion or exclusion criterion.
2. *HRV:* Studies must have reported on one more of the following: time domain parameters: standard deviation between normal-normal intervals (SDNN) or the root mean square of successive differences between normal heart beats (RMSSD) and/or frequency domain

parameters: high-frequency normalised units (HF_{nu}) or absolute units [$HF(ms^2)$], low-frequency normalised units (LF_{nu}) or absolute units [$LF(ms^2)$] or ratio of LF to HF (LF/HF). Methodology for HRV assessment was not considered for inclusion or exclusion criterion. While absolute units reflect the raw data, normalised units (nu) reflect the relative portion of the selected frequency in the total power of the power spectral density.

3. *MSNA:* Studies must have measured and reported resting sympathetic nerve activity as burst incidence (bursts/100 heart beats) and/or burst frequency (bursts/min). Limb nerves utilised (i.e. upper or lower) were not considered for inclusion or exclusion criterion.

Exclusions Abstracts and non-English studies were excluded.

Data extraction

One reviewer (MJP) extracted the data. For each study, the following information was extracted: (1) author, year of publication and study design; (2) demographic and clinical characteristics (e.g., age, gender, NYHA class, ejection fraction); (3) exercise intervention characteristics (e.g., duration, modality, frequency, intensity); (4) mean, SD, SE, *p* value, main results and findings of HRR, HRV and MSNA; (5) characteristics of assessment methodology for HRR, HRV and MSNA and (6) reporting of adverse events and intervention compliance.

Data synthesis

Statistical analyses were performed using Revman 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark). Individual meta-analyses were completed for continuous data by using the change in the mean and standard deviation. Where the change in mean and SD were not reported, the change in mean was calculated by subtracting the pre-intervention mean form the post-intervention mean, and Revman 5.3 enabled calculations of SD using number of participants in each group, within- or between-group *p* values or 95% CI. In cases were exact *p* values were not provided, we used default values, e.g. $p < 0.05$ becomes $p = 0.049$, $p < 0.01$ becomes $p = 0.0099$ and $p =$ not significant becomes $p = 0.051$. Mean difference (MD) was used for all outcome measures. A random-effects inverse variance was utilised as this is a more conservative method that takes into account that study heterogeneity can vary beyond chance. We used a 5% level of significance and a 95% CI to report change in outcome measures. Where a study included multiple intervention groups and a control group, each intervention group was considered separately, and the sample size of the control group was divided by the number of intervention groups to eliminate over inflation of the sample size. If data were reported for multiple time points during the intervention, only the data at the end of the intervention were extracted as long as data were available for both the intervention and control group. Additionally, where an intervention was divided into two phases, with a supervised training phase immediately followed by a home-based phase, and data were only provided for the intervention and control group at the completion of the supervised phase, then the home-based phase was not included in the pooled data analysis. Where it was evident that a study may have contained a crossover of a number of patients with another included study, but the exact number of crossover participants could not be ascertained, we conducted two analyses to determine the effect of each of these studies on the results. Sensitivity analyses were also conducted to assess the impact of non-RCTs and also to gauge the impact of individual studies on the result where weighting and standard deviations were unusual between groups. Where two articles referred to the same study, the article with the highest number of participants was utilised in the review.

As HRV measurements from short-term recordings are obtained under resting controlled conditions in contrast to long-term recordings where patient activity cannot be controlled, the physiological information provided differs. Therefore, we conducted separate analyses of short- and long-term recordings. Where data for long-term HRV parameters were not reported for similar time periods, data were not pooled, instead a descriptive analysis is provided.

Heterogeneity and publication bias

Heterogeneity was quantified using the I^2 test [41]. Values range from 0% (homogeneity) to 100% (high heterogeneity) [41]. Visual inspection of funnel plots [42] assessed risk of publication bias.

Study quality

Study quality was assessed by using the TESTEX, the tool for assessment of study quality and reporting, designed specifically for use in exercise training studies [43]. This is a 15-point scale that assesses study quality (maximum 5 points) and reporting (maximum 10 points). Two reviewers (MJP and NAS) conducted quality assessment.

Results

The initial search generated a total of 2989 articles. After removal of duplicates and exclusion of articles based on abstract and title, 44 full-text articles remained for screening. Full screening resulted in 20 articles meeting the stated inclusion criteria (Fig. 1 PRISMA statement). The characteristics of the studies in the systematic review and meta-analysis are included in Table 1. Details of full-text articles reviewed but excluded are provided, with reasons, in Supplementary File 1.

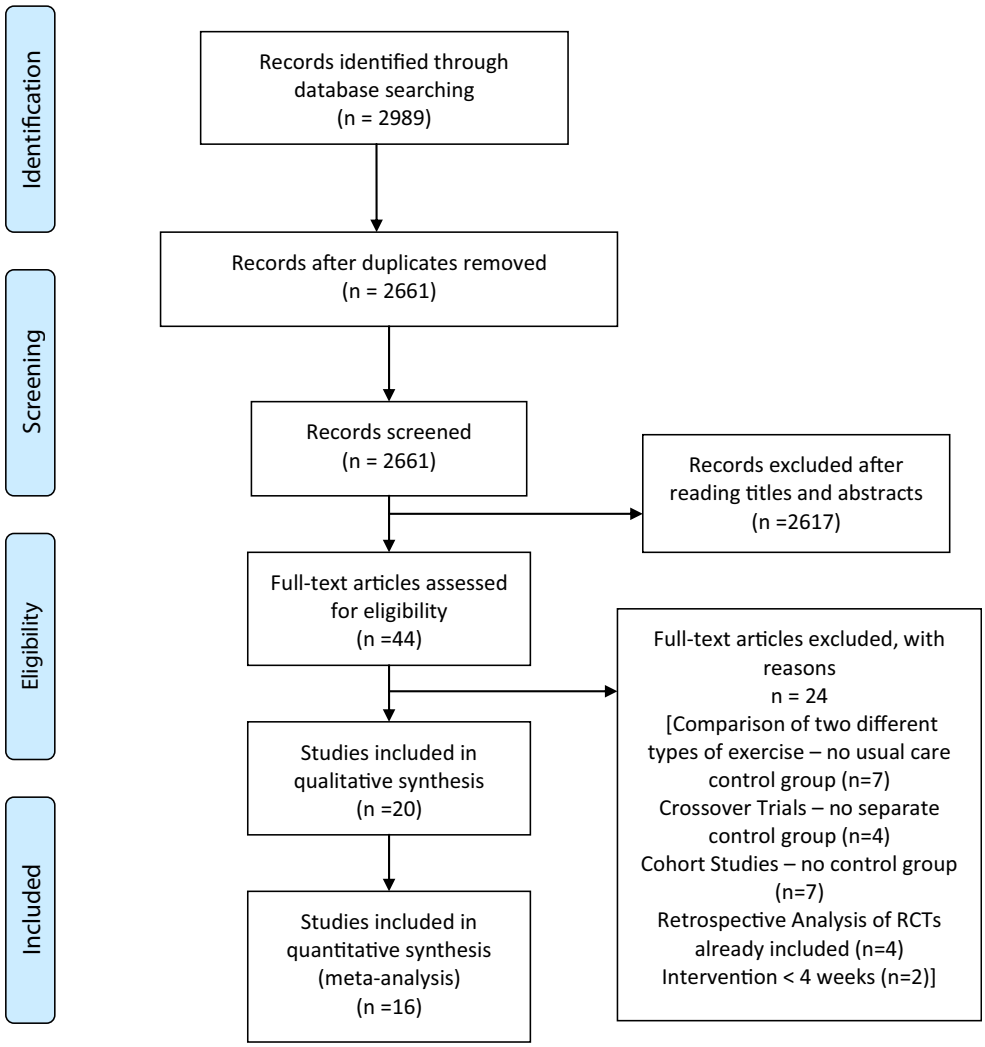


Fig. 1 PRISMA statement

Study and participant characteristics

Of the 20 studies, 17 [44–46, 48–51, 54–63] were RCTs and three [47, 52, 53] were controlled trials but not randomised. All studies contained an exercise intervention group and a non-exercise control group, with one study [48] containing two exercise intervention groups. Trial sample size varied from 16 to 92 participants. The majority of participants were men, with > 50% of male participants in all but one study [54]. The mean age of participants ranged from 49 to 70 years. In all studies except two [50, 54], participants had reduced ejection fractions. The aetiology of participants varied and NYHA class ranged from NYHA Class I–III.

Intervention details

Exercise intervention duration ranged from 8 weeks to 9 months, with the duration of two [52, 61] studies including a supervised phase followed by a home-based phase. Training frequency ranged from 2 to 7 days per week, training duration from 30 to 60 min per session and intensity ranged from light to high. Fifteen studies [44–48, 51, 52, 54–57, 60–63] predominantly utilised endurance/aerobic training; two studies [49, 58] utilised resistance training, one yoga [50], one tai chi [59] and one inspiratory muscle training [53]. The majority of training was supervised, with exercise training predominantly home-based in only three studies [47, 53, 55], with two [52, 61] additional studies including a home-based training phase in a number of participants after a supervised phase.

Autonomic function assessment

Heart Rate Recovery Five [44–48] studies measured HRR. Assessment methodology is presented in Supplementary File 1, Table S2. All five measured and reported HRR_1; two [46, 48] of the studies also reported HRR_2 and one [46] measured HRR_1 through to HRR_6. Three [44, 46, 48] studies conducted exercise testing on a braked cycle ergometers,

Table 1 Studies included in systematic review of heart rate recovery (HRR), heart rate variability (HRV) and muscle sympathetic nerve activity (MSNA)

Study	Design	Participant characteristics	Intervention characteristics	Main findings HRR, HRV and MSNA
HRR				
Fraga et al. [44]	RCT	$n = 27$ randomised and analysed E: $n = 15$ (53% men), 57 ± 3 yrs., LVEF 27 ± 2% C: $n = 12$ (75% men), 53 ± 3 yrs., LVEF 26 ± 2% All NYHA II-III, 100% Carvedilol, 81% ACEI, 19% ARBs, aetiology: Chagas, hypertension, idiopathic, CAD	4 months, endurance training 60 min (40 min aerobic, 10 min strengthening), 3× week, @ HR at ANT up to 10% < RCP (~ 60–72% VO_{2peak})	HRR_1 ↑in E
Keyhani et al. [45]	RCT	$n = 70$ randomised, $n = 65$ analysed E: $n = 33$ (67% men), 62 ± 6 years, LVEF < 35% C: $n = 32$ (53% men), 61 ± 5 years, LVEF < 35% All NYHA II, No specific details on medications. Aetiology: NR	8 weeks, aerobic training 3 times per week, 45–60 min starting @ 60–70%HR_{max} and increasing to 70–80% HR_{max} after week 4	HRR_1 ↑E
Myers et al. [46]	RCT	$n = 24$ randomised and analysed E: $n = 12$ (100% men), 56 ± 5 years, LVEF 32 ± 7% C: $n = 12$ (100% men), 55 ± 7 years, LVEF 35 ± 4% No details on β-Blocker usage, 96% ACEI (E: $n = 12$, C: $n = 11$), aetiology: MI	8 weeks, aerobic training Two outdoor walking sessions ~ 60 min per day @ individualised heart rates, plus 4 × 45 min cycling session per week @ 60–80% heart rate reserve	HRR_1 ↔ E, HRR_2 ↑ E $HRR_{2–6}$ ↑ E
Tsarouhas et al. [47]	Controlled	$n = 28$ completed and analysed E: $n = 18$ (72% men), 64 ± 12 years, LVEF 31 ± 3% C: $n = 10$ (80% men), 65 ± 9 years, LVEF 32 ± 3% All NYHA II–III, 71% β-blockers (E: $n = 13$, C: $n = 7$), 75% ACEI (E: $n = 12$, C:$n = 9$) aetiology 80% ischemic	12 weeks, aerobic training Home-based unsupervised walking, 5 days per week for 10 min @ 40% HR_{max} progressing to 40 min @ 60% HR_{max}	HRR_1 ↑ E
Yaylali et al. [48]	RCT	$n = 49$ randomised, $n = 41$ analysed E1: $n = 17$ (77% men), 64 ± 9 years, LVEF 35–45% E2: $n = 13$ (100% men), 60 ± 7 years, LVEF 35–45% C: $n = 11$ (82% men), 61 ± 10 years, LVEF 35–45% 51% β-blockers (E1: $n = 6$, E2: $n = 10$, C: $n = 5$), 34% ACE, 22% ARBs, aetiology: ischemic or non-ischemic cardiomyopathy,	12 weeks, aerobic training Three sessions per week, EI—interval training 30 min, 30s @ 50–75% HRR followed by 30-s rest. E2—continuous training for 30 min @ 50–75% heart rate reserve	HRR_1 ↔ in E1 or E2. Subanalysis of HRR_1 based on abnormal HRR @ baseline, indicated ↑ in these patients post-training. HRR_2 ↑ E1, ↔E2, Subanalysis indicated that after training, HRR_2 ↑ in those with abnormal baseline HRR_2
HRV				
Cider et al. [49]	RCT	$n = 24$ randomised, $n = 23$ analysed E: $n = 12$ (75% men), 62 ± 10 years C: $n = 12$ (58% men), 65 ± 5 years All NYHA II-III, 50% β-blockers, 46% ACEI Aetiology 95% IHD (E: $n = 10$, C: $n = 11$)	5 months, circuit weight training 2× week, 60 min @ 60%1RM	Long HRV recordings: ↔ time or frequency domain (no data provided)
Krishna et al. [50]	RCT	$n = 130$ randomised, $n = 92$ analysed E: $n = 44$ (73% men), 49 ± 6 years, LVEF 30–50% ($n = 16$PEF) C: $n = 48$ (67% men), 50 ± 5 years, LVEF 30–50% ($n = 18$PEF)	12 weeks, Yoga, 3× week, 60 min	Short HRV recordings: ↓LF_{nu}, ↑HF_{nu}, ↓LF/HF, ↔TP in E and C, *BUT* % change in LF, HF and LF/HF in E significantly different to % change in C

Table 1 (continued)

Study	Design	Participant characteristics	Intervention characteristics	Main findings HRR, HRV and MSNA
		All NYHA I–II, 78% β-blockers (E: $n = 34$, C: $n = 38$), 13% ACE/ARBs, aetiology: 49% CAD		
Kiilavuori et al. [51]	RCT	$n = 18$ randomised and analysed E: $n = 8$ (100% men), 52 ± 8 years, LVEF 24 ± 6% C: $n = 12$ (92% men), 52 ± 1 years, LVEF 24 ± 6% All NYHA II–III, 15% β-blockers ($n = 1$, 2 in E and C), 100% ACEI, aetiology: DCM & ICM	3 months, aerobic training (cycling), 3× week, 30 min @ 50–60%VO_{2peak}	Long HRV recordings: ↑HF [↑HF (day), ↔HF (night)] in E ↑LF in E and C ↔LF/HF (trend to decrease in E) ↓VLF/HF in E
Malfatto et al. [52]	Controlled	$n = 45$ allocated and analysed E: $n = 30$ (87% men), 62 ± 7 years, LVEF 29 ± 7% C: $n = 15$ (80% men), 60 ± 16 years, LVEF 31 ± 8% All NYHA II–III, 50% β-blockers (E: $n = 14$, C: $n = 8$), 100% ACEI, aetiology: ischemic and primitive	3 months (11 patients completed additional 6 months home-based), aerobic training, 3× week, 60 min @ 40–50%$VO_{2peak.}$	Short HRV recordings: @ 3 months: ↔LF/HF (free breathing @ rest), ↓LF/HF (controlled breathing), ↑LF/HF (standing) in E @ 9 months: ↓LF/HF (free breathing and controlled breathing)
Mello et al. [53]	Controlled	$n = 27$ allocated and [a]$n = 25$ analysed for HRV E: $n = 15$ (60% men), 54 ± 2 years, LVEF 34 ± 2% C: $n = 12$ (42% men), 53 ± 2 years, LVEF 38 ± 2% All NYHA II, 100% β-blockers, 100% ACEI/ARBs Aetiology: non-IHD	12 weeks, inspiratory muscle training (IMT) 10 min, 3× per day, 7 days per week 30% PI_{max}	Short HRV recordings: ↓LF_{nu}, ↑HF_{nu}, ↓LF/HF in E
Murad et al. [54]	RCT	$n = 101$ randomised, [a]$n = 66$ analysed for HRV E: $n = 31$ (36% men), 68 ± 5 years, LVEF HFrEF and HFpEF (LVEF > 40% $n = 17$) C: $n = 35$ (37% men), 70 ± 6 years, LVEF HFrEF and HFpEF (LVEF > 40% $n = 20$), All NYHA II–III, 15% β-blockers (E: $n = 6$, C: $n = 4$), 47% ACEI (E: $n = 14$, C: $n = 17$), aetiology: NR	16 weeks, aerobic training, 3× week, 60 min @ 60–70% heart rate reserve (40–50% heart rate reserve weeks 1–2)	Short HRV recordings: ↑SDNN and ↑RMSSD in E, significantly different to change in C
Piotrowicz et al. [55]	RCT	$n = 111$ randomised, $n = 69$ analysed for HRV[a] E: $n = 46$ (85% men), 5 ± 10 years, LVEF 31 ± 7% C: $n = 23$ (96% men), 60 ± 12 years, LVEF 33 ± 7% All NYHA II-III, 100% β-blockers, 88% ACEI, 13% ARBs Aetiology: ischemic and non-ischemic	8 weeks, aerobic training (home-based Nordic walking), 5× week, 45–60 min @ 40–70%HR_{max}	Long HRV recordings: ↓LF/HF, ↓Log LF(ms^2/Hz), ↑Log HF(ms^2/Hz) and ↔SDNN in E group
Ricca-Mallada et al. [56]	RCT	$n = 24$ randomised, n = 20 analysed E: $n = 10$ (80% men), 59 ± 8 years, LVEF 32 ± 8% C: $n = 10$ (80% men), 57 ± 8 years, LVEF 30 ± 8% All NYHA I-II, 90% β-blockers (E: $n = 9$, C: n = 9), 100% ACEI, 95%ARBs, aetiology 55% ischemic	24 weeks, 3× week, 60 min. 10-min warm, up, 20-min breathing and non-resistance arm and leg movements, 20-min circuit RT using a mechanical bike, 5-min cooldown. Work load bike started @50% peak WL, target of max WL, or 80%HR_{peak}	Short HRV recordings: ↑RR interval, ↑LF(ms^2), ↑HF (ms^2),↔LF/HF, ↔ SDNN, ↓AC(ms), ↑DC(ms) in E
Ricca-Mallada et al. [57]	RCT	$n = 40$ randomised, $n = 36$ analysed	24 weeks, aerobic training, 3× week, 60 min. 10-min	Short HRV recordings: ↑RMSSD, ↑HF(ms^2) in E

Table 1 (continued)

Study	Design	Participant characteristics	Intervention characteristics	Main findings HRR, HRV and MSNA
		E: $n = 16$ (81% men), 57 ± 10 years, LVEF 32 ± 8% C: $n = 18$ (78% men), 56 ± 9, LVEF 28 ± 8% All NYHA I-II, 94% β-blockers (E: $n = 15$, C: n = 17), 97% ACEI/ARBs, aetiology 52.5% ischemic	warm, up, 20-min breathing and non-resistance arm and leg movements, 20–30 treadmill or bike, 5-min cooldown. Work load bike started @50% peak WL, target of max WL, or 80%HR_{peak}	
Selig et al. [58]	RCT	$n = 39$ randomised, $n = 27$ analysed for HRV[a] E: $n = 19$ ([a]14) (79% men), 65 ± 13 years, LVEF 31 ± 3% C: $n = 20$ ([a]13) (80% men), 64 ± 9 years, LVEF 28 ± 6% All NYHA II-III, 44% β-blockers (E: $n = 9$, C: $n = 8$), 87% ACEI/ARBs, aetiology IHD and DCM	3 months, resistance training, 3× week, moderate intensity	Short HRV recordings: ↔RR, ↔SDNN ↔ RMSSD, ↓LF_{nu}, ↑HF_{nu}, ↓LF/HF in E
Yeh et al. [59]	RCT	$n = 30$ randomised, $n = 18$ analysed for HRV[a] E: $n = 8$ (50% men), 64 ± 16 years, LVEF 25 ± 6% C: $n = 10$ (50% men), 55 ± 12 years, LVEF 23 ± 9% All NYHA I–III, 100% β-blockers, 89% ACEI Aetiology NR	12 weeks, Tai Chi, 2× week, 60 min	Long HRV recordings: ↔SDNN, ↔RMSSD, ↔LF, ↔HF, ↔LF/HF, ↔AVNN, ↔ PNN30 in E group ↓pNN30 in E group HRV during sleep
MSNA				
Antunes-Correa et al. [60]	RCT	$n = 56$ randomised, $n = 34$ analysed E: $n = 17$ (77% men), 56 ± 2 years, LVEF 28 ± 2% C: $n = 17$ (88% men), 54 ± 2 years, LVEF 29 ± 1% All NYHA II–III, 100% β-blockers, 100% ACEI/ARBs, Aetiology: idiopathic, ischemic, hypertensive, chagasic	4 months, endurance training 3× per week for 60 min (5-min stretching, 40-min aerobic, 10-min strengthening, 5 cooldown), HR at ANT up to 10% < RCP	↓ $MSNA_{(bursts/min)}$ in E ↓ $MSNA_{(bursts/100HB)}$ in E
de Mello Franco et al. [61]	RCT	$n = 29$ randomised, $n = 25$ analysed (@ 4 months) E: $n = 17$ (76% men), 56 ± 3 years, LVEF 29 ± 2% C: $n = 12$ (75% men), 52 ± 2 years, LVEF 27 ± 3% All NYHA II-III, 90% β-blockers (E: $n = 15$, C:$n = 11$), 100% ACEI/ARBs, aetiology: idiopathic, ischemic, hypertensive, Chagasic	4 months supervised, (12 patients completed additional 4 months home training). endurance training, 3× per week for 60 min (5-min stretching, 40-min aerobic, 10-min strengthening, 5 cooldown), HR at ANT up to 10% < RCP	@ 4 months: ↓ $MSNA_{(bursts/min)}$ in E ↓ $MSNA_{(bursts/100HB)}$ in E @ 8 months: MSNA tend to return toward baseline
Fraga et al. [44]	RCT	$n = 27$ randomised and analysed E: $n = 15$ (53% men), 57 ± 3 years, LVEF 27 ± 2% C: $n = 12$ (75% men), 53 ± 3 years, LVEF 26 ± 2% All NYHA II–III, 100% Carvedilol, 81% ACE inhibitor, 19% ARBs, aetiology: chagas, hypertension, CAD	4 months, endurance training 3× per week for 60 min (5-min stretching, 40-min aerobic, 10-min strengthening, 5 cool down), HR at ANT up to 10% < RCP	↓ $MSNA_{(bursts/min)}$ in E ↓ $MSNA_{(bursts/100HB)}$ in E
Mello et al. [53]	Controlled	$n = 27$ allocated and analysed E: $n = 15$ (60% men), 54 ± 2 years, LVEF 34 ± 2% C: $n = 12$ (42% men), 53 ± 2 years, LVEF 38 ± 2%	12 weeks, inspiratory muscle training (IMT) 10 min, 3× per day, 7 days per week 30% PI_{max}	↓ $MSNA_{(bursts/min)}$ in E ↓ $MSNA_{(bursts/100HB)}$ in E

Table 1 (continued)

Study	Design	Participant characteristics	Intervention characteristics	Main findings HRR, HRV and MSNA
		All NYHA II, 100% β-blockers, 100% ACEI/ARBs		
Nobre et al. [62]	RCT	$n = 45$ randomised, $n = 30$ analysed E: $n = 14$ (50% men), 54 ± 4 years, LVEF 28 ± 3% C: $n = 16$ (56% men), 55 ± 2 years, LVEF 27 ± 1% All NYHA I-III, 100% β-blockers, 93% ACEI/ARBs aetiology: idiopathic, ischemic, hypertensive, chagasic	4 months, endurance training 3× per week for 60 min (5-min stretching, 40-min aerobic, 10-min strengthening, 5 cool-down), HR at ANT up to 10% < RCP	↓ $MSNA_{(bursts/min)}$ in E ↓ $MSNA_{(bursts/100HB)}$ in E
Roveda et al. [63]	RCT	$n = 16$ randomised and analysed E: $n = 7$ (71% men), 53 ± 9, LVEF 35 ± 3% C: $n = 9$ (67% men), 53 ± 9 years, LVEF 35 ± 3% All NYHA II-III, 0% β-blockers, 100% ACEI Aetiology: idiopathic, CAD, chagasic	4 months, endurance training 3× per week for 60 min (5-min stretching, 40-min aerobic, 10-min strengthening, 5 cool-down), HR at ANT up to 10% < RCP	↓ $MSNA_{(bursts/min)}$ in E ↓ $MSNA_{(bursts/100HB)}$ in E

AC acceleration capacity, *ACEI* angiotensin converting enzyme inhibitor, *ARBs* angiotensin receptor blocker, *ANT* anaerobic threshold, *AVNN* average of all normal sinus to normal sinus (NN) intervals, *C* control group, *CAD* coronary artery disease, *DC* deceleration capacity, *DCM* dilated cardiomyopathy, *E* exercise group, *HF* high frequency, *HR* heart rate, HR_{max} maximum heart rate, HRR_1 heart rate recovery in first minute after exercise, HRR_2 heart rate recovery in second minute after exercise, *HRV* heart rate variability, *IHD* Ischemic heart disease, *LF* low frequency, *LFnu* low-frequency normalised units, *LF/HF* low-frequency/high-frequency ratio, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *MSNA* muscle sympathetic nerve activity, *NR* not reported, *NYHA* New York Heart Association, *PEP* preserved ejection fraction, *pNN30* percentage of differences between adjacent NN intervals that are > 30 ms, *RCP* respiratory compensation point, *RCT* randomised controlled trial, *RMSSD* root mean square of successive differences between adjacent NN intervals, *RR* RR interval, *SDNN* standard deviation of normal RR intervals, *TP* total power, VO_{2peak} peak oxygen uptake, *VLF* very low frequency, ↓ statistically significant decrease, ↑ statistically significant increase, ↔ no statistically significant change

[a] Number of patients analysed for HRV only, analysis of non-HRV outcomes have different number or patients

while two [45, 47] studies utilised treadmill testing. Two [46, 48] studies calculated HRR during an active recovery period, two [45, 47] studies required patients to be completely at rest and one [44] study did not specify whether HRR was calculated during active or resting recovery.

Heart rate variability Overall, 11 studies [49–59] measured HRV. Full assessment methodology is presented in Supplementary File 1, Table S3. Time domain parameters were reported in seven studies [49, 54–59], four [54, 56–58] of which utilised short-term recordings and three studies [49, 55, 59] long-term recordings. Frequency domain parameters were reported in 10 studies [49–53, 55–59], four [49, 51, 55, 59] of which utilised long-term recordings while six studies [50, 52, 53, 56–58] utilised short-term recordings. Of the four studies that utilised long-term recordings, only one study [59] provided the full 24-h data for both time and frequency domain parameters. One study [49] did not report what particular time or frequency parameters were measured or provide any HRV data and therefore could not be pooled for analysis. Only two [50, 52] of the studies that utilised short-term recordings noted breath rate, and one [52] of these studies applied a controlled breath rate and a free/spontaneous breathing rate in the assessment of HRV and only the free breathing rate was included for data pooling.

Muscle sympathetic nerve activity Six studies [44, 53, 60–63] measured and reported on MSNA. All studies were conducted by the same research group and utilised the same MSNA assessment methodology. MSNA was recorded directly from the peroneal nerve using microneurography in which multi-unit postganglionic muscle sympathetic nerve recordings were made using a tungsten microelectrode.

Outcome measures

A summary of all pooled analyses are provided in Table 2.

Heart rate recovery

HRR_1 Data from four studies [45–48] with five intervention groups (93 exercising participants, 65 controls) were pooled for analysis. One study [44] included in the systematic review, which indicated a statistically significant improvement in HRR_1, was excluded from the pooled analysis due to insufficient data for the control group. Pooled data of four studies [45–48] indicated a statistically significant improvement in HRR_1 in favour of exercise (MD 5.90 bpm (95%CI 5.12, 6.69), $p < 0.00001$ (Fig. 2)). Sensitivity analyses to remove the one non-RCT [47] did not

Table 2 Summary of pooled data analyses for HRR, HRV and MSNA

ANS parameters	No. of studies	No. of participants		MD (95%CI)
		Exercise	Control	
HRR				
HRR_1 (bpm)	4	93	65	MD 5.90 (5.12, 6.69), $p < 0.00001$
HRR_2 (bpm)	2	42	23	MD 6.45 (0.89, 12.02), $p = 0.02$
HRV (Short-term recordings)				
Frequency domain				
HF_{nu}	3	72	72	MD 7.72 (3.32, 12.12), $p = 0.0006$
HF(ms/Hz)	2	26	28	MD 377.25 (188.62, 565.88), $p < 0.0001$
LF_{nu}	3	72	72	MD − 8.96 (− 12.45, − 5.47), $p < 0.00001$
LF/HF	5	109	100	MD − 0.57 (− 0.86, − 0.27), $p = 0.0002$
Time domain				
RMSSD	3	61	66	MD 10.44 (0.60, 20.28), $p = 0.04$
SDNN	3	55	58	MD 7.48 (− 4.41, 19.38), $p = 0.22$
MSNA				
MSNA bursts/min	5[a]	68	64	MD − 11.09 (− 16.18, − 6.01), $p = <0.0001$
	5[b]	68	66	MD − 10.44 (− 14.94, − 5.95), $p < 0.00001$
MSNA bursts/100 heart beats	5[a]	68	64	MD −15.44 (− 20.95, − 9.92), $p < 0.00001$
	5[b]	68	66	MD − 15.02 (− 19.71, − 10.33), $p < 0.00001$

Both studies contain a crossover of a number of patients

[a] Includes de Mello Franco et al. [61] study

[b] Replaces de Mello Franco study with Fraga et al.'s [44] study

significantly alter the result (MD 5.79 bpm (95%CI 4.98, 6.61) $p < 0.0001$). Results also remained statistically significant when sensitivity analyses were conducted to remove each study one by one to assess the impact of each study on the result.

HRR_2 Pooled data from two [46, 48] studies with three intervention groups (42 exercise participants, 23 controls) demonstrated a statistically significant improvement in HRR_2 in favour of exercise (MD 6.45 bpm (95%CI 0.89, 12.02), $p = 0.02$) (see Supplementary File 2).

Heart rate variability

Frequency domain parameters

High frequency *Short-term recordings:* Pooled data from three studies [50, 53, 58] (72 exercise; 72 controls) indicated a statistically significant improvement (increase) in HF_{nu} in favour of exercise training (MD 7.72 (95%CI 3.32, 12.12), $p = 0.0006$) (Fig. 3). Pooled analysis also indicated a statistically significant improvement in HF ms^2/Hz from two studies [56, 57] (MD 377.25 (95%CI 188.62, 565.88), $p < 0.0001$) (see Supplementary File 2).

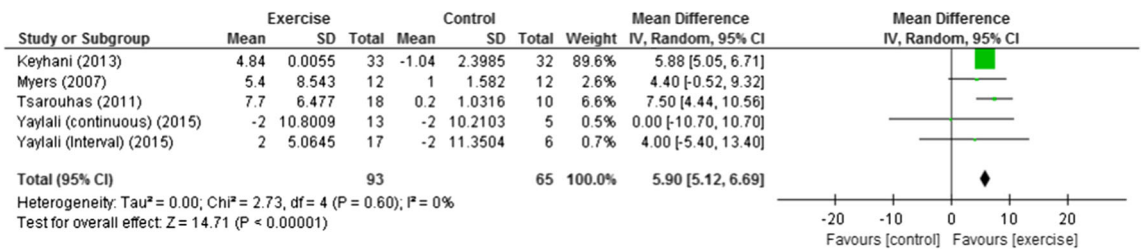


Fig. 2 Change in HRR_1 (bpm) exercise vs. control

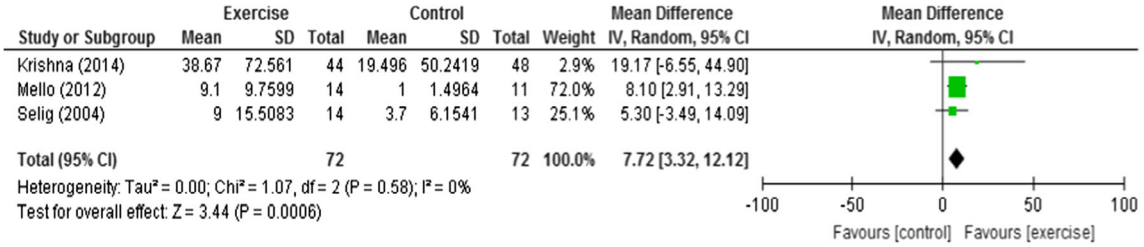


Fig. 3 Change in HF_{nu} exercise vs. control

Long-term recordings: With respect to data reported in three studies [51, 55, 59] utilising long-term recordings, which were not pooled due to different reporting periods, two studies [51, 55] reported a statistically significant increase in HF (see Supplementary File 1).

Low frequency *Short-term recordings*: Pooled data from three studies [50, 53, 58] (72 exercise, 72 controls) indicated a statistically significant decrease (improvement) in LF_{nu} in favour of exercise training (MD −8.96 (95%CI, −12.45, −5.47), $p < 0.00001$) (see Supplementary File 2).

Long-term recordings: In the three studies [51, 55, 59] that reported data from long-term recordings, which were not pooled, only Piotrowicz et al. (2016) [55] reported a statistically significant decrease post-training (see Supplementary File 1).

Low-frequency/high-frequency ratio *Short-term recordings*: Pooled data from five studies [50, 52, 53, 56, 58] (109 exercise, 100 controls) indicated a statistically significant decrease (improvement) the LF/HF ratio; (MD −0.57 (95%CI −0.86, −0.27), $p = 0.0002$) (see Supplementary File 2).

Long-term recordings: With respect to three studies [51, 55, 59] that reported data from long-term recordings which were not pooled, only one [55] reported a statistically significant decrease in the LF/HF ratio (see Supplementary File 1).

Time domain parameters

RMSSD (ms) *Short-term recordings*: Pooled data from three studies [54, 57, 58] (61 exercise; 66 controls) indicated a statistically significant improvement in favour of exercise (MD 10.44 (95%CI 0.60, 20.28), $p = 0.04$) (Fig. 4).

Long-term recordings: Only one study [59] reported RMSSD from long-term recordings, with a trend for improvement in favour of exercise training, but this was not statistically significant.

SDNN (ms) *Short-term recordings*: Pooled data from three studies [54, 56, 58] (55 exercise, 58 control participants) indicated an overall improvement in SDNN in favour of exercise; however, the result was not statistically significant (MD 7.48 (95%CI −4.41, 19.38), $p = 0.22$) (see Supplementary File 2).

Long-term recordings: Neither of the two studies [55, 59] that utilised long-term recordings reported any statistically significant change in SDNN (see Supplementary File 1).

Muscle sympathetic nerve activity

Six studies [44, 53, 60–63] were included in the review of MSNA, two [44, 61] of which contained a crossover of some participants; therefore, to avoid double counting, two separate analyses were conducted for each of $MSNA_{burst/min}$ and $MSNA_{burst/100\ heart\ beats}$.

$MSNA_{(burst/min)}$ Pooled data from five studies [53, 60–63] (68 exercise participants and 64 controls) indicated a statistically significant improvement in $MSNA_{(burst/min)}$ in favour of exercise; (MD −11.09 (95%CI −16.13, −6.00), $p < 0.0001$) (Fig. 5a). The second analysis to replace one study with another did not significantly alter the result (MD −10.44 (95%CI −14.94, −5.95), $p < 0.00001$) (Fig. 5b). Removal of the one inspiratory muscle training study [53] from each of the two analyses

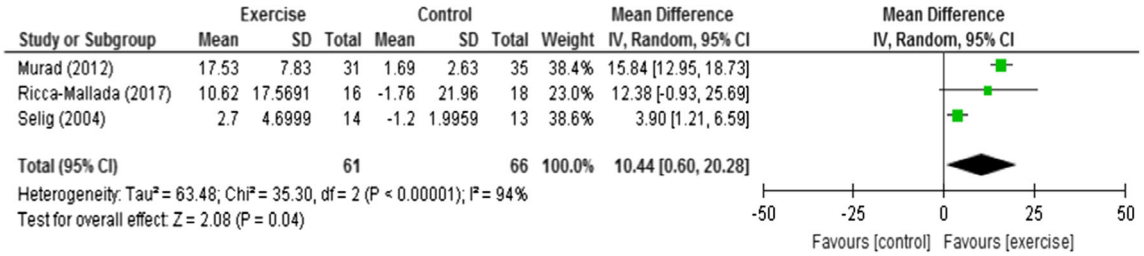


Fig. 4 Change in RMSSD (ms) exercise vs. control

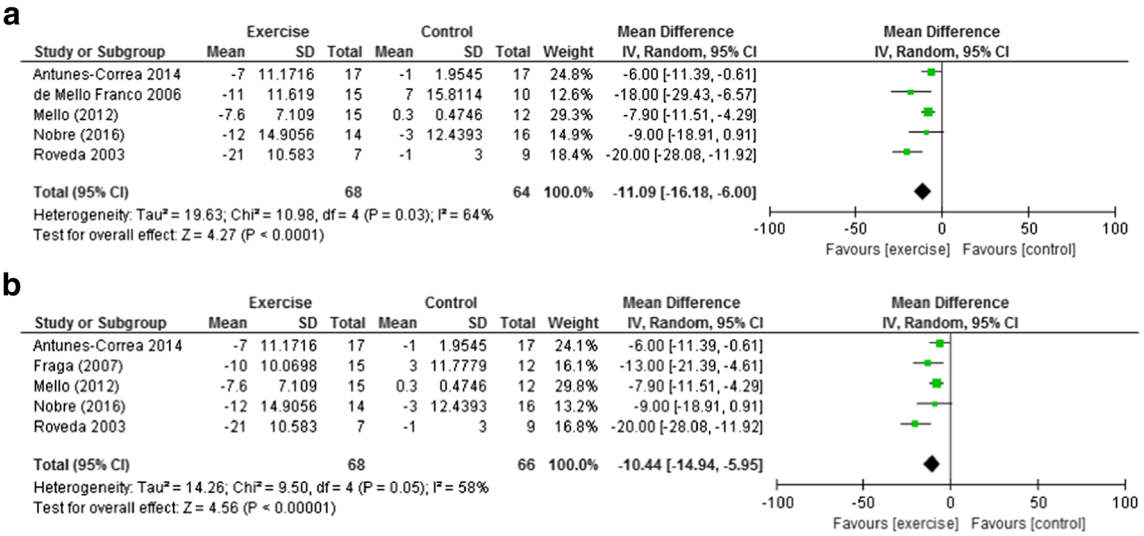


Fig. 5 Change in $MSNA_{burst/min}$ exercise vs. control. **a** Includes study of de Mello Franco et al. [61]. **b** de Mello Franco et al. [61] study replaced with Fraga et al. [44] study. Both studies contain a crossover of a number of patients

indicated a statistically significant improvement in $MSNA_{(burst/min)}$ in favour or endurance training (MD − 12.73 (95%CI − 20.23, − 5.22), $p = 0.0009$ and MD − 11.72 (95%CI − 18.20, − 5.23), $p = 0.004$).

$MSNA_{(burst/100HB)}$ Pooled data from five studies [53, 60–63] (68 exercise participants and 64 controls) indicated a statistically significant improvement in $MSNA_{(burst/100HB)}$ in favour of exercise ($MSNA_{(burst/100HB)}$ MD − 15.44 (95%CI − 20.95, − 9.92), $p < 0.00001$ (Fig. 6a). The second analysis to replace one study with another did not significantly alter the result; (MD − 15.02 (95%CI − 19.71, − 10.33), $p < 0.00001$ (Fig. 6b). Removal of the one inspiratory muscle training study [53] from each analyses indicated a statistically significant improvement in $MSNA_{(burst/min)}$ in favour or endurance training (MD − 17.77 (95%CI − 23.65, − 11.90), $p < 0.00001$ and MD − 17.55 (95%CI − 22.36, − 12.76), $p < 0.00001$).

Adverse events and intervention adherence

Only eight studies reported data on exercise session attendance, while 12 studies reported or noted the absence or occurrence of any adverse events during the intervention period (see Supplementary File 1). However, only one study specifically noted whether adverse events occurred during training or as a result of training.

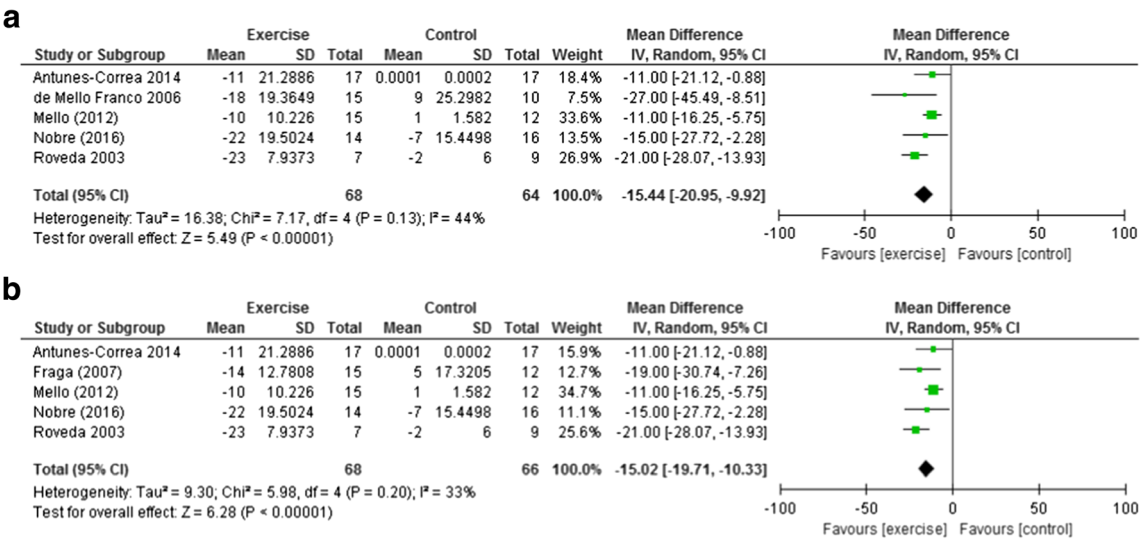


Fig. 6 Change in $MSNA_{burst/100\ heart\ beats}$ exercise vs. control. **a** Includes study of de Mello Franco et al. [61]. **b** de Mello Franco et al. [61] study replaced with Fraga et al. [44] study. Both studies contain a crossover of a number of patients

Study quality assessment (TESTEX)

The median TESTEX score was 7.5 (maximum 15) (see Supplementary File 1). While all RCTs noted participant randomisation, the majority of studies failed to provide specific details on randomisation procedures. The majority of studies also lost points in the areas of allocation concealment, intention-to-treat analysis, activity monitoring in the control group, review of relative exercise intensity and in the provision of adequate details to calculate accurate energy expenditure.

Heterogeneity and publication bias

Only 2 of 12 analyses demonstrated high heterogeneity ($I^2 > 75\%$). Funnel plots demonstrated minimal evidence of publication bias.

Discussion

This work analysed the effects of exercise training on autonomic function assessed by HRR, HRV and MSNA in patients with heart failure. Our results indicated statistically significant improvements in all three examined parameters of ANS function. Pooled data indicated a significant improvement in HRR_1 and HRR_2. While not a direct measure of PNS and SNS activity, the improvements are suggestive of improved autonomic function.

In order to meet the metabolic demands of exercise, SNS activity increases and PNS activity decreases. Upon cessation of exercise, the heart rate returns to pre-exercise levels in an exponential fashion with the largest reductions within the first few minutes [24, 64]. The improvements in HRR_1 predominantly reflect a reactivation of the PNS, with a suggestion that there may be a sympathetic component to this fast phase of recovery [24]. The improvements in HRR_2 reflect a combination of parasympathetic reactivation and sympathetic withdrawal [24].

While only three of the five studies included in the review noted statistically significant improvements in HRR_1 post-training, a subanalysis by Yaylai and colleagues (2015) [48] based on abnormal HRR_1 (defined as ≤ 12 bpm) at baseline noted a significant improvement in these patients. The improvement in patients with an abnormal baseline HRR is in accordance with the earlier findings of Streuber et al. [65] who in their retrospective analysis of 46 CHF patients after 12 weeks of aerobic training found an improvement in HRR_1 in patients with low exercise capacity and abnormal HRR_1 (≤ 12 bpm), with no improvement in patients with normal HRR_1 and higher functional capacity at baseline. The re-analysis of the 2006 study by Dimopoulos and colleagues [66] which compared interval to continuous training also noted that heart failure patients with a greater HRR abnormality at baseline had a significant improvement after exercise training compared to those with normal HRR_1 [67]. It has been suggested that patients with a "normal" baseline HRR and higher exercise capacity may require a greater training stimulus [48, 65] or greater training duration [52] to achieve significant changes in parameters of autonomic function.

While our analysis indicated a statistically significant improvement in HRR, we were unable to conduct any subanalysis to examine the effect of training based on abnormality of HRR at baseline. The majority of studies included in our review had an average baseline HRR_1 value above the 12 bpm cut-off widely considered as abnormal, with statistically significant improvements in three [44, 45, 47] of the studies that had a mean baseline $HRR_1 > 12$ bpm. Of particular importance, it must be noted that to date, there is no one standard definition of abnormal HRR or accepted recovery protocol, which makes comparison of studies more difficult. Although $HRR_1 \leq 12$ bpm [17, 68] is the most widely utilised cut-off for abnormality and increased risk, a variety of thresholds have been reported [64]. Additionally, post-exercise HRR is influenced by a number of factors, including recovery protocol, i.e. active vs. passive recovery and recovery position [69], exercise modality [70, 71] and exercise intensity [72], and in turn, these may influence the threshold applied for abnormality. HRR may also be affected by β-blockers which could influence the effect of training programs [48] on autonomic function, although to what extent is unclear. However, in our review, improvements in HRR_1 occurred in studies [44, 47] where a large percentage of patients were on β-blockers. It was recently demonstrated that in post-acute MI male patients, the combination of 12 weeks of exercise training with β-blockers promoted HRR in all patients, and the combination of both was only more effective than exercise training alone in the subgroup of patients with baseline $HRR_1 \leq 12$ bpm [73].

While the prognostic value of HRR_1 is well established in heart failure patients, less is known about HRR_2; however, it has been suggested that HRR_2 may be more powerful than HRR_1 [69, 74]. While only from two studies (three intervention groups) our review indicated HRR_2 improved post-training, providing evidence for the withdrawal of sympathetic activity in conjunction with improved vagal activity [24]. Whether the result of HRR_2 is more prominent in those with an abnormal baseline HRR_2 is unclear, given that fewer studies have measured HRR_2 and the clinical criterion for abnormality is not as well established as HRR_1. Myers et al. (2007) [46] also recorded HRR up to 6 min post-exercise, an indirect marker of parasympathetic reactivation and sympathetic withdrawal [24]. HRR was significantly faster in the exercise group from minutes 2 to 6 [46]. Overall, while only from a small number of studies, our results of improved HRR are in accordance with the improved HRR found in heart disease patients [75] including acute myocardial infarction patients [76], after aerobic training.

HRR has also been linked to changes in exercise capacity. Four [44–47] studies included in the review reported improvements in various measures of exercise or functional capacity; however, only Myers et al. [46] reported a correlation between the increase in VO_{2peak} and HRR. In CAD patients, Lazzeroni et al. (2017) [77] suggests a possible contributing role of autonomic function in aerobic capacity. They analysed CAD patients based on the level of improvement in VO_{2peak} post-training identifying responders and non-responders (responders defined as improved $VO_{2peak} > 2.6_{ml/kg/min}$) with only responders exhibiting a significant improvement in autonomic indices. Furthermore, both groups had similar HRR prior to training [77].

Only one [49] of the 11 HRV studies included in our review failed to find a statistically significant improvement in any HRV parameter. The findings of our pooled analyses of short-term HRV indicated a statistically significant improvement in all three frequency domain measures (LF, HF and LF/HF) suggestive of improved autonomic function. Both absolute and normalised units of the HF band increased, and with HF largely driven by the PNS, this increase is suggestive of a positive shift in parasympathetic tone [34, 78]. The normalised LF band also significantly improved (decreased) post-training and based on the historical interpretation of the LF band, this would be suggestive of reduced sympathetic activity [34, 35]. However, some controversy remains around the interpretation of LF, and it is suggested that LF is likely reflective of a combination of sympathetic, parasympathetic and baroreflex activities depending on the context [34, 78] and possibly yet-to-be-identified factors [35]. We also found a significant improvement (decrease) in the LF/HF ratio suggestive of an improvement in the overall balance between sympathetic and parasympathetic activity, with a lower ratio indicative of a positive shift away from the predominance of the SNS [27]. While LH/HF is still widely interpreted in research as an indicator of sympathovagal balance, we acknowledge that this concept has been challenged [79].

Additionally, the potential confounding factor of respiration rate must be considered in the clinical interpretation of HRV, with controlled or paced breathing recommended for accurate HRV interpretation [35, 79]. Few studies report breath rate and therefore it is difficult to ascertain if all the changes in HRV are due to changes in autonomic control or if changes could be partially related to changes in breath rate. Only one study [52] specifically noted utilising a paced breathing rate. In addition to resting free breathing, which was pooled for our analysis, Malfatto et al. (2002) [52] also measured the effect of a controlled 20 breaths per minute, finding a statistically significant improvement at 3 months in LF/HF from paced breathing but not free breathing. However, in 11 of the 30 patients to complete an additional 6 months of home-based training, the decrease in LF/HF from free breathing and controlled breathing were both statistically significant.

Due to differences in data reporting from studies utilising long-term HRV recordings, we felt it was inappropriate to pool data from these studies. However, at a descriptive level, the significant improvement in the LF/HF ratio in one study [55] and the trend for improvement in another [51] are suggestive of an overall improvement in autonomic function, which is in accordance with that seen from our analysis of short-term recordings. Two of the studies [51, 59] that utilised long-term recordings were small, and as noted by one [59], it may have been underpowered to detect a statistically significant change in HRV parameters.

In the time domain, our meta-analysis indicted statistically significant improvement in RMSSD from short-term recordings. Reflecting the beat-to-beat variance in heart rate, RMSSD is strongly associated with parasympathetic tone [34], and the improvement in RMSSD is consistent with our finding of improved HF and not surprising given they are closely related [57, 78]. Interestingly, only one study [57] reported on any possible cut-offs or thresholds that may be associated with greater improvements. Ricca-Mallada and colleagues (2017) [57] found that "low-risk" patients with a baseline RMSSD < 20 ms and HF < 150 ms^2/Hz had greater improvements in HRV indices as well as functional capacity, suggesting that patients with more impaired vagal activity will achieve better results.

Whether or not improvements in autonomic function are mediators of improved exercise capacity remains unclear, with only one study [55] reporting a correlation between an improved HRV index and exercise capacity. Overall, our findings of improved HRV support findings from earlier heart failure studies of differing designs [9, 10].

The exact mechanisms by which exercise training improves HRR and HRV are not completely understood. Nitric oxide and angiotensin II are potential mediators, with both involved in cardiac vagal [54] and sympathetic activities and both shown to improve with exercise training [31, 80]. An attenuated HRR is related to endothelial function [81], and exercise training improves endothelial dysfunction in heart failure patients [6]. Exercise training also improves pro-inflammatory cytokine levels in heart failure patients [82], and Youn and colleagues [83] recently confirmed that an impaired HRR is associated with increased levels of pro-inflammatory cytokines. Similarly, HRV has also been shown to be inversely correlated with inflammatory markers [84, 85].

Other underlying factors may also be mediators for improvements in parameters of ANS function. Depression is associated with heart failure and has prognostic value [86–88], and evidence suggests that psychological factors such as depression are related to alterations in ANS function [89]. Exercise training improves depressive symptoms in heart failure [90] and therefore changes in depressive symptoms after exercise training may be a mediating factor in the improvements in ANS function. Piotrowicz et al. [55] reported

that the greatest parasympathetic-sympathetic improvement was observed in heart failure patients where depression was reversed.

Of the three parameters of autonomic function in our analysis, microneurography is the only one that provides a direct measure of activity. Resting MSNA is increased in the majority of heart failure patients [38, 39, 63], and our pooled data indicated a statistically significant reduction in both resting MSNA burst incidence and burst frequency after exercise training. Improvements in MSNA occur regardless of beta-blocker usage [44], age [91], gender [92] and aetiology [93], although greater reductions have been observed in hypertensive heart failure patients compared to those of idiopathic origin [93] and greater reductions occur in patients with sleep apnoea [94]. However, it must be noted that to date, the only published research on the effects of exercise training and resting MSNA in heart failure patients comes from the University of Sao Paulo. Since 2003, the research team has conducted a number of prospective trials and retrospective analyses that report on MSNA in heart failure patients. To date, the majority of published studies from the research group have essentially utilised the same endurance training protocol. However, MSNA is also reduced after inspiratory muscle training [53] and short-term functional electrical stimulation [95] in this population. While all studies reported statistically significant improvements, whether MSNA reductions are maintained or further improved over the long term remains to be seen, given that Franco et al. [61] reported that reduced levels of MSNA after 4 months of supervised training were not maintained after an additional 4-month home training, although a number of factors could explain this result. While the evidence is promising for the use of exercise training to improve MSNA in heart failure patients, the mechanisms involved have not been completely elucidated [96]. Animal studies and recent training studies in humans with heart failure indicate there are likely to be a number of contributors [96] including improvements in arterial baroreflex control, chemoreflex sensitivity [97] and mechanoreflex control [60, 96].

Generalisability

Heart failure category Autonomic balance is present in heart failure irrespective of ejection fraction [1, 3, 4]; however, only two studies [50, 54] included in the review included participants with preserved ejection fractions. Both studies reported statistically significant improvements in ANS parameters, and Murad et al. [54] specifically noted that the effect of exercise training on HRV did not differ by heart failure category. All the MSNA studies to date are in patients with reduced ejection fractions; therefore, we eagerly await the results from the recently registered clinical trial to assess MSNA and exercise training in patients with preserved ejection fractions [98].

Comorbidities Abnormal autonomic function is also seen in diabetes and with the prevalence of diabetes in heart failure patients ranging from 13 to 47% [99]; some heart failure patients may have more impaired parameters of autonomic function [54]. However, we were unable to conduct any analysis to ascertain if the effect of exercise training on ANS function differed between patients with or without diabetes.

Gender The majority of studies were comprised of male participants, and gender differences may also exist in parasympathetic reactivation after exercise [100]. Although, again, Murad [54] noted no differences in HRV parameters based on gender, and no gender differences were found in regard to exercise and MSNA [92].

At this point in time, given the clear imbalance in gender, heart failure categories and comorbidities with the studies, one should exercise caution in generalising the findings of the review across the entire heart failure population.

Strengths and limitations in the systematic review and meta-analysis

To our knowledge, this is the first meta-analysis in heart failure patients that examines and collates the results of ANS function post-training in heart failure patients utilising HRR, HRV and MSNA. While both HRR and HRV have prognostic value, they are both indirect measures of ANS activity and therefore cannot provide accurate quantitative evidence of sympathetic or parasympathetic activity. In addition, controversy still exists as to whether HRV measures provide insight into sympathetic cardiac activity [79, 101]. A strength of this review is the inclusion of both indirect and direct assessment methods of ANS function. The major limitations of the review are the small sample sizes of many of the studies and the minimal number of methodologically rigorous studies examining effects of exercise training on HRR and HRV, and all studies investigating MSNA to date are from one research group. Additionally, differences in the methodological assessment of HRR and HRV may have influenced analyses and contributed to raised heterogeneity among studies. HRR assessment is inexpensive and easy to administer, and therefore in order to improve comparison between studies, particularly in the future, consensus should be reached regarding the assessment protocol. Abstracts were excluded as were trials reported in languages other than English which may lead to publication bias.

Due to the small number of RCTs, we included both randomised and non-randomised controlled trials in our analysis. However, with exercise now strongly recommended in the treatment of stable heart failure patients, due to the ethical considerations of complete randomisation of patients to a standard usual care group, future evidence gathering from studies may need to consider this issue. In regard to data pooling, we measured the difference between pre-intervention and post-intervention means; however, in cases where exact p values within or between groups or 95% CI were not available, default values for p were utilised and this may introduce errors.

Conclusion

Exercise training improves HRR, HRV and MSNA in heart failure patients, suggestive of increased parasympathetic (vagal) tone and decreased sympathetic activity, thereby aiding in the restoration of autonomic function. However, a number of questions remain in regard to exercise prescription for optimal results in ANS function.

Acknowledgements M.J Pearson is supported by an Australian Postgraduate Award Scholarship. This work received no other financial support and has no relationship to industry.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Florea VG, Cohn JN (2014) The autonomic nervous system and heart failure. Circ Res 114(11):1815–1826. https://doi.org/10.1161/CIRCRESAHA.114.302589
2. Verloop WL, Beeftink MM, Santema BT et al (2015) A systematic review concerning the relation between the sympathetic nervous system and heart failure with preserved left ventricular ejection fraction. PLoS One 10(2):e0117332. https://doi.org/10.1371/journal.pone.0117332
3. Floras JS, Ponikowski P (2015) The sympathetic/parasympathetic imbalance in heart failure with reduced ejection fraction. Eur Heart J 36(30):1974–1982. https://doi.org/10.1093/eurheartj/ehv087
4. Phan TT, Shivu GN, Abozguia K et al (2010) Impaired heart rate recovery and chronotropic incompetence in patients with heart failure with preserved ejection fraction. Circ Heart Fail 3:29–34
5. Pearson M, Mungovan S, Smart N (2017) Effect of exercise on diastolic function in heart failure patients: a systematic review and meta-analysis. Heart Fail Rev 22(2):229–242. https://doi.org/10.1007/s10741-017-9600-0
6. Pearson M, Smart N (2017) Effect of exercise training on endothelial function in heart failure patients: a systematic review meta-analysis. Int J Cardiol 231:234–243. https://doi.org/10.1016/j.ijcard.2016.12.145
7. Taylor RS, Sagar VA, Davies EJ et al (2014) Exercise-based rehabilitation for heart failure. Cochrane Libr
8. Dieberg G, Ismail H, Giallauria F, Smart NA (2015) Clinical outcomes and cardiovascular responses to exercise training in preserved ejection fraction heart failure patients: systematic review & meta-analysis. J Appl Physiol 119(6):726–733. https://doi.org/10.1152/japplphysiol.00904.2014
9. Gademan MG, Swenne CA, Verwey HF et al (2007) Effect of exercise training on autonomic derangement and neurohumoral activation in chronic heart failure. J Card Fail 13(4):294–303. https://doi.org/10.1016/j.cardfail.2006.12.006
10. Adamopoulos S, Ponikowski P, Cerquetani E et al (1995) Circadian pattern of heart rate variability in chronic heart failure patients effects of physical training. Eur Heart J 16(10):1380–1386. https://doi.org/10.1093/oxfordjournals.eurheartj.a060746
11. Coats AJ, Adamopoulos S, Radaelli A, McCance A, Meyer TE, Bernardi L, Solda PL, Davey P, Ormerod O, Forfar C (1992) Controlled trial of physical training in chronic heart failure. Exercise performance, hemodynamics, ventilation, and autonomic function. Circulation 85(6):2119–2131. https://doi.org/10.1161/01.CIR.85.6.2119
12. Nanas S, Anastasiou-Nana M, Dimopoulos S, Sakellariou D, Alexopoulos G, Kapsimalakou S, Papazoglou P, Tsolakis E, Papazachou O, Roussos C, Nanas J (2006) Early heart rate recovery after exercise predicts mortality in patients with chronic heart failure. Int J Cardiol 110(3):393–400. https://doi.org/10.1016/j.ijcard.2005.10.032
13. Arena R, Myers J, Abella J, Peberdy MA, Bensimhon D, Chase P, Guazzi M (2010) The prognostic value of the heart rate response during exercise and recovery in patients with heart failure: influence of beta-blockade. Int J Cardiol 138(2):166–173. https://doi.org/10.1016/j.ijcard.2008.08.010
14. Cahalin LP, Arena R, Labate V, Bandera F, Lavie CJ, Guazzi M (2013) Heart rate recovery after the 6 min walk test rather than distance ambulated is a powerful prognostic indicator in heart failure with reduced and preserved ejection fraction: a comparison with cardiopulmonary exercise testing. Eur J Heart Fail 15(5):519–527. https://doi.org/10.1093/eurjhf/hfs216
15. Barretto AC, Santos AC, Munhoz R et al (2009) Increased muscle sympathetic nerve activity predicts mortality in heart failure patients. Int J Cardiol 135(3):302–307. https://doi.org/10.1016/j.ijcard.2008.03.056
16. Galinier M, Pathak A, Fourcade J, Androdias C, Curnier D, Varnous S, Boveda S, Massabuau P, Fauvel M, Senard JM, Bounhoure JP (2000) Depressed low frequency power of heart rate variability as an independent predictor of sudden death in chronic heart failure. Eur Heart J 21(6):475–482. https://doi.org/10.1053/euhj.1999.1875
17. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS (1999) Heart-rate recovery immediately after exercise as a predictor of mortality. N Engl J Med 341(18):1351–1357. https://doi.org/10.1056/NEJM199910283411804
18. Tang Y-D, Dewland TA, Wencker D, Katz SD (2009) Post-exercise heart rate recovery independently predicts mortality risk in patients with chronic heart failure. J Card Fail 15(10):850–855. https://doi.org/10.1016/j.cardfail.2009.06.437
19. Arena R, Guazzi M, Myers J, Peberdy MA (2006) Prognostic value of heart rate recovery in patients with heart failure. Am Heart J 151(4):851. e857–851. e813
20. Guazzi M, Myers J, Peberdy MA, Bensimhon D, Chase P, Arena R (2010) Heart rate recovery predicts sudden cardiac death in heart failure. Int J Cardiol 144(1):121–123. https://doi.org/10.1016/j.ijcard.2008.12.149
21. Carnethon MR, Jacobs DR Jr, Sidney S et al (2005) A longitudinal study of physical activity and heart rate recovery: CARDIA,

1987–1993. Med Sci Sports Exerc 37(4):606–612. https://doi.org/10.1249/01.MSS.0000158190.56061.32
22. Darr KC, Bassett DR, Morgan BJ, Thomas DP (1988) Effects of age and training status on heart rate recovery after peak exercise. Am J Phys Heart Circ Phys 254(2):H340–H343
23. Du N, Bai S, Oguri K, Kato Y, Matsumoto I, Kawase H, Matsuoka T (2005) Heart rate recovery after exercise and neural regulation of heart rate variability in 30–40 year old female marathon runners. J Sports Sci Med 4(1):9–17
24. Peçanha T, Bartels R, Brito LC, Paula-Ribeiro M, Oliveira RS, Goldberger JJ (2017) Methods of assessment of the post-exercise cardiac autonomic recovery: a methodological review. Int J Cardiol 227:795–802. https://doi.org/10.1016/j.ijcard.2016.10.057
25. Jehn M, Halle M, Schuster T, Hanssen H, Koehler F, Schmidt-Trucksäss A (2011) Multivariable analysis of heart rate recovery after cycle ergometry in heart failure: exercise in heart failure. Heart Lung: J Acute Crit Care 40(6):e129–e137. https://doi.org/10.1016/j.hrtlng.2011.01.005
26. Imai K, Sato H, Hori M, Kusuoka H, Ozaki H, Yokoyama H, Takeda H, Inoue M, Kamada T (1994) Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure. J Am Coll Cardiol 24(6):1529–1535. https://doi.org/10.1016/0735-1097(94)90150-3
27. Camm AJ, Malik M, Bigger JT et al (1996) Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 93(5):1043–1065
28. Goldberger AL (1991) Is the normal heartbeat chaotic or homeostatic? Physiology 6(2):87–91
29. Nolan J, Batin PD, Andrews R, Lindsay SJ, Brooksby P, Mullen M, Baig W, Flapan AD, Cowley A, Prescott RJ, Neilson JMM, Fox KAA (1998) Prospective study of heart rate variability and mortality in chronic heart failure. Circulation 98(15):1510–1516. https://doi.org/10.1161/01.CIR.98.15.1510
30. Sandercock GR, Bromley PD, Brodie DA (2005) Effects of exercise on heart rate variability: inferences from meta-analysis. Med Sci Sports Exerc 37(3):433–439. https://doi.org/10.1249/01.MSS.0000155388.39002.9D
31. Routledge FS, Campbell TS, McFetridge-Durdle JA, Bacon SL (2010) Improvements in heart rate variability with exercise therapy. Can J Cardiol 26(6):303–312. https://doi.org/10.1016/S0828-282X(10)70395-0
32. Larsen AI, Gjesdal K, Hall C, Aukrust P, Aarsland T, Dickstein K (2004) Effect of exercise training in patients with heart failure: a pilot study on autonomic balance assessed by heart rate variability. Eur J Cardiovasc Prev Rehabil 11(2):162–167. https://doi.org/10.1097/01.hjr.0000124214.21584.bb
33. Sassi R, Cerutti S, Lombardi F, Malik M, Huikuri HV, Peng CK, Schmidt G, Yamamoto Y, Document Reviewers L, Gorenek B, Lip GYH, Grassi G, Kudaiberdieva G, Fisher JP, Zabel M, Macfadyen R (2015) Advances in heart rate variability signal analysis: joint position statement by the e-Cardiology ESC Working Group and the European Heart Rhythm Association co-endorsed by the Asia Pacific Heart Rhythm Society. Europace 17(9):1341–1353. https://doi.org/10.1093/europace/euv015
34. Shaffer F, McCraty R, Zerr CL (2014) A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability. Front Psychol 5:1040. https://doi.org/10.3389/fpsyg.2014.01040
35. Billman GE (2011) Heart rate variability—a historical perspective. Front Physiol 2:86. https://doi.org/10.3389/fphys.2011.00086
36. Carter JR, Ray CA (2015) Sympathetic neural adaptations to exercise training in humans. Auton Neurosci 188:36–43. https://doi.org/10.1016/j.autneu.2014.10.020
37. Parati G, Esler M (2012) The human sympathetic nervous system: its relevance in hypertension and heart failure. Eur Heart J 33(9):1058–1066. https://doi.org/10.1093/eurheartj/ehs041
38. Leimbach WN, Wallin BG, Victor RG, Aylward PE, Sundlöf G, Mark AL (1986) Direct evidence from intraneural recordings for increased central sympathetic outflow in patients with heart failure. Circulation 73(5):913–919. https://doi.org/10.1161/01.CIR.73.5.913
39. Notarius CF, Millar PJ, Floras JS (2015) Muscle sympathetic activity in resting and exercising humans with and without heart failure 1. Appl Physiol Nutr Metab 40(11):1107–1115. https://doi.org/10.1139/apnm-2015-0289
40. Hsu C-Y, Hsieh P-L, Hsiao S-F, Chien M-Y (2015) Effects of exercise training on autonomic function in chronic heart failure: systematic review. Biomed Res Int 2015:591708. https://doi.org/10.1155/2015/591708
41. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414):557–560. https://doi.org/10.1136/bmj.327.7414.557
42. Egger M, Smith GD, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315(7109):629–634. https://doi.org/10.1136/bmj.315.7109.629
43. Smart NA, Waldron M, Ismail H, Giallauria F, Vigorito C, Cornelissen V, Dieberg G (2015) Validation of a new tool for the assessment of study quality and reporting in exercise training studies: TESTEX. Int J Evid Based Healthc 13(1):9–18. https://doi.org/10.1097/XEB.0000000000000020
44. Fraga R, Franco FG, Roveda F, de Matos LNJ, Braga AMFW, Rondon MUPB, Rotta DR, Brum PC, Barretto ACP, Middlekauff HR, Negrão CE (2007) Exercise training reduces sympathetic nerve activity in heart failure patients treated with carvedilol. Eur J Heart Fail 9(6–7):630–636. https://doi.org/10.1016/j.ejheart.2007.03.003
45. Keyhani D, Kargarfard M, Sarrafzadegan N, Sadeghi M (2013) Autonomic function change following a supervised exercise program in patients with congestive heart failure. ARYA Atheroscler 9(2):150–156
46. Myers J, Hadley D, Oswald U, Bruner K, Kottman W, Hsu L, Dubach P (2007) Effects of exercise training on heart rate recovery in patients with chronic heart failure. Am Heart J 153(6):1056–1063. https://doi.org/10.1016/j.ahj.2007.02.038
47. Tsarouhas K, Karatzaferi C, Tsitsimpikou C, Haliassos A, Kouretas D, Pavlidis P, Veskoukis A, Adamopoulos S, Kyriakides Z, Constantinou L, Koutedakis Y, Rentoukas E (2011) Effects of walking on heart rate recovery, endothelium modulators and quality of life in patients with heart failure. Eur J Cardiovasc Prev Rehabil: Off J Eur Soc Cardiol Work Groups Epidemiol Prev Card Rehabil Exerc Physiol 18(4):594–600. https://doi.org/10.1177/1741826710397099
48. Yaylalı YT, Fındıkoğlu G, Yurtdaş M, Konukçu S, Şenol H (2015) The effects of baseline heart rate recovery normality and exercise training protocol on heart rate recovery in patients with heart failure. Anatol J Cardiol 15(9):727–734. https://doi.org/10.5152/akd.2014.5710
49. Cider A, Tygesson H, Hedberg M, Seligman L, Wennerblom B, Sunnerhagen K (1997) Peripheral muscle training in patients with clinical signs of heart failure. Scand J Rehabil Med 29(2):121–127
50. Krishna BH, Pal P, Pal G et al (2014) Effect of yoga therapy on heart rate, blood pressure and cardiac autonomic function in heart failure. J Clin Diagn Res 8(1):14–16. https://doi.org/10.7860/JCDR/2014/7844.3983
51. Kiilavuori K, Toivonen L, Näveri H, Leinonen H (1995) Reversal of autonomic derangements by physical training in chronic heart failure assessed by heart rate variability. Eur Heart J 16(4):490–495. https://doi.org/10.1093/oxfordjournals.eurheartj.a060941

52. Malfatto G, Branzi G, Riva B, Sala L, Leonetti G, Facchini M (2002) Recovery of cardiac autonomic responsiveness with low-intensity physical training in patients with chronic heart failure. Eur J Heart Fail 4(2):159–166. https://doi.org/10.1016/S1388-9842(01)00221-5
53. Mello PR, Guerra GM, Borile S, Rondon MU, Alves MJ, Negrão CE, Dal Lago P, Mostarda C, Irigoyen MC, Consolim-Colombo FM (2012) Inspiratory muscle training reduces sympathetic nervous activity and improves inspiratory muscle weakness and quality of life in patients with chronic heart failure. J Cardiopulm Rehabil Prev 32(5):255–261. https://doi.org/10.1097/HCR.0b013e31825828da
54. Murad K, Brubaker PH, Fitzgerald DM, Morgan TM, Goff DC Jr, Soliman EZ, Eggebeen JD, Kitzman DW (2012) Exercise training improves heart rate variability in older patients with heart failure: a randomized, controlled, single-blinded trial. Congest Heart Fail 18(4):192–197. https://doi.org/10.1111/j.1751-7133.2011.00282.x
55. Piotrowicz E, Piotrowski W, Piotrowicz R (2016) Positive effects of the reversion of depression on the sympathovagal balance after telerehabilitation in heart failure patients. Ann Noninvasive Electrocardiol 21(4):358–368. https://doi.org/10.1111/anec.12320
56. Ricca-Mallada R, Migliaro ER, Piskorski J, Guzik P (2012) Exercise training slows down heart rate and improves deceleration and acceleration capacity in patients with heart failure. J Electrocardiol 45(3):214–219. https://doi.org/10.1016/j.jelectrocard.2012.01.002
57. Ricca-Mallada R, Migliaro ER, Silvera G, Chiappella L, Frattini R, Ferrando-Castagnetto F (2017) Functional outcome in chronic heart failure after exercise training: possible predictive value of heart rate variability. Ann Phys Rehabil Med 60(2):87–94. https://doi.org/10.1016/j.rehab.2016.12.003
58. Selig SE, Carey MF, Menzies DG et al (2004) Moderate-intensity resistance exercise training in patients with chronic heart failure improves strength, endurance, heart rate variability, and forearm blood flow. J Card Fail 10(1):21–30. https://doi.org/10.1016/S1071-9164(03)00583-9
59. Yeh GY, Mietus JE, Peng CK, Phillips RS, Davis RB, Wayne PM, Goldberger AL, Thomas RJ (2008) Enhancement of sleep stability with Tai Chi exercise in chronic heart failure: preliminary findings using an ECG-based spectrogram method. Sleep Med 9(5):527–536. https://doi.org/10.1016/j.sleep.2007.06.003
60. Antunes-Correa LM, Nobre TS, Groehs RV, Alves MJNN, Fernandes T, Couto GK, Rondon MUPB, Oliveira P, Lima M, Mathias W, Brum PC, Mady C, Almeida DR, Rossoni LV, Oliveira EM, Middlekauff HR, Negrao CE (2014) Molecular basis for the improvement in muscle metaboreflex and mechanoreflex control in exercise-trained humans with chronic heart failure. Am J Physiol Heart Circ Physiol 307(11):H1655–H1666. https://doi.org/10.1152/ajpheart.00136.2014
61. de Mello Franco FG, Santos AC, Rondon MUP, Trombetta IC, Strunz C, Braga AMW, Middlekauff H, Negrão CE, Barretto ACP (2006) Effects of home-based exercise training on neurovascular control in patients with heart failure. Eur J Heart Fail 8(8):851–855. https://doi.org/10.1016/j.ejheart.2006.02.009
62. Nobre TS, Antunes-Correa LM, Groehs RV, Alves MJNN, Sarmento AO, Bacurau AV, Urias U, Alves GB, Rondon MUPB, Brum PC, Martinelli M, Middlekauff HR, Negrao CE (2016) Exercise training improves neurovascular control and calcium cycling gene expression in patients with heart failure with cardiac resynchronization therapy. Am J Physiol Heart Circ Physiol 311(5):H1180–H1188. https://doi.org/10.1152/ajpheart.00275.2016
63. Roveda F, Middlekauff HR, Rondon MUPB, Reis SF, Souza M, Nastari L, Barretto ACP, Krieger EM, Negrão CE (2003) The effects of exercise training on sympathetic neural activation in advanced heart failure: a randomized controlled trial. J Am Coll Cardiol 42(5):854–860. https://doi.org/10.1016/S0735-1097(03)00831-3
64. Dimopoulos S, Manetos C, Panagopoulou N, Karatzanos L, Nanas S (2015) The prognostic role of heart rate recovery after exercise in health and disease. Austin J Cardiovasc Dis Atheroscler 2(2):1014
65. Streuber SD, Amsterdam EA, Stebbins CL (2006) Heart rate recovery in heart failure patients after a 12-week cardiac rehabilitation program. Am J Cardiol 97(5):694–698. https://doi.org/10.1016/j.amjcard.2005.09.117
66. Dimopoulos S, Anastasiou-Nana M, Sakellariou D, Drakos S, Kapsimalakou S, Maroulidis G, Roditis P, Papazachou O, Vogiatzis I, Roussos C, Nanas S (2006) Effects of exercise rehabilitation program on heart rate recovery in patients with chronic heart failure. Eur J Cardiovasc Prev Rehabil 13(1):67–73. https://doi.org/10.1097/00149831-200602000-00010
67. Dimopoulos S (2015) Abnormal heart rate recovery in patients with heart failure: an important target for exercise training treatment. Anatol J Cardiol 15(9):735–736. https://doi.org/10.5152/AnatolJCardiol.2015.16529
68. Nishime EO, Cole CR, Blackstone EH, Pashkow FJ, Lauer MS (2000) Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. JAMA 284(11):1392–1398. https://doi.org/10.1001/jama.284.11.1392
69. Shetler K, Marcus R, Froelicher VF, Vora S, Kalisetti D, Prakash M, Do D, Myers J (2001) Heart rate recovery: validation and methodologic issues. J Am Coll Cardiol 38(7):1980–1987. https://doi.org/10.1016/S0735-1097(01)01652-7
70. Maeder MT, Ammann P, Rickli H, Brunner-La Rocca HP (2009) Impact of the exercise mode on heart rate recovery after maximal exercise. Eur J Appl Physiol 105(2):247–255. https://doi.org/10.1007/s00421-008-0896-2
71. Cunha FA, Midgley AW, Gonçalves T, Soares PP, Farinatti P (2015) Parasympathetic reactivation after maximal CPET depends on exercise modality and resting vagal activity in healthy men. Spring 4(1):100. https://doi.org/10.1186/s40064-015-0882-1
72. Buchheit M, Laursen PB, Ahmaidi S (2007) Parasympathetic reactivation after repeated sprint exercise. Am J Phys Heart Circ Phys 293(1):H133–H141
73. Medeiros WM, Luca FA, Figueredo Júnior AR, Mendes FA, Gun C (2017) Heart rate recovery improvement in patients following acute myocardial infarction: exercise training, β-blocker therapy or both. Clin Physiol Funct Imaging. https://doi.org/10.1111/cpf.12420
74. Lipinski MJ, Vetrovec GW, Gorelik D, Froelicher VF (2005) The importance of heart rate recovery in patients with heart failure or left ventricular systolic dysfunction. J Card Fail 11(8):624–630. https://doi.org/10.1016/j.cardfail.2005.06.429
75. Snoek JA, van Berkel S, van Meeteren N, Backx FJ, Daanen HA (2013) Effect of aerobic training on heart rate recovery in patients with established heart disease; a systematic review. PLoS One 8(12):e83907. https://doi.org/10.1371/journal.pone.0083907
76. Giallauria F, Lucci R, Pietrosante M, Gargiulo G, de Lorenzo A, D'Agostino M, Gerundo G, Abete P, Rengo F, Vigorito C (2006) Exercise-based cardiac rehabilitation improves heart rate recovery in elderly patients after acute myocardial infarction. J Gerontol Ser A Biol Med Sci 61(7):713–717. https://doi.org/10.1093/gerona/61.7.713
77. Lazzeroni D, Castiglioni P, Bini M, Faini A, Camaiora U, Ugolotti PT, Centorbi CS, Brambilla L, Brambilla V, Piepoli MF, Coruzzi P (2017) Improvement in aerobic capacity during cardiac rehabilitation in coronary artery disease patients: is there a role for autonomic adaptations? Eur J Prev Cardiol 24(4):357–364. https://doi.org/10.1177/2047487316681341

78. Kleiger RE, Stein PK, Bigger JT (2005) Heart rate variability: measurement and clinical utility. Ann Noninvasive Electrocardiol 10(1):88–101. https://doi.org/10.1111/j.1542-474X.2005.10101.x
79. Billman GE (2013) The LF/HF ratio does not accurately measure cardiac sympatho-vagal balance. Front Physiol 4:26. https://doi.org/10.3389/fphys.2013.00026
80. Zucker IH, Schultz HD, Patel KP, Wang H (2015) Modulation of angiotensin II signaling following exercise training in heart failure. Am J Phys Heart Circ Phys 308(8):H781–H791
81. Huang P-H, Leu H-B, Chen J-W, Cheng CM, Huang CY, Tuan TC, Ding PYA, Lin SJ (2004) Usefulness of attenuated heart rate recovery immediately after exercise to predict endothelial dysfunction in patients with suspected coronary artery disease. Am J Cardiol 93(1):10–13. https://doi.org/10.1016/j.amjcard.2003.09.004
82. Smart NA, Steele M (2011) The effect of physical training on systemic proinflammatory cytokine expression in heart failure patients: a systematic review. Congest Heart Fail 17(3):110–114. https://doi.org/10.1111/j.1751-7133.2011.00217.x
83. Youn J-C, Lee HS, Choi S-W, Han SW, Ryu KH, Shin EC, Kang SM (2016) Post-exercise heart rate recovery independently predicts clinical outcome in patients with acute decompensated heart failure. PLoS One 11(5):e0154534. https://doi.org/10.1371/journal.pone.0154534
84. Haensel A, Mills PJ, Nelesen RA, Ziegler MG, Dimsdale JE (2008) The relationship between heart rate variability and inflammatory markers in cardiovascular diseases. Psychoneuroendocrinology 33(10):1305–1312. https://doi.org/10.1016/j.psyneuen.2008.08.007
85. Papaioannou V, Pneumatikos I, Maglaveras N (2013) Association of heart rate variability and inflammatory response in patients with cardiovascular diseases: current strengths and limitations. Front Physiol 4:174. https://doi.org/10.3389/fphys.2013.00174
86. Ramos S, Prata J, Bettencourt P, Gonçalves FR, Coelho R (2016) Depression predicts mortality and hospitalization in heart failure: a six-years follow-up study. J Affect Disord 201:162–170. https://doi.org/10.1016/j.jad.2016.05.024
87. Mommersteeg PM, Schoemaker RG, Naudé PJ et al (2016) Depression and markers of inflammation as predictors of all-cause mortality in heart failure. Brain Behav Immun 57:144–150. https://doi.org/10.1016/j.bbi.2016.03.012
88. Gathright EC, Goldstein CM, Josephson RA, Hughes JW (2017) Depression increases the risk of mortality in patients with heart failure: a meta-analysis. J Psychosom Res 94:82–89. https://doi.org/10.1016/j.jpsychores.2017.01.010
89. Gathright EC, Walter FA, Hawkins MA, Spitznagel MB, Hughes JW, Gunstad J (2016) Executive function moderates the relationship between depressive symptoms and resting heart rate variability in heart failure. J Behav Med 39(2):192–200. https://doi.org/10.1007/s10865-015-9684-8
90. Tu RH, Zeng ZY, Zhong GQ, Wu WF, Lu YJ, Bo ZD, He Y, Huang WQ, Yao LM (2014) Effects of exercise training on depression in patients with heart failure: a systematic review and meta-analysis of randomized controlled trials. Eur J Heart Fail 16(7):749–757. https://doi.org/10.1002/ejhf.101
91. Antunes-Correa LM, Kanamura BY, Melo RC, Nobre TS, Ueno LM, Franco FGM, Roveda F, Braga AM, Rondon MUPB, Brum PC, Barretto ACP, Middlekauff HR, Negrao CE (2012) Exercise training improves neurovascular control and functional capacity in heart failure patients regardless of age. Eur J Prev Cardiol 19(4):822–829. https://doi.org/10.1177/1741826711414626
92. Antunes-Correa LM, Melo RC, Nobre TS, Ueno LM, Franco FGM, Braga AMW, Rondon MUPB, Brum PC, Barretto ACP, Middlekauff HR, Negrao CE (2010) Impact of gender on benefits of exercise training on sympathetic nerve activity and muscle blood flow in heart failure. Eur J Heart Fail 12(1):58–65. https://doi.org/10.1093/eurjhf/hfp168
93. Antunes-Correa LM, Ueno-Pardi LM, Trevizan PF, Santos MR, da Silva CHP, Franco FGM, Alves MJNN, Rondon MUPB, Negrao CE (2017) The influence of aetiology on the benefits of exercise training in patients with heart failure. Eur J Prev Cardiol 24(4):365–372. https://doi.org/10.1177/2047487316683530
94. Ueno LM, Drager LF, Rodrigues AC et al (2009) Effects of exercise training in patients with chronic heart failure and sleep apnea. Sleep 32(5):637–647. https://doi.org/10.1093/sleep/32.5.637
95. Groehs RV, Antunes-Correa LM, Nobre TS, Alves MJNN, Rondon MUPB, Barreto ACP, Negrão CE (2016) Muscle electrical stimulation improves neurovascular control and exercise tolerance in hospitalised advanced heart failure patients. Eur J Prev Cardiol 23(15):1599–1608. https://doi.org/10.1177/2047487316654025
96. Negrao CE, Middlekauff HR, Gomes-Santos IL, Antunes-Correa LM (2015) Effects of exercise training on neurovascular control and skeletal myopathy in systolic heart failure. Am J Phys Heart Circ Phys 308(8):H792–H802
97. Groehs RV, Toschi-Dias E, Antunes-Correa LM et al (2015) Exercise training prevents the deterioration in the arterial baroreflex control of sympathetic nerve activity in chronic heart failure patients. Am J Phys Heart Circ Phys 308(9):H1096–H1102
98. (2017) Mechanisms and management of exercise intolerance in older heart failure patients. Retrieved from http://clinicaltrials.gov/ct
99. von Haehling S, Hasenfuß G, Anker SD (2016) Diabetes and heart failure. J Am Coll Cardiol 68(13):1417–1419. https://doi.org/10.1016/j.jacc.2016.07.728
100. Barak OF, Klasnja A, Popadic Gacesa J, Grujic NG (2014) Gender differences in parasympathetic reactivation during recovery from Wingate anaerobic test. Period Biol 116(1):53–58
101. Billman GE, Huikuri HV, Sacha J, Trimmel K (2015) An introduction to heart rate variability: methodological considerations and clinical applications. Front Physiol 6:55. https://doi.org/10.3389/fphys.2015.00055

Online Supplementary Material

- 10741_2017_9662_MOESM1_ESM.docx

- 10741_2017_9662_MOESM2_ESM.docx

Supplementary File 1

Supplementary Tables

Exercise therapy and autonomic function in heart failure patients: a systematic review and meta-analysis

Pearson, M.J and Smart, N.A.

Supplementary Table S1 Overview of studies excluded from the review that have investigated HRR, HRV and MSNA pre and post exercise intervention

Study	Reason for Exclusion
Adamopoulos (1992)	Crossover, no separate control group
Adamopoulos (1995)	Crossover, no separate control group
Antunes-Correa (2010)	Retrospective Analysis of Previous RCTs – data already included
Antunes-Correa (2011)	Retrospective Analysis of Previous RCTs – data already included
Antunes-Correa (2016)	Retrospective Analysis of Previous RCTs – data already included
Coats (1992)	Crossover, no separate control group
Dimopoulos (2006)	Randomised Comparator, no sedentary control
Dobsak (2012)	Randomised Comparator, no sedentary control
dos Santos (2016)	RCT of Exercise & Testosterone intervention vs. exercise vs. testosterone, but no usual care only group
European Heart Failure Training Group (1998)	Analysis of Combined Crossover Studies (Coats & Adamopoulos)
Groehs (2015)	Retrospective Analysis of Previous RCTs of unit – data likely already included
Groehs (2016)	RCT <4 week intervention
Iellamo (2013)	Randomised comparator, no usual care control group, no relevant HRV outcome
Jancik (2004)	Observational Cohort, no control group
Koufaki (2014)	Randomised Comparator, no sedentary control
Larsen (2004)	Cohort, no control group
Laoutaris (2008)	Randomised Comparator, no sedentary control
Pietila (2002)	Cohort, no control group
Piotrowicz (2009)	Cohort, Prospective, no control group
Piotrowicz (2015)	Data already included – Piotrowicz (2016)
Radaelli (1979)	Crossover Trial, no separate control group
Streuber (2006)	Cohort, Retrospective, no control group
Teffaha (2011)	Randomised Comparator, no sedentary control, <4 week intervention
Ueno (2009)	Prospective Interventional, no usual care group

Supplementary Table S2. HRR Assessment methods

Study	Assessment Method
Fraga (2007)	HRR defined as the reduction in heart rate levels from the peak of exercise and the first minute of recovery. CPET performed on cycle ergometer. No details on active or passive recovery or body position.
Keyhani (2013)	HRR_1 was determined as the difference between HR at peak exercise and HR 1 minute after completion of exercise. Participants were instructed to sit after ending the test to determine HRR. There was no cool-down until after HRR was recorded. CPET performed on a treadmill
Myers (2007)	HRR_1 – HRR_6 was determined during active recovery at minutes 1 through to minute 6. CPET performed on cycle ergometer
Tsarouhas (2011)	HRR_1 was determined in the first minute after exercise test. CPET performed on a treadmill. Recovery protocol - all patients remained in the supine position for the recovery period.
Yaylali (2015)	HRR_1 and HRR_2 defined as the difference between heart rate at peak exercise and exactly 1 and 2 minutes into recovery period. Recovery protocol – participants underwent a 3-minute cool-down period, starting at 30 watts and decreasing by 10 watts per minute. CPET performed on cycle ergometer

Supplementary Table S3. HRV Assessment Methods

Study	Assessment Method
Cider (1997)	24hr. Holter recording digested on a Marquette series 8000 Holter Scanner.
Killavuori (1995)	20 Hr. ambulatory ECG recorded during an ordinary non-exercise day. Starting at 12pm and ending at 8am. Fast Fourier transformation to process beta-to-beat fluctuations. HF: 0.15-0.4 Hz, LF: 0.04-0.15 Hz, VLF: 0.003-0.04Hz. HF, LF and LF/HF determined for each hour. In addition LF/HF, VLF/HF determined during day when patients active and sedentary. Sedentary period determined as the stable low heart rate below daytime average and action period was stable heart rate above daytime average. Daytime 1200-2200hrs, night-time 2200-0800hrs.
Krishna (2014)	Short continuous ECG. Recording at 8am following 10 minutes of supine rest and ECG acquired at rate of 200 samples/second for 10 minutes with normal breath rate of 12-18 breaths per minutes. Data transformed by Fast Fourier Transformation.
Malfatto (2002)	Short continuous ECG. HRV in time and frequency domain assessed during 1) 10 min quiet supine resting and free breathing, 2) 10 min of regular breathing at frequency of 10/min and 3) 10 minutes of active standing. Autoregressive power spectrum. VLF: 0.0-0.3 Hz, LF: 0.03-0.15 Hz, HF: 0.15-0.4 Hz. Converted to normalised units.
Mello (2012)	Digital Photoplethysmograph device utilised for 10 minutes, from which beat-by-beat time series of pulse (pulse interval/R-R interval) were extracted. Power spectral density of the R-R interval was obtained by Fast Fourier Transformation using Welch's method. Spectral bands: VLF: 0.0-0.04 Hz, LF: 0.04-0.15 Hz, HF: 0.15-0.4 Hz. Spectral power calculated as absolute values and normalised values
Murad (2012)	Short continuous ECG. Patient's supine for 15 minutes, then a supine resting 10 minute ECG recording obtained.
Piotrowicz (2016)	24 Hr. ambulatory ECG. Frequency domain indices were calculated after FFT of five 10-minute ECG segments recorded between 2am and 6am. HF: 0.15-0.4 Hz, LF: 0.04-0.15 Hz
Ricca-Mallada (2012)	Short continuous ECG. All recordings collected between 9am and 11am to avoid circadian-related HRV differences. Patients rested in supine position for 30 minutes @ 22-23 degrees C. Last 12 minutes from ECG taken. Continuous ECG were obtained by means of a polysomnography instrument.
Ricca-Mallada (2017)	Short continuous ECG. All recordings collected between 9am and 11am to avoid circadian-related HRV differences. Patients rested in supine position for 30 minutes @ 22-23 degrees C. Continuous ECG were obtained by means of a polysomnography instrument First 10 minutes deemed resting period and following 20 minutes a recording period. A 12 minute window of the ECG was analysed minutes from ECG taken. HF: 0.15-0.4 Hz, LF: 0.04-0.15 Hz.
Selig (2004)	Short continuous ECG. Patients underwent a supine 20 minute ECG recording, preceded by 10 minutes rest. HF: (15-0.4 Hz) was normalised over the spectrum HFnu=HF/ (TP-VLF), LF: (0.05-0.15 Hz) normalised over the spectrum LFnu= LF/(TP-VLP).
Yeh (2008)	24 Hr. ambulatory ECG. Series 8500 Holter monitor. Frequency domain spectra calculated using Lomb periodogram for unevenly sampled data. VLF: 0.003-0.04 Hz, LF: 0.04-0.15 Hz, HF: 0.15-0.4Hz.

Supplementary Table S4. Summary of Main Findings Time and Frequency Domain Parameters in Long-term HRV recordings

Author	Main Findings Time and Frequency Domain Parameters in Long-term HRV recordings
Cider (1997)	Frequency and Time Domain No specific details of parameters measured No statistically significant change in an parameter
Kiilavuori (1995)	Frequency Domain *HF(ms)* ↑HF over entire 20-hr recording (p=0.005) in exercise group, due to:- • ↑HF during day • ↔HF during night ↑HF in 30 minute day time active and sedentary periods in exercise group ↔ in any HF in control group *LF(ms)* ↑LF over entire recording (p=0.001) in exercise group and ↑ LF in control group (p=0.02), due to: • ↑ during day (p=0.0001) exercise group • ↑ during day (p=0.005) control group ↔LF in 30 min sedentary or active periods *LF/HF* Over entire period trend for decrease (but not significant, p=0.10) in exercise group • ↓LF/HF during day (p=0.05) ↔LF/HF in 30 minute active or sedentary period(although trend for decrease in sedentary period p=0.06) ↑LF/HF in control group during day (p=0.02) and during night (p=0.03), but ↔ in active or sedentary periods
Piotrowicz (2016)	Frequency Domain *Log HF(ms^2/Hz)* ↑HF in exercise group pre vs. post (5.36±1.02 →5.68±0.94, p=0.0211) *Log LF(ms^2/Hz)* ↓LF in exercise group pre vs. post (5.93±0.87→5.67±0.98, p=0.0129) *LF/HF* ↓LF/HF in exercise group pre vs. post (2.06±1.14→1.19±0.80, p<0.0001) Time-Domain ↔SDNN (ms) in exercise group pre vs. post (120±28→124±27, p=ns)
Yeh (2008)	Frequency Domain *HF(ms^2/Hz)* ↔HF in exercise group pre vs. post (mean Δ 188.6±709.7, p=0.48) 24hr. HRV ↔HF in exercise group pre vs. post (mean Δ 878.3±2539.41, p=0.36) HRV during sleep *LF(ms^2/Hz)* ↔LF in exercise group pre vs. post (mean Δ 57.6±308.5, p=0.61) 24hr. HRV ↔LF in exercise group pre vs. post (mean Δ -209.5±344.6, p=0.13) HRV during sleep *LF/HF* ↔LF/HF in exercise group pre vs. post (mean Δ -0.5±1.2, p=0.24) 24hr. HRV ↔LF/HF in exercise group pre vs. post (mean Δ -0.7±1.2, p=0.16) HRV during sleep Time Domain ↔SDNN in exercise group pre vs. post (mean Δ 8.8±21.6, p=0.29) 24hr. HRV ↔SDNN in exercise group pre vs. post (mean Δ -9.7±20.7, p=0.23) HRV during sleep ↔RMSSD in exercise group pre vs. post (mean Δ4.2±8.8, p=0.22) 24hr. HRV ↔RMSSD in exercise group pre vs. post (mean Δ7.9±13.7, p=0.15) HRV during sleep ↔AVNN in exercise group pre vs. post (mean Δ16.3±37.2, p=0.26) 24hr. HRV ↔AVNN in exercise group pre vs. post (mean Δ31.4±87.2, p=0.34) HRV during sleep ↔pNN30 in exercise group pre vs. post (mean Δ2.3±6.9, p=0.37) 24hr. HRV ↓pNN30 in exercise group pre vs. post (mean Δ10.2±12.1, p=0.049) HRV during sleep

AVNN: average of all normal sinus to normal sinus (NN) intervals, HF: high frequency, HRV: heart rate variability, LF: low frequency, LF/HF: low frequency, high frequency ratio, pNN30: percentage of differences between adjacent NN intervals that are >30ms RMSSD: square root of mean of squares of differences between adjacent NN intervals, SDNN: standard deviation of all NN intervals, ↑ Statistically significant increase, ↓ Statistically significant decrease, ↔ no significant change

Supplementary Table S5 Intervention Adherence and Adverse Events

Study	Intervention Attendance	Adverse Events
Antunes-Correa (2014)	No details of number of sessions attended	No details of any adverse events related to training *During intervention period:* Training Group: 11 HF decompensation (n=4 MI), 2 non-cardiovascular events, 1 death Control group: 11 HF decompensation (n=3 MI), 3 non-cardiovascular events, 1 death
Cider (1997)	Mean compliance 75% (65-100% range)	Training group: 1 patient Asthma attack requiring hospitalisation, no details if this was related to training
De Mello Franco (2006)	No details of number sessions attended	No details of any adverse events related to training *During intervention period:* Training Group: 1 death @ 4 months Control Group: 2 deaths No other details of adverse events reported
Fraga (2007)	No details of number sessions attended	No details of any adverse events related to training
Keyhani (2013)	No details of number sessions attended	No details of any adverse events related to training
Krishna (2014)	No details of number sessions attended	Adverse events not reported in this publication, but safety of Yoga sessions reported in related publications[1], with no cardiac symptoms, cardiac problems or orthopaedic injuries during or in relation to yoga sessions
Kiilavuori (1995)	Sub study of a larger study. No details of compliance in Journal Article, however Thesis details compliance of supervised sessions as 85-100%	No details of any adverse events related to training. Adverse Events detailed in the larger study data as a whole, one patient hospitalised in control group 1.5 months after start
Malfatto (2002)	No details of number sessions attended	No details of any adverse events related to training
Mello (2012)	No details of number sessions attended	No details of any adverse events related to training
Murad (2012)	Average number of sessions 89.1%	No details of any adverse events related to training Adverse events reported in the two studies from which data was drawn[2,3]
Myers (2007)	No details of number sessions attended	No details of any adverse events related to training
Nobre (2016)	> 80% of scheduled sessions attended	No details of any adverse events during training *During intervention period:* Training group: 1 orthopaedic problem, 2 arrhythmia Control group: 1 death, 2 stroke
Piotrowicz (2016)	Details reported in main study paper[4] 94.7% patients completely adherent, 5.3% partly adherent	Details reported in main study paper[4] No major adverse events
Ricca-Mallada (2012)	No details of number sessions attended	No details of any adverse events related to training
Ricca-Mallada (2017)	No details of number sessions attended	No details of any adverse events related to training *During intervention period:* Training Group: 1 patient developed a transient AF Control group: 7/18 patients suffered an adverse event: 1 patient developed permanent AF, 2 patients were admitted for acute heart failure and 2 patients were admitted for angina. 2 Deaths
Roveda (2003)	85% to 98% of exercise sessions attended	No adverse events
Selig (2004)	Adherence was monitored as attendance, but no details of number sessions attended	No details of any adverse events related to training *During intervention period:* Training group: 1 sudden death at home
Tsarouhas (2011)	Exercise adherence monitored using pedometers, mean walking steps: 15740±8800	No details of any adverse events related to training
Yaylali (2015)	No details of number sessions attended	No details of any adverse events related to training
Yeh (2008)	Sub study of Yeh 2004, details reported in Yeh 2004[5] 83% attendance (20/24 classes) & 93% practiced mean of 86 minutes per week at home	Sub study of Yeh 2004, details reported in Yeh 2004[6]. No adverse events during tai chi session n=1 Tai Chi, n=4 control hospitalised during study for exacerbation of heart failure symptoms.

1. Krishna BH, Pal P, Pal GK, et al. A randomized controlled trial to study the effect of yoga therapy on cardiac function and N terminal pro BNP in heart failure. *Integrative medicine insights.* 2014;9:1.
2. Brubaker PH, Moore JB, Stewart KP, Wesley DJ, Kitzman DW. Endurance Exercise Training in Older Patients with Heart Failure: Results from a Randomized, Controlled, Single-Blind Trial. *Journal of the American Geriatrics Society.* 2009;57(11):1982-1989.
3. Kitzman DW, Brubaker PH, Morgan TM, Stewart KP, Little WC. Exercise training in older patients with heart failure and preserved ejection fraction. *Circulation: Heart Failure.* 2010;3(6):659-667.
4. Piotrowicz E, Zieliński T, Bodalski R, et al. Home-based telemonitored Nordic walking training is well accepted, safe, effective and has high adherence among heart failure patients, including those with cardiovascular implantable electronic devices: a randomised controlled study. *European journal of preventive cardiology.* 2015;22(11):1368-1377.
5. Yeh GY, Wood MJ, Lorell BH, et al. Effects of tai chi mind-body movement therapy on functional status and exercise capacity in patients with chronic heart failure: a randomized controlled trial. *The American journal of medicine.* 2004;117(8):541-548.
6. Yeh GY, Mu L, Davis RB, Wayne PM. Correlates of exercise self-efficacy in a randomized trial of mind-body exercise in patients with chronic heart failure. *Journal of Cardiopulmonary Rehabilitation and Prevention.* 2016;36(3):186-194.

Supplementary Table S6 Assessment of study quality and reporting using TESTEX

Study	Eligibility Criteria specified	Randomisation details specified	Allocation concealed	Groups similar at baseline	Assessors blinded	Outcomes measures assessed >85% participants #	Intention to treat analysis	Reporting between group statistical comparison *	Point measures & measures of variability	Activity monitoring in control group	Relative exercise intensity review	Exercise volume & Energy expenditure	Overall TESTEX (/15)
RCTs													
Antunes-Correa (2014)	1	0	0	1	1	1	0	2	1	1	1	0	9
Cider (1997)	1	0	0	1	0	3	0	2	1	0	1	0	9
De Mello Franco (2006)	1	0	0	1	0	2	0	2	1	0	0	0	7
Fraga (2007)	1	0	0	1	1	1	1	2	1	1	1	0	10
Keyhani (2013)	1	0	0	1	0	1	0	2	1	0	0	0	6
Krishna (2014)[(1)]	1	0	0	1	0	1	0	2	1	0	0	0	6
Kiilavuori (1995)	1	0	0	1	0	2	0	0	1	0	1	0	6
Murad (2012)	1	0	0	1	1	1	0	2	1	0	1	1	9
Myers (2007)	1	0	0	1	0	1	1	2	1	0	0	0	7
Nobre (2016)	1	0	0	1	1	2	0	2	1	1	0	0	9
Piotrowicz (2016)[(2)]	1	1	0	1	0	3	0	2	1	0	0	0	9
Ricca-Mallada (2012)	1	0	0	1	1	0	0	2	1	0	0	0	6
Ricca-Mallada (2017)	1	0	0	1	1	3	0	1	1	0	0	0	8
Roveda (2003)	1	0	0	1	1	3	1	2	1	1	1	0	12
Selig (2004)	1	0	0	1	0	2	0	2	1	1	0	0	8
Yaylali (2015)	1	1	1	1	0	0	0	2	1	0	0	0	7
Yeh (2008)[(3)]	1	1	1	1	1	3	1	2	1	1	0	0	13
Non- Randomised													
Malfatto (2002)	1	NA	NA	1	0	1	1	1	1	0	0	0	6
Mello (2012)	1	NA	NA	1	1	1	1	2	1	0	1	0	7
Tsarouhas (2011)	1	NA	NA	1	0	1	0	1	1	0	0	0	5

Key: total out of 15 points. Legend: #three points possible—one point if adherence >85%, one point if adverse events reported, one point if exercise attendance is reported. *Two points possible—one point if primary outcome is reported, one point if all other outcomes reported. TESTEX, Tool for the assessment of Study quality and reporting in Exercise. 0 awarded if no mention was made of this criteria or if it was unclear. (1) (2) (3) Details from main study

Supplementary File 2

Supplementary Figures

Exercise therapy and autonomic function in heart failure patients: a systematic review and meta-analysis

Pearson, M.J. and Smart, N.A.

FOREST PLOTS

HEART RATE RECOVERY

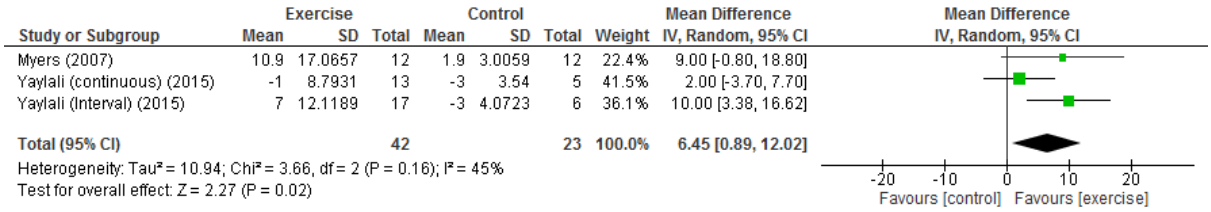


Fig. S1 - HRR_2bpm exercise vs. control

HEART RATE VARIABILITY PARAMETERS

Frequency Domain Measures

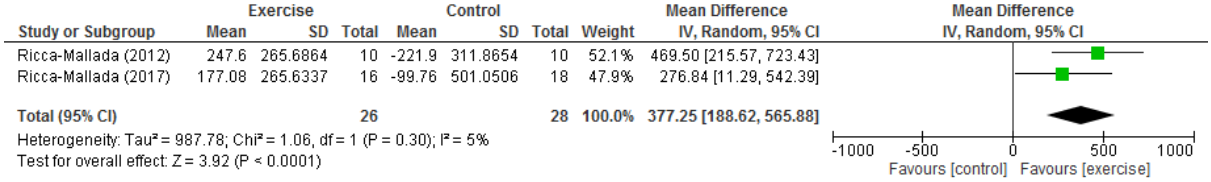


Fig. S2 - HF ms^2/Hz exercise vs. control

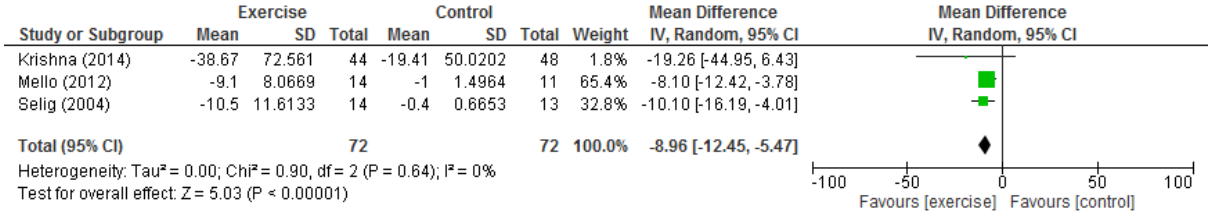


Fig. S3 - LF_{nu} exercise vs. control

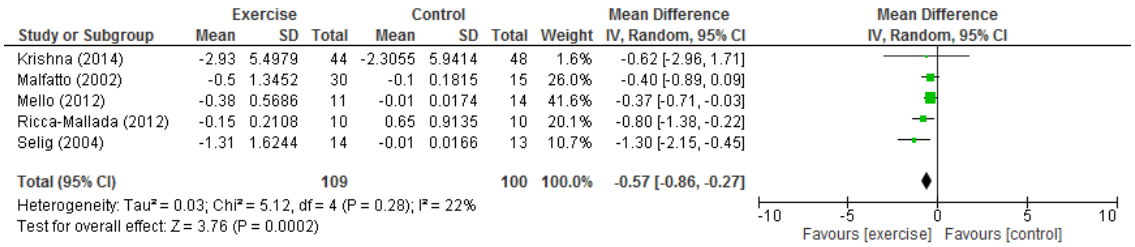


Fig. S4 - LF/HF exercise vs. control

Time-Domain Measures

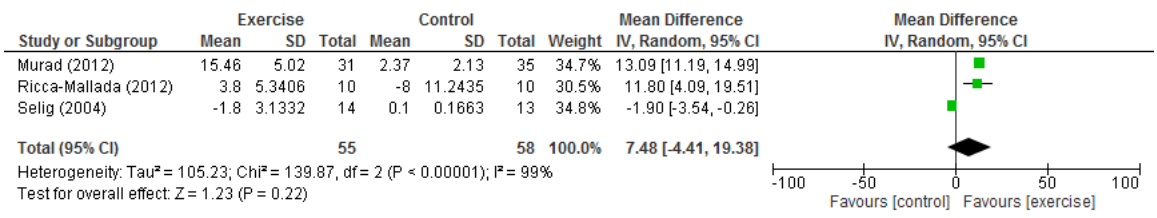


Fig. 5 - SDNN (ms) – Short term HRV exercise vs. control

6 Chapter 6 - Peer reviewed publication: Effect of aerobic and resistance training on inflammatory markers in heart failure patients: systematic review and meta-analysis.

6.1 Manuscript Information

Pearson, M. J., Mungovan, S. F., & Smart, N. A. (2018). Effect of aerobic and resistance training on inflammatory markers in heart failure patients: systematic review and meta-analysis. *Heart Failure Reviews*, *23*(2), 209-223. https://doi.org/10.1007/s10741-018-9677-0

Submitted 13th December 2017, Accepted 19th January 2018, Available Online 2nd February 2018

20th June 2018

Candidate

Principal Supervisor 20th June 2018

6.2 Statement of author's contribution

Higher Degree Research Thesis by Publication

University of New England

STATEMENT OF AUTHORS' CONTRIBUTION

We, the PhD candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated in the *Statement of Originality*.

	Author's Name (please print clearly)	**% of contribution**
Candidate	Melissa Pearson	80%
Other Authors	Neil Smart	15%
	Sean Mungovan	5%

Name of Candidate: Melissa Jane Pearson

Name/title of Principal Supervisor: Professor Neil Smart

[redacted]

Candidate

20th June 2018
Date

[redacted]

Principal Supervisor

20th June 2018
Date

6.3 Statement of originality

Higher Degree Research Thesis by Publication

University of New England

STATEMENT OF ORIGINALITY

We, the PhD candidate and the candidate's Principal Supervisor, certify that the following text, figures and diagrams are the candidate's original work.

Type of work	**Page number(s)**
Systematic Review & Meta-analysis	139-168

Name of Candidate: Melissa Jane Pearson

Name/title of Principal Supervisor: Professor Neil Smart

20th June 2018

Candidate Date

20th June 2018

Principal Supervisor Date

6.4 Full manuscript as published

Heart Failure Reviews (2018) 23:209–223
https://doi.org/10.1007/s10741-018-9677-0

Effect of aerobic and resistance training on inflammatory markers in heart failure patients: systematic review and meta-analysis

M. J. Pearson[1] · S. F. Mungovan[2,3] · N. A. Smart[1]

Published online: 2 February 2018

Abstract

Elevated levels of pro-inflammatory markers are evident in patients with heart failure and are associated with disease severity and prognosis. Exercise training has been shown to reduce circulating levels of pro-inflammatory cytokines and other pro-inflammatory markers in healthy and clinical populations. The aim of the systematic review and meta-analysis was to investigate the effect of aerobic (AT) and resistance training (RT) interventions on circulating concentrations of inflammatory markers; tumour necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), C-reactive protein (CRP), fibrinogen, soluble intercellular adhesion molecule (sICAM) and soluble vascular adhesion molecule (sVCAM) in heart failure patients. We conducted database searches (PubMed, EMBASE and Cochrane Trials Register to 30 June 2017) for exercise-based trials in heart failure, using the following search terms: exercise training, inflammation, tumour necrosis factor-alpha, interleukin 6, C-reactive protein, fibrinogen, soluble intercellular adhesions molecule-1, soluble vascular adhesion molecule-1. Twenty studies, representing 18 independent trials, were included in the review. Pooled data of six studies indicated a minimally favourable effect of exercise training on circulating TNF-α [SMD 0.42 (95% CI 0.15, 0.68), $p = 0.002$)]. However, together the pooled and descriptive analyses failed to provide strong evidence for a reduction in other pro-inflammatory markers. However, given the complexity of heart failure and the pathways involved in the immune and inflammatory process, large prospective trials considering aetiology, comorbidities and local skeletal muscle inflammation are required to elucidate on the anti-inflammatory effect of exercise in this population.

Keywords Heart failure · Inflammatory markers · TNF-α · IL-6 · CRP · Fibrinogen · sVCAM-1 · sICAM-1

Introduction

Chronic heart failure remains a major global health issue and leading cause of morbidity and mortality. While it is a complex clinical syndrome of multiple aetiologies, it is characterised by increased inflammation, evidenced by elevated levels of pro-inflammatory markers [1–3]. Furthermore, the association of inflammation with heart failure (HF) is evident irrespective of ejection fraction [1, 4], and elevated levels of pro-inflammatory markers are associated with disease severity and adverse outcomes [1, 5–7]. While the role of inflammation in the development and progression of HF is increasingly recognised, inflammation is likely both a cause and consequence, with HF phenotype and aetiology influencing factors [3, 4].

Inflammation is an essential immune response and a critical component of tissue repair [2, 8]. However, a persistence of inflammation beyond the initial repair, leading to chronically elevated levels of pro-inflammatory markers, exerts deleterious effects, including endothelial dysfunction, cardiac hypertrophy, left ventricular dysfunction, apoptosis and fibrosis [5], with associated functional consequences [2]. Furthermore, inflammation likely has a key role in skeletal muscle wasting and dysfunction [9, 10]. A number of mediators and signalling pathways are involved in the inflammatory response to injury or infection [2, 8], and in HF, the sources of the pro-

The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10741-018-9677-0) contains supplementary material, which is available to authorized users.

✉ M. J. Pearson
mpears23@myune.edu.au

[1] School of Science and Technology, University of New England, Armidale, NSW 2351, Australia

[2] Westmead Private Physiotherapy Services and The Clinical Research Institute, Sydney, Australia

[3] Department of Physiotherapy, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Melbourne, Australia

inflammatory markers, while not completely established, are believed to be numerous [9, 11]. Since Levine and colleagues (1990) [12] first reported increased levels of the circulating pro-inflammatory cytokine tumour necrosis factor-alpha (TNF-α) in HF patients compared to healthy controls, a growing number of inflammatory markers have been investigated in this population.

Given the recognition of inflammation in the progression of HF, pharmacological approaches to modify the inflammatory status have and continue to be investigated [5]. However, despite some improvements in left ventricular ejection fraction and symptoms, large trials have shown limited success [5]. It is well recognised that physical activity may reduce inflammation [13] and exercise training has demonstrated improvements in pro-inflammatory markers thereby establishing an "anti-inflammatory" effect in both healthy and clinical populations [14–17]. Exercise training is now an established and recommended therapeutic intervention in stable HF patients [18], conferring a range of benefits. Evidence from early studies to examine the effect of exercise training on pro-inflammatory markers in HF patients demonstrated improvements in circulating levels of numerous markers such as TNF-α [19, 20], IL-6 [19], sICAM and sVCAM [21]. Improvements in these markers were also associated with improved exercise capacity [19–21]. However, findings from studies since this time have been inconsistent [7]. Furthermore, published literature has also demonstrated that exercise training can lower other markers of inflammation such as C-reactive protein (CRP) in clinical populations [14, 16], including HF [22], but again the results have been inconsistent [23].

A previous systematic review of pro-inflammatory cytokines and exercise training in HF patients concluded that exercise training likely reduces TNF-α but not IL-6 [7]. This was supported by the analysis of pooled data from four studies [24]. However, a recent review [25] investigating the effects of exercise training on anabolic and catabolic markers in HF patients, which included circulating serum TNF-α and IL-6, among other outcomes, failed to find any statistically significant effect when data were pooled. Recently, evidence has emerged indicating that patients with different inflammatory profiles respond differently to exercise training, with VO_{2peak} improvements blunted in patients with higher levels of inflammatory markers [26]. An increasing number of controlled exercise training studies have explored the response of a number of pro-inflammatory markers to exercise training in HF patients. The aim of this review is to expand on the current body of literature firstly by updating the previous reviews, and where possible quantifying the effect of exercise training on TNF-α and IL-6. Secondly, we aimed to extend on the previous reviews by incorporating results from studies that examined a wider range of pro-inflammatory markers (CRP, fibrinogen, sICAM and sVCAM), that are elevated in HF patients, and associated with HF severity and adverse outcomes [27–30].

Methods

Search strategy

A systematic search of PubMed, EMBASE and the Cochrane Library of Controlled Trials up until 30 June 2017 was performed. Searches included a mix of MeSH and free text terms related to the key concepts of heart failure, exercise training and inflammatory makers. Additionally, systematic reviews, meta-analyses and reference lists of papers were hand searched for additional studies. One reviewer (MJP) conducted the search and full articles were assessed for eligibility by two reviewers (MJP and NAS).

Study selection

Study type and participants Randomised controlled trials and controlled trials of exercise training in adult HF patients were included. Heart failure type (i.e. preserved, moderately reduced and reduced ejection fraction) was not considered as inclusion or exclusion criteria.

Exercise intervention Exercise training interventions that utilised aerobic training (AT), resistance training (RT) or combined aerobic and resistance (CT) were included. The minimum length of the exercise interventions was ≥ 4 weeks, studies must have compared an exercise intervention to a usual care group and patients must not have been involved in a formal exercise intervention in the immediate 3 months prior to the study. Studies in which control groups were prescribed a specific amount of physical activity per day above usual current and daily activities were excluded.

Exclusion The following were excluded (1) articles for which abstracts only were available; (2) studies where patients were not clearly identified and reported as having HF; (3) studies where the exercise intervention was an adjunct intervention to another therapy, and no separate exercise group was incorporated; (4) non-English studies; and (5) randomised crossover trials.

Outcomes Studies were eligible to be included if they reported on one or more of the following inflammatory makers in serum or plasma: TNF-α, IL-6, CRP, fibrinogen, VCAM-1 and ICAM-1.

Data extraction

Data were extracted by two reviewers (MJP and SFM). We extracted all relevant data from studies that met the eligibility criteria: (1) author, year of publication and study design; (2) baseline demographic and clinical characteristics; (3) intervention characteristics; (4) pre- and post-intervention inflammatory marker concentrations or change in concentrations; (5) inflammatory marker assay and assessment methodology; and (6) adverse events and intervention compliance. No additional data was provided by the three authors contacted to provide additional information.

Data synthesis and analysis

Statistical analyses were performed using Revman 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark). Individual meta-analyses were completed for continuous data by using the change in the mean and standard deviation (SD). Where the change in mean and SD were not reported, the change in mean was calculated by subtracting the pre-intervention mean form the post-intervention mean, and Revman 5.3 enabled calculations of SD using number of participants in each group, within or between group p values or 95% CI. Where p values were not provided, the standard deviation of the mean difference was calculated using the formula: SD = square root $[(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$, assuming a correlation coefficient $(R) = 0.5$, which is considered a conservative estimate [31]. Data not provided in main text or tables were extracted from figures where possible.

Data were pooled for meta-analysis when two or more studies measured the same outcome and provided data in a format suitable for pooling. Where a study included multiple intervention groups and data were not provided for the combined intervention, data was entered separately for each group and the sample size of the control group was divided by the number of intervention groups to eliminate over inflation of the sample size. A random effects inverse variance was used with the effects measure of standardised mean difference (SMD). A decrease in pro-inflammatory markers following exercise training is presented as a positive effect size (ES). For interpretation of SMDs, the guideline of Cohen was applied, with an SMD of 0.2 considered a small ES, 0.5 as medium and ≥ 0.8 as a large ES [32]. We used a 5% level of significance and a 95% CI to report change in outcome measures. For studies included in the pooled analyses, in order to evaluate the influence of each study on the overall effect size, sensitivity analysis using the leave-one-out approach was conducted. For studies where the mean or SD of outcomes was not reported, but median, interquartile range (IQR) or median and range were reported, we performed a descriptive analysis, as this is usually an indication that data are skewed and hence non-normally distributed.

Heterogeneity and publication bias

Heterogeneity was quantified using the I^2 test [33]. Values range from 0% (homogeneity) to 100% (high heterogeneity) [33]. Funnel plots [34] assessed risk of publication bias.

Study quality and reporting

Study quality was assessed by using TESTEX; the Tool for assessment of study quality and reporting, designed specifically for use in exercise training studies [35]. This is a 15-point scale that assesses study quality (maximum 5 points) and reporting (maximum 10 points). Two reviewers (MJP and SFM) independently conducted the study quality and reporting assessment with discrepancies resolved by consensus with a third reviewer (NAS).

Results

The search identified 2190 manuscripts that were screened and evaluated for eligibility. After removal of duplicates and exclusion of articles based on abstract and title, we examined the remaining 45 full-text articles. A total of 20 articles met the inclusion criteria, representing 18 independent trials, and were therefore included in the systematic review (Fig. 1 PRISMA statement). Excluded studies with associated reasons are shown in Supplementary Table S1. Of the 20 included articles, 11 were suitable for meta-analyses.

Study characteristics

The main characteristics of the included studies are shown in Table 1. Studies were published between 2002 and 2017. Of the 18 independent trials, 15 were RCTs, 2 were controlled studies but not randomised and 1 trial randomised participants between three intervention groups, but the control group was not randomised.

Participants Altogether, the 18 independent trials provided 1665 participants (902 exercising and 763 controls), of which 928 of the participants (56%) were from a sub-study of the HF Action Trial [23]. In all but two [36, 37] studies, males comprised > 50% of the participants. In all trials except three [37–39], participants had a mean ejection fraction < 50%. Additional details of baseline inflammatory concentrations in exercise participants are shown in Supplementary Table 2.

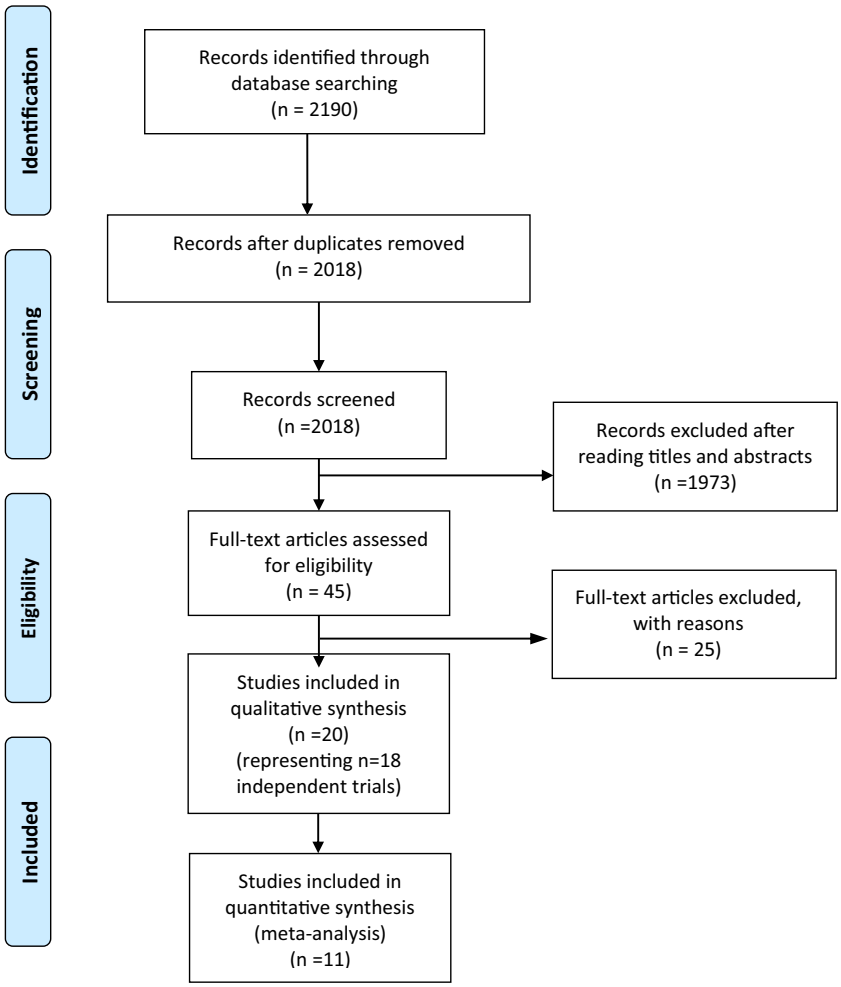


Fig. 1 PRISMA statement

Intervention details

A detailed description of exercise intervention characteristics is provided in Supplementary Table S3. The duration of exercise training interventions ranged from 4 weeks to 6 months. Of the 18 trials, 5 [26, 38, 40–42] included two separate HF exercise intervention groups and 1 [43] trial included three exercise intervention groups. Fourteen [22, 23, 26, 38–42, 44–49] trials included one or more intervention groups utilising AT. One [50] trial utilised RT only, CT was utilised in three [36, 37, 51] trials and one [43] trial included an AT group, a RT group and a CT group. Training frequency ranged from 2 to 7 days per week, session duration from 10 to 90 min and exercise intensity ranged from low to high.

Assay

Studies included in the review utilised a variety of assays. Assay details, methods of serum/plasma collection and preparation are provided in Supplementary Table S4.

Outcomes

Pre-intervention, post-intervention and/or change data were reported as mean ± SD or mean ± SEM in 11 studies [22, 36, 38, 39, 42, 43, 46, 48–50, 52], with 6 studies [23, 26, 37, 44, 45, 51] reporting data as median (IQR) or median (range). One study [40] reported data in graphical format and two [41, 47] additional studies did not report pre- and post-intervention data, simply noting no change post-intervention or compared to control. Summary of meta-analyses are provided in Table 2 and non-pooled analyses are provided in Table 3.

Pro-inflammatory cytokines

TNF-α Overall, 11 studies representing 10 independent trials reported on TNF-α concentration. Only six [36, 43, 46, 48, 49, 52] studies reported data suitable for pooling.

Meta-analysis: Pooled analysis of six [36, 43, 46, 48, 49, 52] studies with 244 participants (145 exercising, 99 controls) revealed a small but statistically significant improvement in TNF-α, exercise compared to control; SMD 0.42 (95% CI 0.15, 0.68), $p = 0.002$ (Fig. 2). The effect

Table 1 Studies included in the review that investigated the effects of exercise training on TNF-α, IL-6, CRP, Fibrinogen, ICAM, and VCAM

Study	Study design	Participants	Intervention	Main findings for TNF-α, IL-6, CRP, fibrinogen, ICAM, VCAM
Ahmad (2014) HF ACTION sub-analysis	RCT	*n* = 928 analysed E: *n* = 477 (68% male), 59 (51, 68) years, LVEF 25% (20, 30)%** C: *n* = 451 (73% male), 59 (51, 68) years, LVEF 25% (20, 31)%** NYHA Class II-III (< 1% IV)	Aerobic 3 months, 3 × week	↔hsCRP pre vs. post or between groups Data reported as median and IQR
Aksoy (2015)	RCT	*n* = 57 randomised, n = 45 analysed E1: *n* = 15 (87% male), 64 ± 9 years, LVEF 50 ± 7% E2: *n* = 15 (87% male), 60 ± 7 years, LVEF 52 ± 5% C: *n* = 15 (87% male), 58 ± 11 years, LVEF 52 ± 6% NYHA Class II-III	Aerobic, E1: interval, E2: continuous 10 weeks, 3 × week	↔hsCRP E1 or E2 pre vs. post, but ↓hsCRP in E2 compared to C ↓ Fibrinogen E2 pre vs. post, ↔E1 ↓ sICAM E2 pre vs. post, ↔ E1, ↔ between groups ↓sVCAM E1 pre vs. post, ↔E2, ↔ between groups
Byrkjeland (2011)	RCT	*n* = 80 randomised and analysed E: *n* = 40 (75% male), 69 ± 8 years, LVEF 30 ± 8% C: *n* = 40 (83% male), 72 ± 8 years, LVEF 31 ± 10% NYHA Class II-III	Aerobic 4 months, 2 × week	↔CRP, ↔IL-6 and ↔TNF-α, ↔ICAM, ↔ VCAM pre vs. post and no significant difference between groups Subgroup analysis: patients with IDCM aetiology: ↓ CRP pre vs. post and borderline significant in ICAM in E compared to C Data reported as median, 25th and 75th percentile
Conraads (2002)	Non-RCT	*n* = 41 allocated and analysed E: *n* = 23 (70% male), 57 (27–78) years, LVEF 27 (11–45)%** C: *n* = 18 (67% male), 70 (28–80) years, LVEF 28 (10–37)%** NYHA Class I-IV	Combined 4 months, 3 × week	↔IL-6, ↔TNF-α pre vs. post or E compared to C (↓sTNFR1 and ↓sTNFR2 pre vs. post in patients CAD aetiology) Data reported as median and range
De Meirelles (2014)	RCT	*n* = 30 randomised and analysed E: *n* = 15 (47% male), 54 ± 3 years, LVEF 31 ± 2% C: *n* = 15 (47% male), 55 ± 2 years, LVEF 32 ± 2% NYHA Class II-III	Combined 6 months, 3 × week	↓hsCRP pre vs. post and significant difference E compared to C ↓TNF-α pre vs. post and significant difference E compared to C ↓ Fibrinogen pre vs. post and significant difference E compared to C groups ↔IL-6
Eleuteri (2013)	RCT	*n* = 21 randomised and analysed E: *n* = 11 (100% male), 66 ± 2 years, LVEF 28 ± 2%* C: *n* = 10 (100% male), 63 ± 2 years, LVEF 30 ± 2%* NYHA Class II	Aerobic 3 months, 5 × week	↔CRP, ↔IL-6 pre vs. post or E compared to C Data reported as median and range
Erbs (2010)	RCT	*n* = 37 randomised *n* = 34 analysed E: *n* = 18 (100% male), 60 ± 11 years, LVEF 24 ± 5% C: *n* = 19 (100% male), 62 ± 10 years, LVEF 25 ± 4% *NB: age, LVEF based on *n* = 37 NYHA Class III(b)	Aerobic 12 weeks, daily + one group session weekly	↓ TNF-α in E compared to C
Feiereisen (2013)	RCT[a]	*n* = 60 randomised and analysed E1: *n* = 15 (73% male), 59 ± 7 years, LVEF 25 ± 5% E2: *n* = 15 (87% male), 61 ± 6 years, LVEF 23 ± 4%	E1 endurance, E2 combined E3 strength 40 sessions, 3 × week	All groups combined (E1, E2, E3) ↓IL-6 pre vs. post and compared to C ↓ TNF-α pre vs. post, but ↔ compared to C

Table 1 (continued)

Study	Study design	Participants	Intervention	Main findings for TNF-α, IL-6, CRP, fibrinogen, ICAM, VCAM
		E3: $n = 15$ (93% male), 58 ± 6 years, LVEF 24 ± 7% C: $n = 15$ (87% male), 56 ± 8 years, LVEF 25 ± 6% NYHA Class II-III		By training modality ↓IL-6 in E1, E2, borderline ↓E3 pre vs. post ↔TNF-α E1, E2, E3 (however TNF decreased, with borderline statistical significance) pre vs. post
Fernandes-Silva (2017)	RCT	$n = 52$ randomised, $n = 44$ analysed E: $n = 28$ (50% male), 51 ± 7 years, LVEF 30 ± 6% C: $n = 16$ (62% male), 48 ± 7 years, LVEF 29 ± 7% NYHA Class I-III	Aerobic (interval and continuous groups) 12 weeks, 3 × week	↔IL-6 and ↔TNF-α for changes between E and C Data reported as median, 25th and 75th percentile
Fu (2013)	RCT	$n = 45$ randomised and analysed E1: $n = 15$ (67% male), 68 ± 2 years, LVEF 38 ± 4%* E2: $n = 15$ (60% male), 66 ± 7 years, LVEF 39 ± 5%* C: $n = 15$ (67% male), 68 ± 3 years, LVEF 38 ± 4%* NYHA Class II-III	Aerobic, E1: interval training, E2: moderate continuous training 12 weeks, 3 × week	↓IL-6 pre vs. post, and compared to C in E1, ↔IL-6 in E2
Gielen (2003)	RCT	$n = 20$ randomised and analysed E: $n = 10$ (100% male), 55 ± 2 years, LVEF 26 ± 3%* C: $n = 10$ (100% male), 53 ± 3 years, LVEF 25 ± 2%* NYHA Class II-III	Aerobic 6 months, daily and one weekly group session	↔TNF-α, ↔ IL-6 ↓ TNF-α mRNA and ↓ IL-6 mRNA Post-intervention data not reported for TNF-α and IL-6
Helmy (2013)	RCT	$n = 40$ randomised and analysed E: $n = 20$ (100% male), 56 ± 3 years, LVEF 35 ± 2% C: $n = 20$ (100% male), 55 ± 3 years, LVEF 34 ± 2% NYHA Class II-III	Resistance training 12 weeks, 3 × week	↔IL-6 pre vs. post or between groups
Kitzman (2016)	RCT	$n = 51$ randomised and $n = 46$ completed[b] E: $n = 26$ (81% women), 68 ± 6 years, LVEF 61 ± 6% C: $n = 25$ (80% women), 66 ± 5 years, LVEF 63 ± 6% NYHA Class II-III	Aerobic 20 weeks, 3 × week	↔hsCRP, ↔IL-6
LEICA Study Gielen (2012) and Sandri (2015)	RCT	$n = 60$ randomised and analysed E1 (< 55 years): $n = 15$ (80% male), 50 ± 5 years, LVEF 27 ± 6%* C1 (< 55 years): $n = 15$ (87% male), 49 ± 5 years, LVEF 28 ± 5%* E2 (> 65 years): $n = 15$ (80% male), 72 ± 4 years, LVEF 29 ± 6%* C2 (> 65 years): $n = 15$ (80% male), 72 ± 3 years, LVEF 28 ± 6%* NYHA Class II-III	Aerobic 4 weeks, 4 sessions per weekday, + one weekly group session	↔TNF-α, ↓TNF-α mRNA (skeletal muscle) ↔sICAM, ↔sVCAM
Linke (2005)	RCT	$n = 23$ randomised, $n = 21$ analysed E: $n = 12$ (100% male), 55 ± 2 years, LVEF 26 ± 3%* C: $n = 11$ (100% male), 52 ± 3 years, LVEF 27 ± 3%* NYHA Class II-III	Aerobic 6 months, daily + one weekly group session	↔TNF-α, ↓TNF-α mRNA (skeletal muscle) for change E vs. C. ↓TNF-α protein expression pre vs. post in E
Parrinello (2009)	RCT	$n = 22$ randomised and analysed E: $n = 11$ (73% male), 62 ± 5 years, LVEF 39 ± 4% C: $n = 11$ (64% male), 63 ± 5 years, LVEF 39 ± 4% NYHA Class II-III	Aerobic 10 weeks, 5 × week	↓hsCRP and significant difference between end values in favour of E
Trippel (2016) Post hoc analysis of EX-DHF Trial	RCT	$n = 67$ randomised, $n = 64$ analysed, $n = 62$ analysed for inflammatory markers E: $n = 44$ (43) (44% male), 64 ± 8 years, LVEF 68 ± 7% C: $n = 20$ (19) (44% male), 65 ± 6 years, LVEF 67 ± 7%	Combined, 12 weeks, initially aerobic 2 × week,	↔IL-6, ↔TNF-α Data reported as median and IQR

Table 1 (continued)

Study	Study design	Participants	Intervention	Main findings for TNF-α, IL-6, CRP, fibrinogen, ICAM, VCAM
		NYHA Class II-III	at week 5 increase to 3 × week plus RT 2 × week	
Tsarouhas (2011)	Non-RCT	*n* = 39 allocated and analysed E: *n* = 27 (74% male), 67 ± 13 years, LVEF 31 ± 4% C: *n* = *n* (75% male), 67 ± 6 years, LVEF 31 ± 5% NYHA Class II-III	Aerobic 12 weeks, 5 × week	↓TNF-α in E
Wisloff (2007)	RCT	*n* = 27 randomised, *n* = 26 analysed E1: *n* = 9 (78% male), 77 ± 9 years, LVEF 28 ± 7% E2: *n* = 9 (78% male), 74 ± 12 years, LVEF 33 ± 5% C: *n* = 9 (67% male), 76 ± 13 years, LVEF 26 ± 8%	Aerobic, E1 aerobic interval training, E2 moderate continuous training 12 weeks, 3 × week	↔ hsCRP in E1 or E2 Individual group pre-post data not reported

All data mean ± SD unless otherwise noted: *SEM, **median (IQR) or median (range), (1) 15 control patients were not randomised. (2) Only includes the exercise only and control only groups; excludes diet and diet+ exercise groups

AIT aerobic interval training, *ADMA* asymmetric dimethylarginine, *CAD* coronary artery disease, *CAE* continuous aerobic exercise, *C* control, *CRP* C-reactive protein, *DCM* dilated cardiomyopathy, *E* exercise group, *E1* exercise group 1, *E2* exercise group 2, *FES* functional electrical stimulation, *HIIT* high-intensity interval training, *hsCRP* high sensitivity C-reactive protein, *HT* hypertension, *IAE* intermittent aerobic exercise, *ICM* ischemic cardiomyopathy, *IDCM* idiopathic dilated cardiomyopathy, *IHD* ischemic heart disease, *IL-6* interleukin-6, *IL-1β* interleukin-1beta, *IL-10* interleukin-10, *IMT* inspiratory muscle training, *LVEF* left ventricular ejection fraction, *NMES* neuromuscular electrical stimulation, *MCT* moderate continuous training, *MI* myocardial infarction, *NYHA* New York Heart Association, *RCT* randomised control trial, *sICAM-1* soluble intercellular adhesion molecule-1, *sVCAM-1* soluble vascular cell adhesion molecule-1, *sTNFR-1* soluble tumour necrosis factor receptor 1, *sTNFR2* soluble tumour necrosis factor receptor 2, *TNF-α* tumour necrosis factor-alpha

[a] Fifteen control patients were not randomised

[b] Only includes the exercise only and control only groups; excludes diet and diet + exercise groups

Table 2 Summary of results of meta-analyses

Random model				Effect size		Heterogeneity
Marker	*n* = studies	*n* = exercise	*n* = control	SMD (95% CI)	*p* value	I squared
TNF-α	6	145	99	0.42 (0.15, 0.68)	0.002	0%
IL-6	4	110	65	0.41 (0.09, 0.72)	0.01	0%
CRP	3	56	41	1.61 (− 0.01, 3.23)	0.05	90%
Fibrinogen	2	45	30	0.40 (− 0.52, 1.32)	0.39	72%
sICAM-1	2	60	45	0.33 (− 0.13, 0.79)	0.16	25%
sVCAM-1	2	60	45	0.33 (− 0.07, 0.73)	0.10	0%

size remained small and statistically significant when sensitivity analysis using the leave-one-out approach was conducted (Supplementary Table S5).

Non-pooled studies: Five studies did not provide data suitable for pooling. Four [26, 37, 44, 51] studies comprised of 227 participants (149 exercising and 93 controls) reported data as median (IQR) or median (range). All failed to find a statistically significant effect of exercise on TNF-α concentrations post training or a significant difference to the control group. Additionally, the study of Gielen et al. (2003) [47] did not provide pre- and post-intervention data, simply noting no change.

Table 3 Summary of findings of studies unable to be pooled for meta-analysis

Study	Design	Intervention	*n* = exercise/control	Result
TNF-α				
Byrkjeland 2011	RCT	Aerobic	40/40	↔
Conraads 2002	Controlled	Combined	23/18	↔
Fernandez-Silva 2017	RCT	Aerobic	28/16	↔
Trippel 2017	RCT	Combined	43/19	↔
Gielen 2003[a]	RCT	Aerobic	10/10	↔
IL-6				
Byrkjeland 2011	RCT	Aerobic	40/40	↔
Conraads 2002	Controlled	Combined	23/18	↔
Eleuteri 2013	RCT	Aerobic	11/10	↔
Fernandez-Silva 2017	RCT	Aerobic	28/16	↔
Gielen 2003	RCT	Aerobic	10/10	↔
Kitzman 2016	RCT	Aerobic	26/25	↔
Trippel 2017	RCT	Combined	43/19	↔
CRP				
Ahmad 2014	RCT	Aerobic	477/451	↔
Byrkjeland 2011	RCT	Aerobic	40/40	↔, ↓ Subgroup IDCM aetiology
Eleuteri 2013	RCT	Aerobic	11/10	↔
Kitzman 2016	RCT	Aerobic	26/25	↔
Wisloff 2007	RCT	Aerobic	17/9	↔
ICAM				
Byrkjeland 2011	RCT	Aerobic	40/40	↔
VCAM				
Byrkjeland 2011	RCT	Aerobic	40/40	↔

↓ statistically significant decrease pre vs. post, ↔ no statistically significant change pre vs. post and/or compared to control

CRP C-reactive protein, *IDCM* idiopathic dilated cardiomyopathy, *IL-6* interleukin 6, *RCT* randomised controlled trial, *sICAM* soluble intercellular adhesion molecule, *sVCAM* soluble vascular adhesion molecule, *TNF-α* tumour necrosis factor-alpha

[a] Data from Linke et al. (2005) included in TNF-α meta-analysis

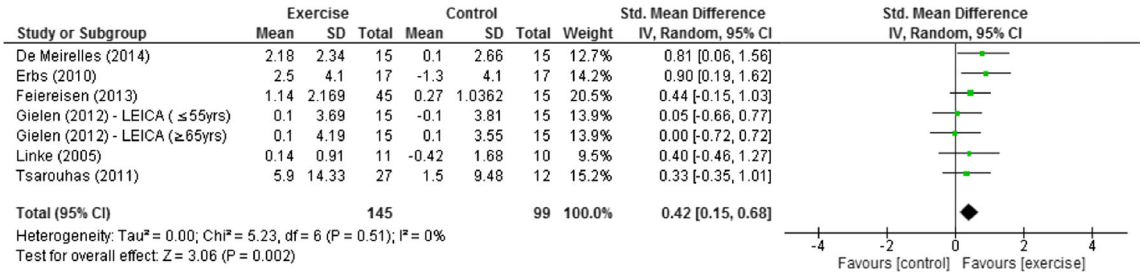


Fig. 2 Change in TNF-α exercise vs. control

IL-6 Overall, 11 studies reported on IL-6 concentrations; however, only four [36, 40, 43, 50] studies provided data suitable for pooling. An additional seven [26, 37, 39, 44, 45, 47, 51] studies (319 participants) measured IL-6 concentrations, however, due to differences in data reporting these were not pooled for analysis.

Meta-analysis: Four [36, 40, 43, 50] studies (five intervention groups) with 175 participants (110 exercising, 65 controls) demonstrated a small and statistically significant improvement in IL-6 concentrations in exercise compared to control; SMD 0.41 (95% CI 0.09, 0.72), $p = 0.01$ (Fig. 3). However, sensitivity analysis using the leave-one-out approach indicated the statistical significance of the results was due to the inclusion of the study by Feiereisen and Colleagues (2013) [43] (Supplementary Table S5).

Non-pooled studies: Five [26, 37, 44, 45, 51] studies reported data as median (IQR) or median (range). All failed to find a statistically significant effect of exercise on IL-6 concentrations post training or a significant difference compared to the control group. One additional study [39] reported mean post data and noted no significant difference between exercise and control groups and one [47] study simply noted no change in serum IL-6 concentrations.

Acute-phase reactants

CRP Eight [22, 23, 36, 38, 39, 41, 44, 45] studies reported on CRP concentrations, with only three [22, 36, 38] studies providing data suitable for pooling.

Meta-analysis: Pooled data from three [22, 36, 38] studies (four intervention groups) (56 exercising and 41 controls) demonstrated a borderline statistically significant improvement in CRP, exercise compared to control; SMD 1.61 (95% CI −0.01, 3.23), $p = 0.05$ (Fig. 4).

Non-pooled studies: Five [23, 39, 41, 44, 45] additional studies (1106 participants, of which 928 were from the one trial [23]) measured and reported CRP concentrations pre- and post-intervention. Three [23, 44, 45] of the studies, (1029 participants: 528 exercising and 501 controls) reported data as median (IQR) or median (range) and all failed to find a statistically significant effect of exercise on CRP post training or a significant difference compared to the control group. One [41] study did not report any individual group data but specifically noted no statistically significant change and one study [39] reported post mean data and noted no significant difference between exercise and control groups.

Fibrinogen *Meta-analysis*: Pooled data from two [36, 38] studies (three intervention groups) with 75 participants (45 exercising and 30 controls) failed to find a statistically significant improvement in fibrinogen; SMD 0.40 (95% CI −0.53, 1.32), $p = 0.39$ (Supplementary Fig. S1).

Adhesion molecules

ICAM *Meta-analysis*: Pooled data from two [38, 42] studies (four intervention groups) with 105 participants (65 exercising, 40 controls) failed to demonstrate a statistically significant change in sICAM in exercise vs. controls; SMD 0.33 (95% CI −0.13, 0.79), $p = 0.16$) (Supplementary Fig. S2)

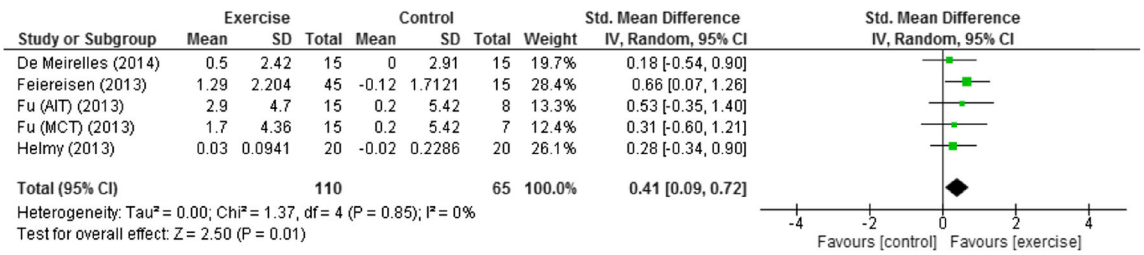


Fig. 3 Change in IL-6 exercise vs. control

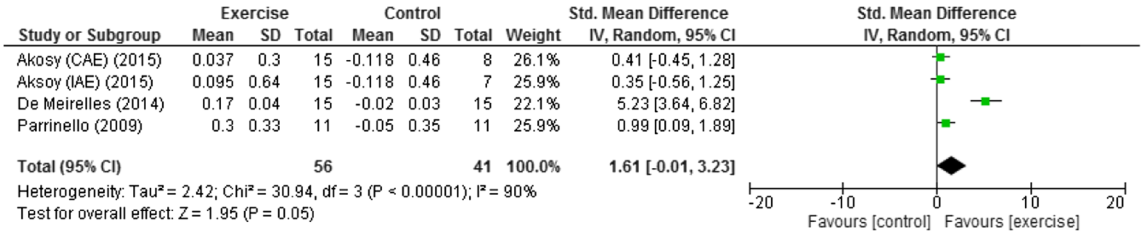


Fig. 4 Change in CRP exercise vs. control

Non-pooled studies: One [44] study reporting data as median (IQR) failed to find a statistically significant effect of exercise on ICAM.

VCAM *Meta-analysis*: Pooled data from two [38, 42] studies (four intervention groups) with 105 participants (65 exercising, 40 controls) failed to demonstrate a statistically significant change in exercise vs. controls; SMD 0.33 (95% CI −0.07, 0.73), $p = 0.10$ (Supplementary Fig. S3)

Non-pooled studies: One [44] study reporting data as median (IQR) failed to find a statistically significant effect of exercise on VCAM.

Adverse events and exercise session attendance/compliance

All but six studies reported on adverse events [22, 36, 40, 49–51] and compliance [22, 36, 47, 48, 50, 51] (Supplementary Table S6). Exercise training was safe, with no major adverse events during or as a result of the training intervention; excluding the HF Action sub group analysis, which did not provide details of adverse events specific to the participants utilised in the analysis of high sensitive C-reactive protein (hsCRP).

Assessment of study quality and reporting

The median TESTEX score was 10 (maximum 15) (Supplementary Table S7). While RCTs noted participant randomisation, details of the specific procedure were provided in less than half the studies.

Heterogeneity and publication bias

Visual inspection of funnel plot for meta-analysed studies suggested minimal evidence of publication bias.

Discussion

This work analysed the effects of exercise training on selected pro-inflammatory markers in patients with HF. The pooled analysis of TNF-α indicated a statistically significant improvement, consistent with earlier analyses [7, 24]. However, while meta-analysis of TNF-α demonstrated a small, but statistically significant improvement, this is inconsistent with data from studies that could not be pooled. The pooled data of IL-6 also demonstrated a small but statistically significant improvement; however, sensitivity analysis utilising the leave-one-out approach indicated that the study of Feiereisen et al. (2013) [43] heavily impacted the statistical significance of the result.

Pro-inflammatory cytokines Taking account of both our pooled and non-pooled analyses, it is difficult to provide robust and conclusive evidence that exercise training improves circulating concentrations of TNF-α in HF patients. Furthermore, together both our analyses of circulating IL-6 provide limited evidence for improvements from training interventions, in agreement with a previous review [24]. Larsen et al. (2001) [20] and Adamopoulos et al. (2002) [19] provided the early evidence for reductions in TNF-α, although the studies reported conflicting results in regard to IL-6. Importantly, our review only considered the effect of exercise training on circulating concentrations of TNF-α and IL-6. However, changes in serum or plasma may not reflect changes occurring at the level of skeletal muscle [47]. In addition to elevated circulating pro-inflammatory cytokine levels, the local muscular expression is also elevated in HF patients [47]. Reductions in the local expression of these pro-inflammatory cytokines (TNF-α mRNA, IL-6 mRNA) after training interventions have been observed in the absence of changes in circulating cytokines levels, albeit from only minimal trials to date in HF patients [47, 52]. However they may more accurately reflect the anti-inflammatory effect of exercise training [47, 52].

Acute-phase reactants Further amplifying the inflammatory response, IL-6 and TNF-α induce the synthesis of acute-phase proteins such as CRP and fibrinogen [53, 54]. As a non-specific marker of systemic inflammation, CRP is associated with increased risk of cardiovascular disease (CVD) [14, 16], is elevated in HF patients and associated with disease severity and prognosis [29]. Furthermore, elevated levels of CRP have been associated with reduced exercise capacity [55]. Both our pooled and descriptive analyses failed to find

strong evidence for a reduction in CRP. In considering the studies individually, only two of the eight studies reported a statistically significant reduction. While the majority of all studies are small which may account for non-significant results in some instances, no difference was observed between the exercise and control groups for hsCRP concentrations in a sub group analysis of the large HF Action Trial [23]. Furthermore, any reductions in hsCRP in this cohort were not associated with improvements in clinical outcomes [23]. In contrast to our findings, meta-analyses [14, 16] of controlled trials in both healthy adults and those with CVD demonstrate that exercise training decreases CRP. Weight loss may be associated with demonstrated CRP reductions after training interventions [14]. However, as not all studies included in our review provided relevant weight loss data, we were unable to analyse the effect of any weight loss on changes in CRP concentrations, and therefore we cannot discount the fact that changes in CRP may be reflective of changes or lack of changes in weight or fat. Interestingly though, all three [22, 36, 38] studies included in our pooled analysis of CRP reported statistically significant changes in weight or percentage body fat (%fat). A recent meta-analysis [14], however, indicates that while weight loss is a significant factor associated with CRP reductions, exercise training reduces CRP regardless of weight loss, albeit greater reductions occur with a decrease in weight and %fat.

In addition to being a major component of the coagulation pathway, fibrinogen is a major determinant of blood viscosity and platelet aggregation, and it is also considered a marker of inflammation [53]. Elevated levels of fibrinogen may increase the risk of thrombotic events and is associated with adverse prognosis in HF patients [56]. The possible anti-inflammatory effect of exercise on fibrinogen was not supported by our findings. However this is only representative of two [36, 38] studies, and individually, two of the three exercise intervention groups involved reported a statistically significant decrease in fibrinogen post-intervention, and De Meirelles et al. (2014) [36] observed a significant difference between groups. Recently, 4 weeks of stretching exercises was observed to significantly reduce fibrinogen in HF patients with implantable cardioverter defibrillators [57], while Mongirdiene et al. (2015) demonstrated that 1 year of training in HF patients also reduced fibrinogen concentration. In contrast to our result, a meta-analysis of patients with CVD reported a statistically significant decrease in fibrinogen in exercising patients compared to controls [58].

Adhesion molecules Our analysis failed to find a statistically significant improvement in sICAM and sVCAM; however, this only represents three [38, 42, 44] studies. Our result is in contrast to the earlier positive findings of Adamopoulos et al. (2001) [21]. Bjornstad and colleagues (2008) [59], in a pre-post study, failed to find any significant reduction in VCAM although improvements were observed in another adhesion molecule, P-selectin. In contrast, 6 weeks of functional electrical stimulation reduced sICAM and sVCAM in HF patients [60]. Cellular adhesion molecules are induced by pro-inflammatory markers such as TNF-α, IL-6 and CRP, expressed on endothelial cells, and are crucial to the recruitment of inflammatory cells to vessel walls [27]. sVCAM and sICAM are also considered markers of endothelial function; and despite no improvement in these two markers based on our analysis, exercise training has been shown to improve endothelial function as assessed by flow-mediated dilation [61].

The anti-inflammatory effect of exercise training is attributed to the chronic adaptations stimulated by regular acute bouts of exercise with various mediators involved [15, 62]. During an acute bout of exercise, IL-6 is released from contracting skeletal muscle, inducing elevations in circulating IL-6 concentrations; triggering an increase in a number of anti-inflammatory cytokines such as IL-10 and IL-1ra, which inhibit TNF-α and IL-1β [15, 63]. Exercise also likely inhibits TNF-α via IL-6 independent pathways [15, 62], such as exercise-induced increases in epinephrine which contribute to the anti-inflammatory effect of an acute exercise bout [15]. Exercise also exerts its anti-inflammatory effects via reduction in adiposity and changes within skeletal muscle, including upregulating anabolic myokines and reducing local inflammation [63]. While various mechanisms contribute to the induction of the anti-inflammatory environment from exercise training, the underlying signalling pathways are complex and yet to be completely elucidated [63].

Individually, while some studies found a positive effect of exercise training on selected inflammatory markers, a larger number of studies did not. A number of confounding factors may contribute to the contrasting results of studies, including disease severity, age [44], aetiology [44, 51], baseline inflammatory status, the inflammatory marker measured and comorbidities; these warrant careful consideration when designing future trials. Furthermore, intervention characteristics could account for differences between studies. We were unable to clearly identify any aspects of the interventions that may be more effective at improving the assessed inflammatory markers. Only 6 [22, 38, 40, 43, 46, 49] of the 15 AT intervention groups demonstrated a statistically significant reduction in any of the inflammatory markers post training or compared to controls. Compared to AT, studies on the impact of RT or CT on inflammatory status in HF patients are more scarce. Conflicting results were observed between the two [43, 50] RT intervention groups; notably training protocols differed in intensity. Interestingly, two [36, 43] of the four, intervention groups that utilised CT, demonstrated statistically significant or borderline significant reductions in several inflammatory markers. Additionally, while Conraads et al. (2002) [51] failed to find a reduction in TNF-α or IL-6 after

CT, they did observe reductions in soluble TNF receptors. Furthermore, CT has been suggested as possibly conferring greater improvements in inflammatory markers in some populations [64–67]. Given the exercise-mediated rise in IL-6 is related to the muscle mass involved and the intensity and duration of the exercise [15], it is possible that the combination of AT and RT is a greater stimulus. No pattern was observed for the possible effect of session duration or frequency. Across healthy and clinical populations, longer program duration [54], greater training frequency [7, 64], training modality [64, 65] and training intensity [65] including both moderate [68] and high [65, 69, 70] intensity are suggested as having a greater impact on improving a number of inflammatory markers. However, a recent analysis of CRP observed no significant association between frequency, duration or mode [14].

Exercise capacity Whether reductions in pro-inflammatory markers after exercise training is one of the mechanisms associated with improved exercise capacity remains unclear. Minimal studies included in the review assessed or reported on associations between reductions in circulating inflammatory concentrations and improved exercise capacity. Of note, in a large cohort of patients from the HF Action Trial [23], no association was observed between reductions in hsCRP and improvements in exercise capacity. The earlier cross over study of Adamopoulos et al. (2002) [19] demonstrated an association of change in VO_{2peak} with cytokines after 12 weeks of training; however, this finding is in contrast to pooled data of four later studies [24]. Of particular interest, Fernandes-Silva et al. (2017) [26], despite not finding a statistically significant change in TNF-α or IL-6 after 12 weeks of AT, observed that patients with low concentrations of these markers at baseline significantly improved VO_{2peak} compared to controls, highlighting a possible area for future research.

Generalisability Our review included HF patients irrespective of ejection fraction, as a correlation exists between elevated inflammatory markers and adverse outcomes across the HF spectrum [1, 3, 5]. However, only three [37–39] studies in our review included patients with a mean LVEF > 50% and only the study of Aksoy et al. (2015) [38] demonstrated any improvements in inflammatory markers. It is postulated that non-cardiac comorbidities drive HFpEF by inducing a pro-inflammatory state, leading to coronary microvascular endothelial dysfunction [4]. More studies are needed to address the degree of heterogeneity in HFpEF population, exploring the associations between comorbidities and the inflammatory response to exercise. It may be that the role of inflammation in HF may be different based on the presence and combination of different comorbidities [71] and this may mean exercise training may be a beneficial treatment from an "anti-inflammatory" perspective in particular subgroups of HF patients.

Strengths and limitations in the systematic review and meta-analysis

To our knowledge, this is the first systematic review and meta-analysis of controlled studies to evaluate the effect of exercise training on pro-inflammatory markers in HF patients. We aimed to provide a meta-analysis of studies reporting on a selected number of inflammatory markers. However, as inflammatory marker distributions can be skewed, study data may often be presented as median (IQR) or median (range), which precludes it from inclusion in meta-analyses. While the inclusion criteria of a systematic review and meta-analysis can stipulate that only those studies that report data as mean ± SD are included, valuable information may be ignored if a number of other studies are excluded. Upon our initial systematic review, and identification of a number of studies that had examined inflammatory markers and reported data as median, we felt that the inclusion of these studies would enhance the value of the analysis. Therefore, to avoid exclusion of valuable findings, we included results of studies reporting data that was considered inappropriate for pooling and provided a descriptive analysis of these studies. We acknowledge that a number of methods have been proposed and utilised to allow for median data to be included in meta-analysis, however, this is still based on the assumption that data are normally distributed [72]. In regard to data pooling, we measured the difference between pre-intervention and post-intervention means; however, in cases where exact *p* values within or between groups, or 95% CI were not available, we imputed the SD and this may introduce errors. Our imputation however, was conservative.

A number of studies were small, which may have resulted in them being underpowered to detect statistically significant changes. Cytokine concentrations may also be affected by methods used in collection and preparation of samples, time elapsed since previous exercise session and measurement in plasma or serum, and all may be a source of differences in results between studies [73]. Additionally, medication usage, particularly statins which are considered to have an anti-inflammatory effect [74], may have contributed to differing results and level of heterogeneity between studies. Abstracts and trials not reported in English were excluded and could have led to publication bias. We also included both RCTs and non-RCTs in this review.

Conclusion

While meta-analyses demonstrated a small but statistically significant reduction in TNF-α and IL-6, an overall analysis of all studies included in the review does not provide strong evidence for improvements in circulating concentrations of TNF-α, IL-6, CRP, fibrinogen, sICAM or sVCAM.

However, future trials quantifying the effect of exercise on the local expression of cytokines in skeletal muscle may provide more robust evidence for the anti-inflammatory effect of exercise in this population. Furthermore, we only included a selected number of inflammatory markers. This does not rule out the beneficial effect of exercise on other biomarkers involved in the immune and inflammatory pathways. Additionally, large prospective, multicentre trials, stratified according to aetiology, baseline inflammatory status and comorbidities may aid in the identification of groups of HF patients that would likely obtain an "anti-inflammatory" effect of exercise.

Acknowledgements M.J Pearson is supported by an Australian Postgraduate Award Scholarship. This work received no other financial support and has no relationship to industry.

Compliance with ethical standards

Conflict of interest The authors report no relationships that could be construed as a conflict of interest.

References

1. Dick SA, Epelman S (2016) Chronic heart failure and inflammation. Circ Res 119(1):159–176. https://doi.org/10.1161/CIRCRESAHA.116.308030
2. Briasoulis A, Androulakis E, Christophides T, Tousoulis D (2016) The role of inflammation and cell death in the pathogenesis, progression and treatment of heart failure. Heart Fail Rev 21(2):169–176. https://doi.org/10.1007/s10741-016-9533-z
3. Van Linthout S, Tschöpe C (2017) Inflammation—cause or consequence of heart failure or both? Curr Heart Fail Rep 14(4):251–265. https://doi.org/10.1007/s11897-017-0337-9
4. Paulus WJ, Tschöpe C (2013) A novel paradigm for heart failure with preserved ejection fraction. J Am Coll Cardiol 62(4):263–271. https://doi.org/10.1016/j.jacc.2013.02.092
5. Shirazi LF, Bissett J, Romeo F, Mehta JL (2017) Role of inflammation in heart failure. Curr Atheroscler Rep 19(6):27
6. Hartupee J, Mann DL (2013) Positioning of inflammatory biomarkers in the heart failure landscape. J Cardiovasc Transl Res 6(4):485–492. https://doi.org/10.1007/s12265-013-9467-y
7. Smart NA, Steele M (2011) The effect of physical training on systemic proinflammatory cytokine expression in heart failure patients: a systematic review. Congest Heart Fail 17(3):110–114. https://doi.org/10.1111/j.1751-7133.2011.00217.x
8. Medzhitov R (2010) Inflammation 2010: new adventures of an old flame. Cell 140(6):771–776. https://doi.org/10.1016/j.cell.2010.03.006
9. Lavine KJ, Sierra OL (2017) Skeletal muscle inflammation and atrophy in heart failure. Heart Fail Rev 22(2):179–189. https://doi.org/10.1007/s10741-016-9593-0
10. Adams V, Linke A, Winzer E (2017) Skeletal muscle alterations in HFrEF vs. HFpEF. Curr Heart Fail Rep 1–9
11. Yndestad A, Damås JK, Øie E, Ueland T, Gullestad L, Aukrust P (2006) Systemic inflammation in heart failure—the whys and wherefores. Heart Fail Rev 11(1):83–92. https://doi.org/10.1007/s10741-006-9196-2
12. Levine B, Kalman J, Mayer L, Fillit HM, Packer M (1990) Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N Engl J Med 323(4):236–241. https://doi.org/10.1056/NEJM199007263230405
13. Beavers KM, Brinkley TE, Nicklas BJ (2010) Effect of exercise training on chronic inflammation. Clin Chim Acta 411(11):785–793. https://doi.org/10.1016/j.cca.2010.02.069
14. Fedewa MV, Hathaway ED, Ward-Ritacco CL (2016) Effect of exercise training on C reactive protein: a systematic review and meta-analysis of randomised and non-randomised controlled trials. Br J Sports Med. bjsports-2016-095999
15. Pedersen BK (2017) Anti-inflammatory effects of exercise: role in diabetes and cardiovascular disease. Eur J Clin Investig 47(8):600–611. https://doi.org/10.1111/eci.12781
16. Hammonds TL, Gathright EC, Goldstein CM, Penn MS, Hughes JW (2016) Effects of exercise on c-reactive protein in healthy patients and in patients with heart disease: a meta-analysis. Heart Lung 45(3):273–282. https://doi.org/10.1016/j.hrtlng.2016.01.009
17. Kasapis C, Thompson PD (2005) The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. J Am Coll Cardiol 45(10):1563–1569. https://doi.org/10.1016/j.jacc.2004.12.077
18. Ponikowski P, Voors AA, Anker SD et al (2016) ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 37(27):2129–2200m
19. Adamopoulos S, Parissis J, Karatzas D et al (2002) Physical training modulates proinflammatory cytokines and the soluble Fas/soluble Fas ligand system in patients with chronic heart failure. J Am Coll Cardiol 39(4):653–663
20. Larsen AI, Aukrust P, Aarsland T, Dickstein K (2001) Effect of aerobic exercise training on plasma levels of tumor necrosis factor alpha in patients with heart failure. Am J Cardiol 88(7):805–808. https://doi.org/10.1016/S0002-9149(01)01859-8
21. Adamopoulos S, Parissis J, Kroupis C et al (2001) Physical training reduces peripheral markers of inflammation in patients with chronic heart failure. Eur Heart J 22(9):791–797
22. Parrinello G, Torres D, Paterna S, Di Pasquale P, Trapanese C, Licata G (2010) Short-term walking physical training and changes in body hydration status, B-type natriuretic peptide and C-reactive protein levels in compensated congestive heart failure. Int J Cardiol 144(1):97–100. https://doi.org/10.1016/j.ijcard.2008.12.130
23. Ahmad T, Fiuzat M, Mark DB et al (2014) The effects of exercise on cardiovascular biomarkers in patients with chronic heart failure. Am Heart J 167(2):193–202.e191
24. Smart NA, Larsen AI, Le Maitre JP, Ferraz AS (2011) Effect of exercise training on interleukin-6, tumour necrosis factor alpha and functional capacity in heart failure. Cardiol Res Pract 1(1)
25. Lee CT, Chen LW, Chien MY (2017) Effects of exercise training on anabolic and catabolic markers in patients with chronic heart failure: a systematic review. Heart Fail Rev 1–8
26. Fernandes-Silva MM, Guimarães GV, Rigaud VOC, Lofrano-Alves MS, Castro RE, de Barros Cruz LG, Bocchi EA, Bacal F (2017) Inflammatory biomarkers and effect of exercise on functional capacity in patients with heart failure: insights from a randomized clinical trial. Eur J Prev Cardiol 24(8):808–817. https://doi.org/10.1177/2047487317690458
27. Savic-Radojevic A, Radovanovic S, Pekmezovic T et al (2013) The role of serum VCAM-1 and TNF-α as predictors of mortality and morbidity in patients with chronic heart failure. J Clin Lab Anal 27(2):105–112
28. Yin WH, Chen JW, Jen HL, Chiang MC, Huang WP, Feng AN, Lin SJ, Young MS (2003) The prognostic value of circulating soluble cell adhesion molecules in patients with chronic congestive heart failure. Eur J Heart Fail 5(4):507–516. https://doi.org/10.1016/S1388-9842(03)00009-6

29. Araújo JP, Lourenço P, Azevedo A et al (2009) Prognostic value of high-sensitivity C-reactive protein in heart failure: a systematic review. J Card Fail 15(3):256–266
30. Mongirdienė A, Kubilius R (2015) Effect of physical training on indices of platelet aggregation and fibrinogen concentration in patients with chronic heart failure. Medicina (Kaunas, Lithuania) 51(6):343–350
31. Fu R, Vandermeer BW, Shamliyan TA, et al. Handling continuous outcomes in quantitative synthesis. 2013
32. Cohen J (1988) Statistical analysis for the behavioral sciences. Hillsdale, Lawrance Erlbaum
33. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414):557–560. https://doi.org/10.1136/bmj.327.7414.557
34. Egger M, Smith GD, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315(7109):629–634. https://doi.org/10.1136/bmj.315.7109.629
35. Smart NA, Waldron M, Ismail H et al (2015) Validation of a new tool for the assessment of study quality and reporting in exercise training studies: TESTEX. Int J Evid Based Healthc 13(1):9–18
36. de Meirelles LR, Matsuura C, Resende Ade C et al (2014) Chronic exercise leads to antiaggregant, antioxidant and anti-inflammatory effects in heart failure patients. Eur J Prev Cardiol 21(10):1225–1232
37. Trippel TD, Holzendorf V, Halle M et al (2017) Ghrelin and hormonal markers under exercise training in patients with heart failure with preserved ejection fraction: results from the Ex-DHF pilot study. ESC Heart Fail 4(1):56–65
38. Aksoy S, Findikoglu G, Ardic F, Rota S, Dursunoglu D (2015) Effect of 10-week supervised moderate-intensity intermittent vs. continuous aerobic exercise programs on vascular adhesion molecules in patients with heart failure. Am J Phys Med Rehabil Assoc Acad Physiatrists 94(10):898–911. https://doi.org/10.1097/PHM.0000000000000306
39. Kitzman DW, Brubaker P, Morgan T et al (2016) Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. JAMA 315(1):36–46
40. Fu TC, Wang CH, Lin PS et al (2013) Aerobic interval training improves oxygen uptake efficiency by enhancing cerebral and muscular hemodynamics in patients with heart failure. Int J Cardiol 167(1):41–50. https://doi.org/10.1016/j.ijcard.2011.11.086
41. Wisløff U, Støylen A, Loennechen JP et al (2007) Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients. Circulation 115(24):3086–3094
42. Sandri M, Viehmann M, Adams V et al (2016) Chronic heart failure and aging—effects of exercise training on endothelial function and mechanisms of endothelial regeneration: results from the Leipzig Exercise Intervention in Chronic heart failure and Aging (LEICA) study. Eur J Prev Cardiol 23(4):349–358
43. Feiereisen P, Vaillant M, Gilson G, Delagardelle C (2013) Effects of different training modalities on circulating anabolic/catabolic markers in chronic heart failure. J Cardiopulm Rehabil Prev 33(5):303–308. https://doi.org/10.1097/HCR.0b013e3182a1e4e5
44. Byrkjeland R, Nilsson BB, Westheim AS, Arnesen H, Seljeflot I (2011) Inflammatory markers and disease severity in patients with chronic heart failure. Limited effects of exercise training. Atheroscler Suppl 12(1):66. https://doi.org/10.1016/S1567-5688(11)70308-7
45. Eleuteri E, Mezzani A, Di Stefano A et al (2013) Aerobic training and angiogenesis activation in patients with stable chronic heart failure: a preliminary report. Biomarkers 18(5):418–424
46. Erbs S, Höllriegel R, Linke A et al (2010) Exercise training in patients with advanced chronic heart failure (NYHA IIIb) promotes restoration of peripheral vasomotor function, induction of endogenous regeneration, and improvement of left ventricular function. Circ Heart Fail 3(4):486–494
47. Gielen S, Adams V, Möbius-Winkler S et al (2003) Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. J Am Coll Cardiol 42(5):861–868
48. Linke A, Adams V, Schulze PC et al (2005) Antioxidative effects of exercise training in patients with chronic heart failure. Circulation 111(14):1763–1770
49. Tsarouhas K, Tsitsimpikou C, Haliassos A et al (2011) Study of insulin resistance, TNF-alpha, total antioxidant capacity and lipid profile in patients with chronic heart failure under exercise. In Vivo 25(6):1031–1037
50. Helmy ZM, Mohammed SH, Soliman GS Effect of resisted exercise training on interleukin-6 in patients with chronic heart failure
51. Conraads VM, Beckers P, Bosmans J, de Clerck LS, Stevens WJ, Vrints CJ, Brutsaert DL (2002) Combined endurance/resistance training reduces plasma TNF-alpha receptor levels in patients with chronic heart failure and coronary artery disease. Eur Heart J 23(23):1854–1860. https://doi.org/10.1053/euhj.2002.3239
52. Gielen S, Sandri M, Kozarez I, et al. Exercise training attenuates MuRF-1 expression in the skeletal muscle of patients with chronic heart failure independent of age: the randomized Leipzig Exercise Intervention in Chronic Heart Failure and Aging (LEICA) catabolism study. Circulation. 2012:CIRCULATIONAHA. 111.047381
53. Davalos D, Akassoglou K (2012) Fibrinogrn as a key regulator of inflammation in disease. Paper presented at. Semin Immunopathol
54. Hayashino Y, Jackson JL, Hirata T, Fukumori N, Nakamura F, Fukuhara S, Tsujii S, Ishii H (2014) Effects of exercise on C-reactive protein, inflammatory cytokine and adipokine in patients with type 2 diabetes: a meta-analysis of randomized controlled trials. Metabolism 63(3):431–440. https://doi.org/10.1016/j.metabol.2013.08.018
55. Canada JM, Fronk DT, Cei LF et al (2016) Usefulness of C-reactive protein plasma levels to predict exercise intolerance in patients with chronic systolic heart failure. Am J Cardiol 117(1):116–120. https://doi.org/10.1016/j.amjcard.2015.10.020
56. Chin B, Blann A, Gibbs C, Chung N, Conway D, Lip G (2003) Prognostic value of interleukin-6, plasma viscosity, fibrinogen, von Willebrand factor, tissue factor and vascular endothelial growth factor levels in congestive heart failure. Eur J Clin Investig 33(11):941–948. https://doi.org/10.1046/j.1365-2362.2003.01252.x
57. Kato M, Masuda T, Ogano M et al (2017) Stretching exercises improve vascular endothelial dysfunction through attenuation of oxidative stress in chronic heart failure patients with an implantable cardioverter defibrillator. J Cardiopulm Rehabil Prev 37(2):130–138
58. Swardfager W, Herrmann N, Cornish S et al (2012) Exercise intervention and inflammatory markers in coronary artery disease: a meta-analysis. Am Heart J 163(4):666–676. e663
59. Bjornstad HH, Bruvik J, Bjornstad AB, Hjellestad BL, Damas JK, Aukrust P (2008) Exercise training decreases plasma levels of soluble CD40 ligand and P-selectin in patients with chronic heart failure. Eur J Cardiovasc Prev Rehabil 15(1):43–48. https://doi.org/10.1097/HJR.0b013e3281ca7023
60. Karavidas AI, Raisakis KG, Parissis JT et al (2006) Functional electrical stimulation improves endothelial function and reduces peripheral immune responses in patients with chronic heart failure. Eur J Cardiovasc Prev Rehabil 13(4):592–597. https://doi.org/10.1097/01.hjr.0000219111.02544.ff
61. Pearson M, Smart N (2017) Effect of exercise training on endothelial function in heart failure patients: a systematic review meta-analysis. Int J Cardiol 231:234–243. https://doi.org/10.1016/j.ijcard.2016.12.145

62. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA (2011) The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nat Rev Immunol 11(9):607–615. https://doi.org/10.1038/nri3041
63. Sallam N, Laher I (2016) Exercise modulates oxidative stress and inflammation in aging and cardiovascular diseases. Oxidative Med Cell Longev 2016:1–32. https://doi.org/10.1155/2016/7239639
64. Ihalainen J, Schumann M, Eklund D et al (2017) Combined aerobic and resistance training decreases inflammation markers in healthy men. Scand J Med Sci Sports
65. Nimmo M, Leggate M, Viana J, King J (2013) The effect of physical activity on mediators of inflammation. Diabetes Obes Metab 15(s3):51–60. https://doi.org/10.1111/dom.12156
66. Theodorou AA, Panayiotou G, Volaklis KA et al (2016) Aerobic, resistance and combined training and detraining on body composition, muscle strength, lipid profile and inflammation in coronary artery disease patients. Res Sports Med 24(3):171–184
67. Balducci S, Zanuso S, Nicolucci A et al (2010) Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. Nutr Metab Cardiovasc Dis 20(8):608–617
68. Fedewa MV, Hathaway ED, Higgins S, Forehand RL, Schmidt MD, Evans EM (2017) Moderate, but not vigorous, intensity exercise training reduces C-reactive protein. Acta Cardiol 1–8. https://doi.org/10.1080/00015385.2017.1364832
69. Cronin O, Keohane DM, Molloy MG, Shanahan F (2017) The effect of exercise interventions on inflammatory biomarkers in healthy, physically inactive subjects: a systematic review. QJM Int J Med hcx091
70. Lin X, Zhang X, Guo J et al (2015) Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc 4(7):e002014
71. van Empel V, Brunner-La Rocca H-P (2015) Inflammation in HFpEF: key or circumstantial? Int J Cardiol 189:259–263. https://doi.org/10.1016/j.ijcard.2015.04.110
72. Wan X, Wang W, Liu J, Tong T (2014) Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 14(1):135. https://doi.org/10.1186/1471-2288-14-135
73. Parkitny L, McAuley JH, Kelly PJ, Di Pietro F, Cameron B, Moseley GL (2013) Multiplex cytokine concentration measurement: how much do the medium and handling matter? Mediat Inflamm 2013:1–13. https://doi.org/10.1155/2013/890706
74. Bonsu KO, Reidpath DD, Kadirvelu A (2015) Effects of statin treatment on inflammation and cardiac function in heart failure: an adjusted indirect comparison meta-analysis of randomized trials. Cardiovasc Ther 33(6):338–346. https://doi.org/10.1111/1755-5922.12150

Online supplementary material

-10741_2018_9677_MOESM1_ESM.docx

-10741_2018_9677_MOESM2_ESM.docx

Supplementary Material

Appendix 1

Supplementary Tables

Effect of Aerobic and Resistance Training on inflammatory markers in heart failure patients: a systematic review and meta-analysis

Pearson, M.J., S.F. Mungovan and Smart, N.A.

Supplementary Table S1 Overview of studies excluded from the review

Study	Reason for Exclusion
Adamopoulos (2014)	Randomised comparator of Aerobic and IMT vs. Aerobic/SHAM IMT, no non-exercise control group
Adamopoulos (2001)	Randomised crossover trial, no separate non-exercise control group
Adamopoulos (2002)	Randomised crossover trial, no separate non-exercise control group
Bjornstad (2008)	Observational pre-post study, no separate control group
Dobask (2012)	Randomised comparator of combined training vs. NMES, no non-exercise control group
Gatta (2012)	No comparator control group, study <4 weeks duration
Hagglund (2017)	Randomised comparator of Yoga vs. Hydrotherapy, no non-exercise control group
Hemati (2016)	Exercise + creatine vs. usual care, no exercise only group
Karavidas (2006)	Functional Electrical Stimulation Intervention
Kato (2017)	Stretching exercise intervention
Krishna (2014)	Yoga Intervention
Laoutaris (2007)	Randomised comparator of high intensity IMT vs. Low intensity IMT, no non-exercise control group
Larsen (2001)	Observational pre-post study, no separate control group
LeMaitre (2004)	Randomised comparator of Aerobic vs. FES, no non-exercise control group
Marco (2013)	Inspiratory muscle training intervention
Mongirdiene (2015)	Control group recommended 30 minutes of physical exercise everyday
Niebauer (2005)	Randomised crossover trial, no separate non-exercise control group
Prescott (2009)(a)	Observational pre-post study, no separate control group
Prescott (2009)(b)	RCT, However, all patients had previously completed an 8 week exercise rehabilitation program
Pullen (2008)	Yoga Intervention
Pullen (2010)	Yoga Intervention
Smart (2008)	Observational pre-post study, no separate control group
Stout (2012)	Exercise + testosterone vs. Testosterone only, no usual care control group
Tsarouhas (2011)(b)	IL-6 and TNF-α not reported in control group post exercise
Yeh (2011)	Tai Chi Intervention

Supplementary Table 2 Baseline concentrations of inflammatory markers in exercise participants

Study	Baseline CRP	Baseline IL-6	Baseline TNF-α	Baseline Fibrinogen	Baseline sICAM and VCAM
Ahmad (2014)	3.2 (1.4, 7.5) mg/dL				
Aksoy (2015)	0.485±0.62 mg/dL 0.267±0.34 mg/dL			408.2±154.42 mg/dL 310.28±98.14 mg/dL	2.88±1.38 ng/ml (sICAM) 2.53±0.85 ng/ml (sICAM) 51.85±8.14 ng/ml (sVCAM) 53.98±12.33 ng/ml (sVCAM)
Byrkjeland (2011)	4.52 (2.38, 7.97) mg/L	3.44 (2.34, 5.36) pg/ml	2.38 (1.82, 2.96) pg/ml		314 (259, 352) ng/ml (ICAM) 1240 (1042, 1610) ng/ml (VCAM)
Conraads (2002)		2.1 (0.0-16.7) pg/ml	3.5 (1.33-7.2) pg/ml		
De Meirelles (2014)	0.41±0.03 mg/dL	4.5±2.8 pg/ml	3.9±2.7 pg/ml	378.5±44.3 mg/dL	
Eleuteri (2013)	2.1 (0.3-6.9) mg/L	2.3 (0.3-9.2) pg/ml			
Erbs (2010)			9.8±6.3 pg/ml		
Feiereisen (2013)		4.57±2.40 pg/ml	5.54±2.50 pg/ml		
Fernandes-Silva (2017)		1.9 (0.9, 3.8) pg/ml	5.4 (4.2, 6.5) pg/ml		
Gielen (2003)* [1]		1.5±0.6 pg/ml [(1)]	2.2±0.2 pg/ml [(1)]		
Fu (2013)* [2]		~5.3 pg/ml ~4.9 pg/ml			
Helmy (2013)		6.92±0.79 pg/ml			
Kitzman (2016)[3]	8.3±8.9 (µg/L)	6.7±24.8 (pg/ml)			
LEICA Study * Gielen (2012) & Sandri (2015)			2.5±0.9 pg/ml 2.6±0.9 pg/ml		9048±413 pg/ml (sICAM) 9106±307 pg/ml (sICAM) 8367±271 pg/ml (sVCAM) 8461±362 pg/ml (sVCAM)
Linke (2005)*			2.24±0.21 pg/ml		
Parrinello (2009)	0.69±0.34 mg/dL				
Trippel (2016) *EX-DHP Trial*		1.56 (1.26, 2.63) pg/ml	1.54 (1.07, 2.55) pg/ml		
Tsarouhas (2011)			23.9±15.6 pg/ml		

Wisloff (2007)	5.6 (95%CI 3.8,1 2.8) mg/L[4]

Data mean±SD or median (IQR) or median (range), except *mean ±SEM, (1) Data is for all the CHF patients (exercise and control), (2) Data extracted from graph, (3) Overall baseline data for all groups, (4) Data for all groups combined

Supplementary Table S3 Detailed Exercise Intervention Characteristics

Study	Modality	Duration	Frequency (sessions/week)	Total Time per session	Intensity
Ahmad 2014 *HF Action*	Aerobic, group based walking, treadmill or cycling. Supervised	3 months	3	15-30 min	60%HRR and ramped up
Aksoy 2015	Aerobic, bicycle ergometer @ 50RPM, 2 groups: Interval: 60s work to 30s recovery (17 cycles), Continuous. Supervised	10 weeks	3	35 min (includes 5 min WU & 5 min CD)	Starting power @50%VO_{2peak}, ↑every 2 weeks to power @ 75% VO_{2peak} @ week 10
Byrkjeland 2011	Aerobic, group based high intensity interval training, 3 intervals of high intensity and 2 intervals of moderate intensity, 5-10 min each interval, aerobic based dance moves and walking	4 months	2	50 min	High intensity @ 15-18 RPE (~90-95% HR_{max}) Moderate intensity @ 11-13 RPE (~50-60%HR_{max})
Conraads 2002	Combined Training, high intensity aerobic training - cycling and/or jogging (20 min) and resistance training (30 min) (9 exercises in circuit)	4 months	3	60 min (includes 5 min WU & 5 min CD)	RT: @ 50% 1RM (2 x 10 reps) Endurance: HR @ 90% VT
De Meirelles 2014	Combined Training, Aerobic - treadmill (30 min), resistance training (8-10 exercise major muscle groups) and stretching. Supervised	6 months	3	~90 min	AT: HR @ 5-15% > VT RT: 2-3 sets of 10–15 RM
Eleuteri 2013	Aerobic, bicycle ergometer (30 min) @ 60RPM. Home-based	3 months	5	40 min (includes 5 min WU & 5 min CD)	Power & HR @ VAT
Erbs 2010	Aerobic, bicycle ergometer, home-based after 3 weeks of in hospital training One supervised weekly group training (calisthenics, walking, ball games)	12 weeks	7	20-30 min 60 min (group)	HR @ 60% VO_{2max}
Feireisen 2013	Aerobic (bicycle and treadmill 40 min), Strength (10 exercises 40 min), Combined	13.3 weeks	3	40 min	AT: @ 60%VO_{2peak} ↑ to 75% VO_{2peak} RT: @60%1RM ↑ to 75%1RM

	Training (20 min bicycle + 20 min strength 5 exercises). Supervised				CT: AT + RT intensities
Fernandez-Silva 2017	Aerobic, bicycle ergometer, 2 groups, Interval (1 min: 2 min) and Continuous. Supervised	12 weeks	3	40 min (includes 5 min WU & 5 min CD)	Interval: THR= 1 min @ HR @ RCP, 2 min @ HR @ AT, Continuous: THR = [HR @ RCP + 2 (HR @ AT)]/3 (NB: both groups same average workload @ end 30 min)
Fu 2013	Aerobic, bicycle ergometer, supervised, 2 groups, Intervals 5 x 3 with 3 min recovery (30 min), Continuous (30 min), both programs isocaloric. Supervised	12 weeks	3	30 min (+ 3 min WP & 3 min CD)	Interval: 5 x 3 @ 80% VO_{2peak}, 3 min recovery @ 40% VO_{2peak} between each interval Continuous @ 60% VO_{2peak}
Gielen 2003	Aerobic, bicycle ergometer, home-based after 2 weeks of in hospital training (4-6 x per day for 10 min). One weekly group training (calisthenics, walking, ball games)	6 months	7	20 min 1x week 60 min (group)	HR @ 70% VO_{2max}
Helmy 2013	Resistance Training, Circuit training starting @ 2-3 circuits of 8 exercises	12 weeks	3	40-50 min (includes 5-10 min WU & 5-10 min CD on bike)	30-40% 1RM upper body, 50-60% 1RM lower body
Kitzman 2016	Aerobic, primarily walking. Supervised	20 weeks	3	60 min	Individualised, Intensity based on HRR and progressed as tolerated
LEICA Study: Gielen 2012 & Sandri 2015	Aerobic, bicycle ergometer, (4 sessions per weekday, 20 min per session). Supervised. One weekly group training (calisthenics, walking, ball games) (60 min)	4 weeks	20 (4/weekday)	15-20 min (+ 5 WU & CD) 1 x week 60 min (group)	70% VO_{2max}
Linke 2005	Aerobic, bicycle ergometer, home-based after 2 weeks of in hospital training (4-6 x per day for 10 min). One weekly group training (calisthenics, walking, ball games)	6 months	7	20 min 1 x week 60 min (group)	HR @ 70% VO_{2max}

Parrinello 2009	Aerobic, walking	10 weeks	5	30 min	Mild to moderate
Trippel 2016 *EX-DHF study*	Combined Training, initially aerobic (cycling) weeks 1-4 (20-40 min), with addition of resistance training @ week 5. Supervised	12 weeks	2↑3 x (AT) 2 x RT	40 min +	AT: HR @ 50-60% VO_{2peak} (weeks 1-4) ↑HR @ 70% VO_{2peak} 2 week 5, RT @ 60-65%1RM (15 reps)
Tsarouhas 2011	Aerobic, walking, home-based	12 weeks	5	10↑40 min	40%HR_{max} progressing to 60%HR_{max}
Wisloff 2007	Aerobic, uphill treadmill walking, 2 supervised sessions, 1 home-based per week, 2 groups: Interval Training (4 x 4) and Continuous. Isocaloric protocols	12 weeks	3	38 min (AIT) (includes 10 min WU) 47 min (MCT)	Interval: 4x4 @ 90-95%HR_{peak}, 3 min recovery @ 50-70%HR_{peak} between intervals Continuous @ 70-75%HR_{peak}

Supplementary Table S4 Inflammatory marker analysis and assay

Study	Plasma/ Serum	Assay/Supplier	Collection/Preparation
CRP			
Ahmad 2014	P	ELISA - Roche Diagnostics, Indianapolis IN	Blood obtained same day as exercise testing, but before , stored at -70°C until analysis
Aksoy 2015	S	Not reported - Measured with standard procedures	Blood samples were drawn after an overnight fast. All serum stored @ -20°C until analysis
Byrkjeland 2011	S	ELISA - DRG Instruments, GmbH, Germany (detection limit 0.1 mg/L)	Blood drawn after overnight fast, serum prepared within 1hr. stored @ -80° C until analysis
De Meirelles 2014	P	Measured by DLE laboratories	Blood collected in fasting state
Eleuteri 2013	S	Modular analytics, Roche Diagnostics (lower detection limit 0.42 pg/ml)	Blood drawn after overnight fast, serum immediately frozen @ -80° until analysis
Kitzman 2016	P	Chemiluminescent immunoassay- IMMULITE, Diagnostics Products Corporation, LA (Sensitivity 0.10μg/ml)	Blood was collected after overnight fasting and stored @ −80°C.
Parrinello 2009	S	ELISA, Ultra-Sensitive - N Latex CRP mono, Roche S.p.A and Boehringer Mannheim, Milan, Italy	Blood collected after overnight fast
Wisloff 2007	S	Not reported - Measured by standard procedures @ St Olav's University Hospital, Trondheim, Norway	Blood collected and stored @ °C
IL-6			
Byrkjeland 2011	S	ELISA - Abingdon, Oxon, UK	Blood collected after overnight fast, serum prepared within 1hr. , stored @ -80c and thawed only once
Conraads 2002	P	ELISA - Quantikine, R&D Systems (sensitivity 0.7 pg/ml)	Blood collected in fasting state, plasma stored @ --20°C until analysis, samples run in duplicate
De Meirelles 2014	P	Not reported - Measured by DLE laboratories	Blood collected in fasting state
Eleuteri 2013	S	ELISA – R & D Systems (lower detection limit 0.039 pg/ml)	Blood collected in fasting state, serum frozen @ -80° C until analysis
Feiereisen 2013	S	Chemiluminescence technology, IMMULITE 2000 automated immunoassay analyser, Siemens, Los Angeles, CA	Blood collected in fasting state, all measurements in duplicate
Fernandez-Silva 2017	S	Milliplex MAP using Luminex xMAP technology - EMD Millipore Corporation, Germany	Blood collected in fasting state, serum stored @ -70°C until analysis
Gielen 2003	S	ELISA (high sensitive) – R & D Systems, Wiesbaden, Germany (sensitivity 0.09 pg/ml)	
Fu 2013	P	ELISA - eBioscience, San Diego, CA	Plasma samples stored @ -80° until assay
Helmy 2013	?	ELISA	Stored on ice
Kitzman 2016	P	High sensitive Quantikinea Immunoassay, R & D systems, Minneapolis, MN (sensitivity >0.10 pg/ml, detection range 0.156-10.0 pg/ml)	Blood was collected after overnight fasting and stored at −80°C.
Trippel 2016	S	ELISA – HS 600B R & D Systems	Blood sampling at same time of day, preferably fasting, samples stored @ −80°C

TNF-α			
Byrkjeland 2011	S	ELISA - Abingdon, Oxon, UK	Blood collected in fasting state, serum prepared within 1hr. Stored @ -80c and thawed only once
Conraads 2002	P	ELISA – Quantikine High Sensitive, R&D Systems (sensitivity 0.18 pg/ml)	Blood collected in fasting state, plasma stored @ --20°C until analysis, samples run in duplicate
De Meirelles 2014	P	Measured by DLE laboratories	Blood collected in fasting state
Erbs 2010	P	ELISA highly sensitive, R & D Systems	
Feiereisen 2013	S	Chemiluminescence technology, IMMULITE 2000 automated immunoassay analyser, Siemens, Los Angeles, CA	Blood collected in fasting state, all measurements in duplicate
Fernandez-Silva 2017	S	Milliplex MAP using Luminex xMAP technology - EMD Millipore Corporation, Germany	Blood collected in fasting state, serum stored @ -70°C until analysis
Gielen 2003	S	ELISA (high sensitive) – R & D Systems, Wiesbaden, Germany (sensitivity 0.18 pg/ml)	
Gielen 2012	S	ELISA, Quantikine High Sensitive, R&D Systems, Minneapolis USA (sensitivity <0.18 pg/ml)	Blood collected in fasting state, samples run in duplicate
Linke 2005	S	ELISA (high sensitive) – R & D Systems, Wiesbaden, Germany	
Tsarouhas 2011	S	IMMULITE 1000 TNF-α assay- Siemens Medical Solutions Diagnostics, Llanberis, Caernarfon, UK	Fasting blood collected, stored @ -20°C until analysis
Trippel 2016		ELISA – HSTA 00D, R & D Systems	Blood sampling at same time of day, preferably fasting state, samples stored @ −80°C
sVCAM & sICAM			
Aksoy 2015	S	ELISA - eBioscience, San Diego, CA	Blood drawn after overnight, serum prepared within 1hr, serum stored @ -20°C until analysis
Byrkjeland 2011	S	ELISA - Abingdon, Oxon, UK	Blood collected in fasting state, serum prepared within 1hr. Stored @ -80c and thawed only once
Sandri 2015	P	ELISA (high sensitive) - R &D Systems, Wiesbaden, Germany	
Fibrinogen			
Aksoy 2015	P	Not reported – measured using standard procedures	Blood drawn after overnight, serum prepared within 1hr, serum stored @ -20°C until analysis
De Meirelles 2014	P	Measured by DLE laboratories	Blood collected in fasting state

Supplementary Table S5 Sensitivity Analysis using the leave-one-out approach

Study removed	**SMD (95% CI)**	***p*-value**
TNF-α		
de Meirelles (2014)	0.36 (0.07, 0.65)	0.01
Erbs (2010)	0.34 (0.05, 0.62)	0.02
Feiereisen (2013)	0.41 (0.10, 0.72)	0.009
Gielen (2012)	0.57 (0.25, 0.88)	0.0004
Linke (2005)	0.42 (0.13, 0.71)	0.004
Tsarouhas (2011)	0.43 (0.14, 0.73)	0.004
IL-6		
de Meirelles (2014)	0.46 (0.11, 0.82)	0.01
Feiereisen (2013)	0.30 (-0.07, 0.68)	0.11
Fu (2013)	0.40 (0.03, 0.77)	0.03
Helmy (2013)	0.45 (0.08, 0.82)	0.02
CRP		
Aksoy (2015)	3.06 (-1.10, 7.21)	0.15
de Meirelles (2014)	0.58 (0.07, 1.09)	0.03
Parrinello (2009)	1.89 (-0.52, 4.31)	0.12

Supplementary Table S6 Intervention Compliance, Withdrawals, Adverse Events

Study	Adverse Events	Compliance
Ahmad (2014) *HF Action subgroup analysis*	No Details of AE related to the subgroup analysis *Details from entire HF Action total Cohort:* n= 37 in exercise group had at least 1 hospitalization due to an event that occurred during or within 3 hours after exercise initial 36 sessions training, % of patients with an event that caused at least 1 session to be cut short or the goal training intensity to not be achieved: 10% for angina, 7% for arrhythmia, 4% for presyncope or syncope, and 2% for hypoglycemia.	*Details from HF Action Total Cohort:* 41% achieved full adherence (≥90 mins/week). Median exercise time overall of 76 min/week.
Aksoy (2015)	No adverse events during training period	100% sessions attended (for those that completed the study n=45)
Byrkjeland (2011)	No adverse events during the exercise training	95%
Conraads (2002)	NR	NR
De Meirelles (2014)	NR	NR
Eleuteri (2013)	No adverse events occurred during training sessions	non-adherence < 1%
Erbs (2010)	No serious adverse events as a result of training n=1 death control group	~90%
Feireisen (2013)	No serious adverse events. ET group, n=1 paroxysmic AF after treadmill (but could resume training at next session without further problems). ST group, n=1 had to rest for 1 week due to low-back pain that not be directly related to the training program.	100%
Fernandes-Silva (2017)	No details of any events related to training n=2 acute HF episode (in training group)	>70% of sessions (those not attending min 70 not included in analysis)
Gielen (2003)	No deaths occurred during the study period. One patient of the training group was admitted to hospital due to symptomatic bradyarrhythmia requiring pacemaker implantation.	NR
Fu (2013)	NR	AIT 93.3%, MCT 86.7%
Helmy (2013)	NR	NR
Kitzman (2016)	No study-related serious adverse events. Events possibly related to exercise training, n=1 stress foot fracture, n=1 episode of unusual shortness of breath during exercise (exercise group). Hospitalisations unrelated to exercise program.	84%
LEICA -Sandri (2015) & Gielen (2012)	No serious adverse or cardiac events	100%
Linke (2005)	No death or cardiac decompensation occurred, and none of the patients was admitted to the hospital during the study period.	NR
Parrinello (2009)	NR	NR
Trippel (2016) [(1)] *Ex-DHF post hoc analysis*	No serious adverse events in any group. Training group 25% patients had an adverse event during or immediately following exercise, but without clinical relevance	n=34% participated in >90%, n=52% participated in 70-90% sessions, n=6% participated in <70% sessions
Tsarouhas (2011)	NR	Compliance estimated to be good or excellent in 64% of the exercise group.
Wisloff (2007)	No adverse events as a result of training. One patient in moderate-intensity group died of cardiac causes, unrelated to exercise training	92±2% AIT session attendance 95±3% MCT session attendance

(1) Reported in original study Edelmann et al. (2011), NR: not reported

Supplementary Table S7 Assessment of study quality and reporting using TESTEX

Study	Eligibility Criteria specified	Randomisation details specified	Allocation concealed	Groups similar at baseline	Assessors blinded	Outcome measures assessed >85% participants#	ITT	Reporting between group statistical comparison*	Point measures & measures of variability	Activity monitoring in control group	Relative exercise intensity reviewed	Exercise volume & EE	Overall TESTEX (/15)
RCTs													
Ahmad (2014)[1]	1	1	1	1	1	2	0	2	1	0	1	0	11
Aksoy (2015)	1	1	0	1	1	2	0	2	1	0	0	1	10
Byrkjeland (2011) [1]	1	1	1	1	1	3	1	2	1	0	0	0	12
De Meirelles (2014)	1	0	0	1	1	1	1	2	1	0	0	0	8
Erbs (2010)	1	1	1	1	1	3	0	2	1	0	0	0	11
Eleuteri (2013)	1	0	0	1	1	3	1	2	1	0	1	1	12
Ex-DHP Trippel (2016) [1]	1	1	1	1	1	3	0	2	1	0	0	0	11
Feiereisen (2013)	1	0	0	1	1	3	1	2	1	0	0	0	10
Fernandes-Silva (2017)	1	1	1	1	1	2	0	2	1	0	0	0	10
Gielen (2003)	1	0	0	1	1	2	0	2	1	0	0	0	8
Fu (2013)	1	0	0	1	1	2	1	2	1	0	1	1	11
Helmy (2013)	1	0	0	1	1	1	1	2	1	0	0	0	8
Kitzman (2016)	1	1	1	1	1	3	0	2	1	0	0	0	11
LEICA Study Sandri (2015) & Gielen (2012)	1	1	1	1	1	3	1	2	1	0	0	0	12
Linke (2005)	1	0	0	1	1	2	0	2	1	0	0	0	8
Parrinello (2009)	1	0	0	1	1	1	1	2	1	0	0	0	8
Wisloff (2007)	1	1	1	1	1	3	0	2	1	0	1	0	12
Non- Randomised													
Conraads (2002)	1	0	0	1	1	1	0	2	1	0	1	0	8
Tsarouhas (2011	1	0	0	1	1	1	0	2	1	0	0	0	7

Key: total out of 15 points. Legend: #three points possible—one point if adherence >85%, one point if adverse events reported, one point if exercise attendance is reported. *Two points possible—one point if primary outcome is reported, one point if all other outcomes reported. TESTEX, Tool for the assessment of Study quality and reporting in Exercise. 0 awarded if no mention was made of this criteria or if it was unclear whether criteria was meet. (1) Information for some items obtained from original study publication if not presented in current publication. If ITT was not specifically mentioned, but it was noted that no participants withdrew and all analysed 1 point was awarded.

Supplementary Material

Appendix 2

Supplementary Figures

Effect of Aerobic and Resistance Training on inflammatory markers in heart failure patients: a systematic review and meta-analysis

Pearson, M.J., S.F. Mungovan, Smart, N.A

Fig. S1 Change in Fibrinogen, exercise vs. control

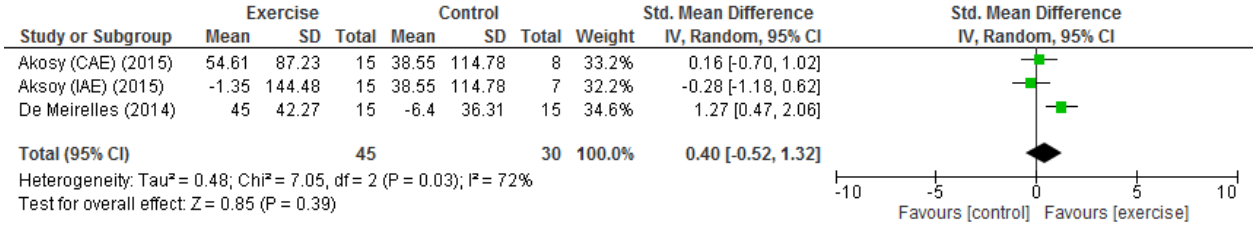


Fig. S2 Change in sICAM, exercise vs. control

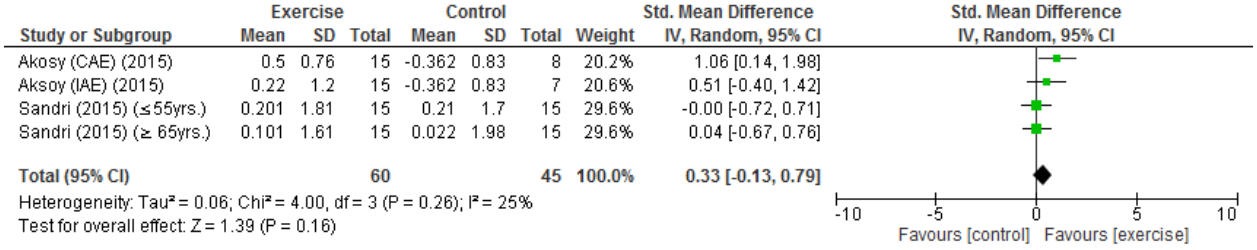
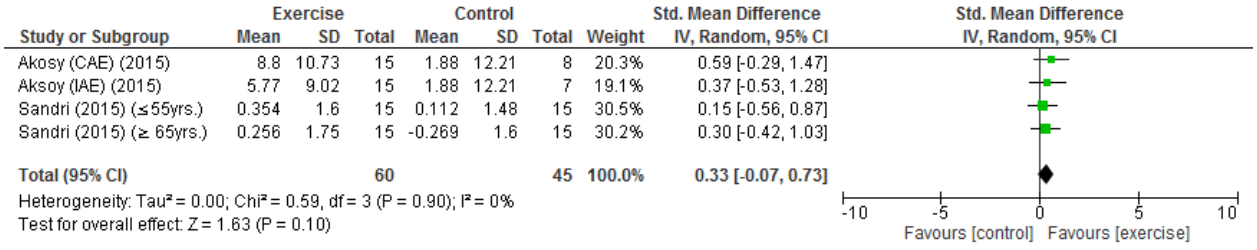


Fig. S3 Change in sVCAM, exercise vs. control



7 Chapter 7 - Peer reviewed publication: Effect of exercise therapy on established and emerging circulating biomarkers in heart failure patients: A systematic review and meta-analysis

7.1 Manuscript Information

Pearson, M. J., King, N., & Smart, N. A. (2018). Effect of exercise therapy on established and emerging circulating biomarkers in heart failure patients: A systematic review and meta-analysis. **ARTICLE IN PRESS** *Open Heart* http://dx.doi.org/10.1136/openhrt-2018-000819

Submitted to Open Heart 13th March 2018, Revised Submission 4th May 2018, Accepted: 24th May, 2018

20th June 2018

Candidate

Principal Supervisor 20th June 2018

7.2 Statement of author's contribution

Higher Degree Research Thesis by Publication

University of New England

STATEMENT OF AUTHORS' CONTRIBUTION

We, the PhD candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated in the *Statement of Originality*.

	Author's Name (please print clearly)	**% of contribution**
Candidate	Melissa Pearson	85%
Other Authors	Neil Smart	10%
	Nicola King	5%

Name of Candidate: Melissa Jane Pearson

Name/title of Principal Supervisor: Professor Neil Smart

Candidate

20th June 2018
Date

Principal Supervisor

20th June 2018
Date

7.3 Statement of originality

Higher Degree Research Thesis by Publication

University of New England

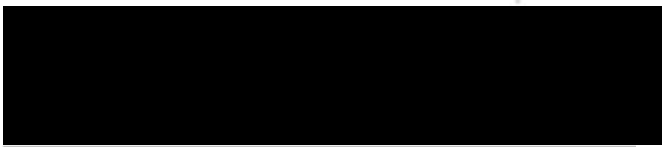
STATEMENT OF ORIGINALITY

We, the PhD candidate and the candidate's Principal Supervisor, certify that the following text, figures and diagrams are the candidate's original work.

Type of work	Page number(s)
Systematic Review & Meta-analysis	173-216

Name of Candidate: Melissa Jane Pearson

Name/title of Principal Supervisor: Professor Neil Smart



Candidate

20th June 2018

Date

Principal Supervisor

20th June 2018

Date

7.4 Full manuscript – As accepted IN PRESS

Effect of exercise therapy on established and emerging circulating biomarkers in heart failure patients: A systematic review and meta-analysis.

Melissa J Pearson[1]*, Nicola King[2], Neil A Smart [1]

* Corresponding author at: School of Science and Technology, University of New England, Armidale, NSW 2351, Australia

Email: mpears23@myune.edu.au

Words (excluding abstract, references, tables and figures): 4471
Tables: 2
Figures: 7

[1] School of Science and Technology, University of New England, Armidale, NSW, Australia 2351
[2] School of Biomedical and Healthcare Sciences, University of Plymouth, Plymouth, PL8 4AA UK
The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

ABSTRACT

Background Biomarkers are important in the diagnosis, risk stratification and management of heart failure patients. The established biomarkers of myocardial stretch, BNP and NT-proBNP have been extensively studied and early analyses have demonstrated response to exercise training. Several other biomarkers have been identified over the last decade and may provide valuable and complementary information which may guide treatment strategies, including exercise therapy.

Methods A systematic search of PubMed, EMBASE and Cochrane Trials Register to 31st October 2017 was conducted for exercise based rehabilitation trials in heart failure. Randomised and controlled trials that reported biomarkers, BNP, NT-proBNP, sST2, Gal-3, MR-proANP, MR-proADM and CT-proAVP, were included.

Results Forty three studies were included in the systematic review, with 27 studies suitable for meta-analyses. Data pooling was only possible for NT-proBNP and BNP. Meta-analyses of conventional training studies demonstrated a statistically significant improvement in NT-proBNP (pmol/L); MD -32.80 (95%CI -56.19, -9.42), p=0.006, and in BNP (pmol/L); MD -17.17 (95%CI -29.56, -4.78), p=0.007. Pooled data of non-conventional training failed to demonstrate any statistically significant improvements.

Conclusion Pooled data indicated a favourable effect of conventional exercise therapy on the established biomarkers NT-proBNP and BNP; however, this was in contrast to a number of studies that could not be pooled. Limited evidence exists as to the effect of exercise training on emerging biomarkers.

Keywords Heart Failure, Exercise, Biomarkers, Brain Natriuretic Peptide, B-type Natriuretic peptide

Key Messages

What is already known about this subject?

Early reviews indicate that exercise training may improve BNP and NT-proBNP in heart failure patients. A number of new trials have compared different types of conventional and non-conventional modes of training on BNP and NT-proBNP but the optimal exercise prescription for reducing heart failure biomarkers is unknown.

What does this study add?

The review updates the evidence in regard to the effect of exercise training on the established heart failure biomarkers BNP and NT-proBNP. Additionally the response of a number of emerging biomarkers to exercise training has been investigated in heart failure patients. The pooled analysis of conventional exercise training confirms improvements in BNP and NT-proBNP but demonstrates only limited evidence for non-conventional training. Exercise training may also improve a number of other biomarkers representative of different pathophysiological pathways involved in heart failure progression.

How might this impact on clinical practice?

The exercise prescription for heart failure patients can be optimised to improve biomarker profile and hence prognosis, providing a valuable resource for both clinicians and patients.

INTRODUCTION

Heart failure (HF) is a complex syndrome resulting from multiple conditions and underlying disorders, and continues to be a significant burden on the health care system. Over the past three decades an increasing number of studies have provided evidence on a range of benefits of exercise training in patients with HF[1-5]. In stable HF patients exercise training is now a Class 1 recommendation in HF guidelines[6 7].

Numerous pathways are involved in the development and progression of HF, and the discovery of biomarkers has and will hopefully continue to enhance our understanding of the pathophysiology[8 9]. Circulating biomarkers are important in the diagnosis, risk stratification and management of HF patients[6 10 11]. Heart failure biomarkers tend to be classified according to the associated pathophysiological processes[12 13]. These include biomarkers of myocardial stretch, myocyte injury, fibrosis, matrix remodelling, inflammation, oxidative stress, neurohumoral activation and renal dysfunction[10 12 13]. Some biomarkers may bridge several pathophysiological processes. Currently brain (B-type) natriuretic peptide (BNP) and its more stable inert form, the amino (N terminal) portion (NT-proBNP), markers of myocardial stretch, are recognized as gold standard diagnostic and prognostic biomarkers in HF[6 7 11].

Over recent decades the role of circulating biomarkers in HF has evolved, with the emergence of a number of novel biomarkers[12]. Among these biomarkers, suppression of tumorigenicity-2 (ST2) and Galectin-3 (Gal-3) have demonstrated prognostic value in HF[14-17], and both are shown to be predictors of sudden cardiac death[18 19]. In fact, the combination of the gold standard cardiac biomarkers of BNP/NT-proBNP with the newer biomarkers such as soluble ST2 (sST2) and Gal-3 may improve risk stratification and prognosis[10 11]. Other emerging biomarkers, mid-regional atrial natriuretic peptide (MR-proANP), mid-regional adrenomedullin (MR-proADM) and copeptin (CT-proAVP) have also been shown to have prognostic value in HF[9 20].

In addition to their diagnostic and prognostic utility, biomarker profiles may prove beneficial in guiding HF therapy and improving treatment strategies[10], including the

identification of HF patients that may respond to exercise training[21-23]. A 2010 meta-analysis[24] suggested exercise training had a favourable effect on both BNP and NT-proBNP. The results of which were confirmed by a 2011 individual patient data (IPD) meta-analysis, with a 37.4% and 28.3% reduction in NT-proBNP and BNP respectively[25]. Furthermore, BNP and NT-proBNP changes are correlated with changes in VO_{2peak}[25].

The aim of this systematic review and meta-analysis was first to update the previous reviews as a number of additional studies have investigated BNP and/or NT-proBNP after training interventions. Secondly, given the emergence of new biomarkers in HF trials, we intended to add to the current literature with the inclusion of a selected number of emerging biomarkers. Furthermore, differing to previous analyses, we expanded our review to include additional modalities of exercise therapy due to their increasing utilisation in cardiac rehabilitation programs and trials, which may provide alternatives for subgroups of HF patients.

METHODS

Search Strategy

Potential studies were identified by conducting systematic searches of PubMed, EMBASE, CINHAL and the Cochrane Library of Controlled Trials up until 31st October 2017. Searches included a mix of MeSH and free text terms related to the key concepts of heart failure, exercise training and biomarkers. Additionally, systematic reviews, meta-analyses and reference lists of papers were hand searched for additional studies. One reviewer (MJP) conducted the search and full articles were assessed for eligibility by two reviewers (MJP and NAS). A sample search strategy is presented in Supplementary Files. Additional information was requested from five authors, with three responses.

Study Selection

Study type and participants Randomised controlled trials and controlled trials of exercise therapy in HF patients 18 years or older were included. Heart failure type (i.e., preserved, moderately reduced and reduced ejection fraction) was not considered as an inclusion or exclusion criteria. Only studies in which the authors

specifically reported a patient diagnosis of HF were included. Studies assessing intervention effect on acute or decompensated HF were excluded.

Intervention Exercise therapy included both conventional training, defined as aerobic training (AT), resistance training (RT) and combined AT and RT (CT), and non-conventional modes of therapy defined as Yoga, Tai Chi, Stretching and the physical therapies of Functional Electrical Stimulation (FES) and Inspiratory Muscle Training (IMT). Studies must have compared an exercise intervention to a usual care or education control group, with no formally prescribed exercise, and the duration of the exercise training must have been for a minimum of 4 weeks. Studies in which the participants had participated within a formal exercise rehabilitation program within the last six months were excluded.

Outcomes Studies were eligible to be included in the review if they reported one or more of the following outcomes in serum or plasma: BNP, NT-proBNP, cardiac troponin (cTnT), sST2, Gal-3, MR-proANP, MR-proADM and CT-proAVP.

Exclusions Abstracts and non-English studies were excluded.

Data extraction One reviewer (MJP) extracted the data. For each study the following information was extracted: 1) author, year of publication and study design, 2) demographic and clinical characteristics, 3) exercise intervention characteristics 4) mean, SD, p value and main findings in regards to biomarkers, and 5) details of assessment methodology for biomarkers.

Data Synthesis Statistical analyses were performed using Revman 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark). Individual meta-analyses were completed for continuous data by using the change in the mean and standard deviation. Where the change in mean and SD were not reported, the change in mean was calculated by subtracting the pre-intervention mean form the post-intervention mean, and Revman 5.3 enabled calculations of SD using number of participants in each group, within or between group p values or 95% CI. Where p values were not provided, the standard deviation of the mean difference were calculated using the formula: SD = square root $[(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2r \times$

$SD_{pre\text{-}treatment}$ x $SD_{post\text{-}treatment}$)], assuming a correlation coefficient (r) = 0.5, which is considered a conservative estimate[26]. Where data was not presented in text or tables, and authors could not be reached, data presented in figures or reported in prior meta-analyses was extracted or accessed where possible.

Data were pooled for meta-analysis when two or more studies measured the same outcome and provided data in a format suitable for pooling. Where a study included multiple intervention groups and data were not provided for the combined intervention, data was entered separately for each group and the sample size of the control group was divided by the number of intervention groups to eliminate over inflation of the sample size. A random effects inverse variance was used with the effects measure of mean difference (MD). We used a 5% level of significance and a 95% CI to report change in outcome measures. Both BNP and NT-proBNP are commonly reported in SI units (pmol/L) or conventional units (pg/ml). Due to large values associated with NT-proBNP, change data was converted from pg/ml to pmol/L for both NT-proBNP and BNP for presentation. Data were converted using the following factors: for NT-proBNP pmol/L = pg/ml x 0.118 and BNP pmol/L = pg/ml x 0.289.

For meta-analysis, we did not pool studies in which participants were clearly identified as only having HFpEF, with other studies. We grouped studies for analysis according to conventional or non-conventional training modalities. For studies where the mean or SD of outcomes were not reported, but median, interquartile range (IQR) or median and range were reported or where only a descriptive result was reported in regard to post intervention changes, a table and descriptive analysis are utilised.

Sensitivity analysis In order to evaluate the influence of each study on the overall effect size, sensitivity analysis using the leave-one-out approach was conducted. Where SD was imputed, additional analyses were also carried out with different values for the correlation coefficient (r=0.75 and 0.25) to determine whether the overall results of the analyses were robust to the use of imputed correlation coefficients.

Heterogeneity and Publication Bias Heterogeneity was quantified using the I^2 test[27]. Values range from 0% (homogeneity) to 100% (high heterogeneity)[27]. Visual inspection of funnel plots[28] assessed risk of publication bias.

Study Quality Study quality was assessed using the Tool for the Assessment of Study Quality and Reporting in Exercise (TESTEX)[29] by two authors (MJP and NK). In the case of discrepancies a third author (NAS) was consulted.

RESULTS

The initial search generated a total of 3419 articles. After removal of duplicates and exclusion of articles based on abstract and title, 77 full-text articles remained for screening. Full screening resulted in 43 articles meeting the stated inclusion criteria (Fig. 1 PRISMA statement), of which 27 studies were included in meta-analyses. Details of full-text articles reviewed but excluded are provided, with reasons, in Supplementary Table S1.

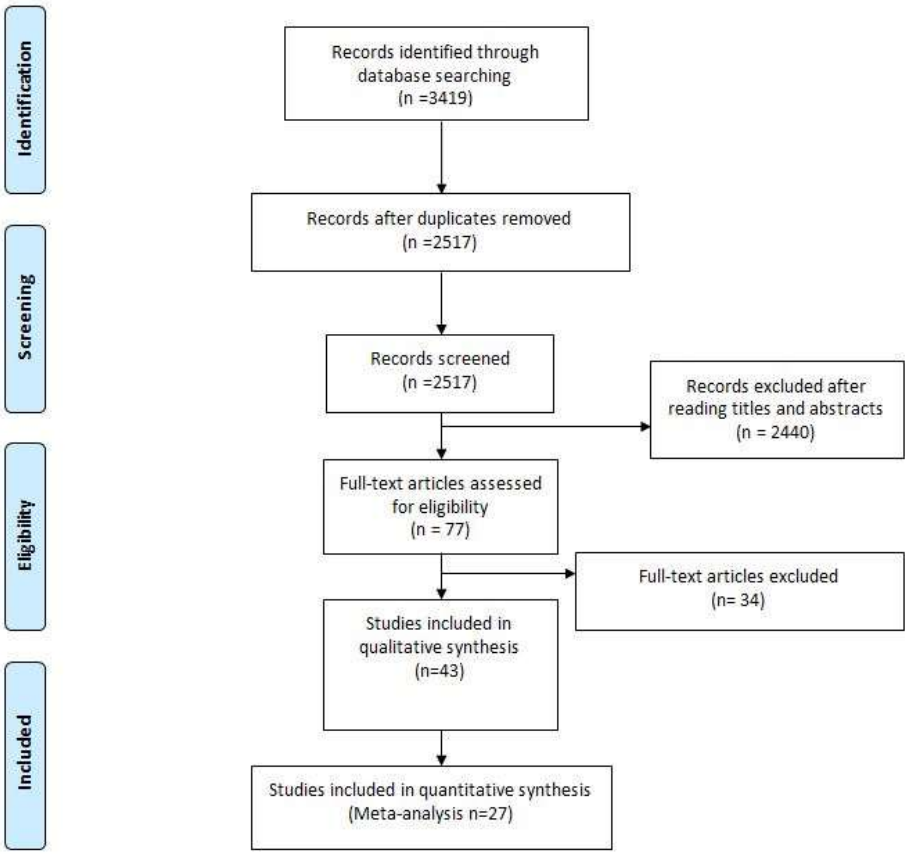


Fig. 1 PRISMA Flow diagram

Study and Participant Characteristics

A general description of included studies is provided in Table 1. Of the 43 included studies, two[30 31] studies were from the same trial, but provided different biomarker information and two[32 33] studies contained an overlap of some participants, and data was combined into one dataset for meta-analysis to eliminate data overlap. Four[22 34-36] of the studies were controlled but not randomised, one[37] study randomised.

Table 1 Overview of studies included in the review

Study	Design	Participant Characteristics	Intervention
Ahmad (2014)	RCT	n=928 analysed, *Biomarker sub study HF ACTION Trial* E: n=477 (68% male), 59 (51-68)yrs, LVEF 25 (20-30)%* C: n=451 (73% male), 59 (51-68)yrs, LVEF 25 (20-31)% Class II-IV (<1% IV)	3 months Aerobic
Aksoy (2015)	RCT	n=57 randomised, n=45 analysed E1: n=15 (87% male), 64±9yrs, LVEF 50±7% E2: n=15 (87% male), 60±7yrs, LVEF 52±5% C: n=15 (87% male), 58±11yrs, LVEF 52±6% NYHA Class II-III	10 weeks Aerobic (E1: IAE, E2: CAE)
Antonicelli (2016)	RCT	n=343 randomised, n= 313 completed 6 months E: n=170 (61% male), 76±5yrs, LVEF 48±13% C: n=173 (53% male), 78±6yrs, LVEF 49±13% NYHA Class ≥2	6 months Aerobic
Berendoncks (2010)	Non-RCT Cohort with control group	n= 80 analysed E: n=46 (70% male), 58±10yrs, LVEF 17 (14-22)%* C: n=34 (59% male), 61±12yrs, LVEF 19 (15-24)% NYHA Class II-III	4 months Aerobic & Combined
Billebeau (2017)	Non-RCT Cohort with control group	n=131 enrolled E: n=107 (86% male), 59 (52-66)yrs, LVEF 30 (25-39)%* C: n=24 (79% male), 63 (53-72)yrs, LVEF 35 (30-40)% NYHA Class II-IV	4-6 months Aerobic
Brubaker (2009)	RCT	n=59 randomised, n=44 analysed E: n=30 (63% male), 70±5yrs, LVEF 32±9% C: n=29 (69% male), 70±6yrs, LVEF 30±9% NYHA Class II-IV (n=1 class IV)	16 weeks Aerobic
Butterfield (2008)	RCT	n=19 randomised, n=17 analysed E: n=11 (82% male), 66±10yrs, LVEF 34±11% C: n=6 (50% male), 75±12yrs, LVEF 35±14% NYHA Class II-III	12 weeks Combined
Conraads (2007)	RCT	n=17 randomised & analysed E: n=8 (38% male), 57±2yrs, LVEF 27±5% C: n=9 (56% male), 61±4yrs, LVEF 28±5% NYHA Class III	4 months Aerobic
Conraads (2004)	Non-RCT Cohort with control group	n=49 enrolled & analysed E: n=27 (78% male), 59±2yrs, LVEF 26±1% C: n= 22 (68% male), 59±2yrs, LVEF 26±1% NYHA Class II-III	4 months Combined

Delagardelle (2008)	RCT/Non-RCT[1]	n=60 randomised & analysed E: n=45 (84% male), 59±6yrs, LVEF 24±5% C: n=15 (87% male), 56±8yrs, LVEF 25±6% NYHA Class II	~13.3 weeks, Combined, Aerobic or Strength
Edelmann (2011) *Ex-DHF Pilot Study*	RCT	n= 67 randomised, n=64 analysed E: n=44 (45% male), 64±8yrs, LVEF 68±7% C: n=20 (40% male), 65±6yrs, LVEF 67±7% NYHA Class II & III	12 weeks Combined
Eleuteri (2013)	RCT	n= 21 randomised & analysed E: n=11 (100% male), 66±2yrs, LVEF 28±2% C: n=10 (100% male), 63±2yrs, LVEF 30±2% NYHA Class II	3 months Aerobic
Fernandes-Silva (2017)	RCT	n=52 randomised, n=40 analysed E: n=28 (50% male), 51±7yrs, LVEF 30±6% C: n=16 (62% male), 48±7yrs, LVEF 29±7% NYHA Class I-III	12 weeks Aerobic
Fu (2013)	RCT	n=45 randomised, n=40 analysed E1: n=15 (67% male), 68±5%, LVEF 38±4% E2: n=15 (60% male), 66±2yrs, LVEF 39±5% C: n=15 (67% male), 68±3yrs, LVEF 38±4% NYHA Class II-III	12 weeks Aerobic (E1: AIT, E2: MCT)
Gary (2011)	RCT	n=24 randomised & analysed E: n=12 (58% male), 59±11yrs, LVEF 23±8% C: n=12 (42% male), 61±10yrs, LVEF 27±9% NYHA Class II-III	12 weeks Combined
Guazzi (2012)	RCT	n=26 randomised & analysed E: n=18, C: n=8, 68±6yrs, LVEF 37±5% NYHA Class II-III	24 weeks Aerobic
Jonsdottir (2006)	RCT	n=51 randomised, n=43 analysed E: n=21 (76% male), 68±7yrs, LVEF 42±14% C: n=22 (82% male), 69±5yrs, LVEF 41±14% NYHA Class II-III	5 months Combined
Karavidas (2008)	RCT	n=30 randomised & analysed E: n=20 (80% male), 62±12yrs, LVEF 28±7% C: n=10 (80% male), 64±8 yrs, LVEF 27±5% NYHA Class II-III	6 weeks FES
Karavidas (2013)	RCT	n=30 randomised & analysed E: n=15(60% male), 69±9yrs, LVEF 64±8% C:n=15 (60% male), 69±8yrs, LVEF 63±5% NYHA Class II-III	6 weeks FES
Kato (2017)	RCT	n= 50 randomised & analysed E: n=25 (80% male), 70±11yrs, LVEF 28±9% C: n=25 (76% male), 70±8yrs, LVEF 29±9% NYHA Class II-IV	4 weeks Stretching
Kawauchi (2017)	RCT	n= 53 randomised, n=35 analysed E1: n=13 (46% male), 54±10yrs, LVEF 30±6% E2: n=13 (62% male), 56±7yrs, LVEF 28±5% C: n=9 (56% male), 56±7yrs, LVEF 29±7% NYHA Class II-III	8 weeks IMT + Resistance
Kitzman (2010)	RCT	n=53 randomised, n=46 completed E: n=26 (17% male), 70±6yrs, LVEF 61±5% C: n=27 (9% male), 69±5yrs, LVEF 60±10% NYHA Class II-III	16 weeks Aerobic

Kitzman (2016)	RCT	n=51 randomised [2] E: n=26 (19% male), 68±6yrs, LVEF 61±6% C: n=25 (20% male), 66±5%, LVEF 63±6% NYHA Class II-III	20 weeks Aerobic
Kobayashi (2003)	RCT	n= 28 randomised & analysed E: n=14 (86% male), 55±2yrs, LVEF 29±2% C: n=14 (57% male), 62±2yrs, LVEF 33±2% NYHA Class II & III	12 weeks Aerobic
Krishna (2014)	RCT	n=130 randomised, n=92 analysed E: n=44 (73% male), 49±6yrs, LVEF 39±5% C: n=48 (67% male), 50±5yrs, LVEF 40±5% NYHA Class I-II	12 weeks Yoga
Malfatto (2009)	RCT	n=54 randomised & analysed E: n=27 (70% male), 65±11yrs, LVEF 31±6%, C: n=27 (74% male), 67±9yrs, LVEF 33±6%, NYHA Class I & II	12 weeks Aerobic
Marco (2013)	RCT	n=22 randomised & analysed E: n=11 (64% male), 69±9yrs, LVEF 38±16% C: n=11 (91% male), 70±11yrs, LVEF 36±17% NYHA Class II- III	4 weeks IMT
Meyer (2004)	RCT	n=42 randomised & analysed E: n=19 (79% male), 58±10yrs, LVEF 29±13% C: n=23 (78% male), 54±9yrs, LVEF 30±11% NYHA Class II- III	12 week Aerobic
Nilsson (2010)	RCT	n=78 randomised, n=70 for BNP @ follow-up E: n=39 (77% male), 69±8yrs, LVEF 30±8% C: n=39 (79% male), 72±8yrs, LVEF 31±10% NYHA Class II- III	4 months Aerobic
Nishi (2011)	Retrospective Analysis	n=45 randomised, n=31 analysed BNP E: n=33 (88% male), 51±14yrs, LVEF 18±4%, C: n=12 (83% male), 52±16yrs, LVEF 18±5% NYHA Class II- III	3 months Aerobic
Norman (2012)	RCT	n=42 randomised, n=39 analysed for BNP E: n=20 (55% male), 56±3yrs, LVEF 34±1% C: n=20 (60% male), 63±3yrs, LVEF 32±1% NYHA Class II- IV	24 weeks Combined
Palau (2014)	RCT	n=27 randomised, n=26 analysed E: n=14 (50% male), 68(60-76)yrs, LVEF 69(63-77)%* C: n=12 (50% male), 74(73-77)yrs, LVEF 76(68-83)% NYHA Class II- IV	12 weeks IMT
Parrinello (2009)	RCT	n=22 randomised & analysed E: n=11 (73% male), 62±5yrs, LVEF 39±4% C: n=11 (64% male), 63±5ys, LVEF 39±4% NYHA Class II- III	10 weeks Aerobic
Passino (2006)	RCT	n=95 randomised, n=85 analysed E: n=44 (89% male), 60±2yrs, LVEF 35±2% C: n=41(85% male), 61±2yrs, LVEF 32±2% NYHA Class I- III	9 months Aerobic
Passino (2008)	RCT	n= 97 randomised, n=90 analysed E: n=71 (87% male), 61±2yrs, LVEF 35±1% C: n=19 (74% male), 63±2yrs, LVEF 36±2% NYHA class I-III	9 months Aerobic

Sandri (2012) *LEICA Study*	RCT	*n*=60 randomised & analysed E1: n=15 (80% male), 50±5yrs, LVEF 27±1% C1: n=15 (87% male), 49±5yrs, , LVEF 28±1% E2: n=15 (80% male), 72±4yrs, LVEF 29±2% C2: n=15 (80% male), 72±3yrs, LVEF 28±2% NYHA Class II- III	4 weeks Aerobic
Sarullo (2006)	RCT	n=60 randomised & analysed E: n=30 (77% male), 53±6yrs, LVEF 29±5% C: n=30 (74% male), 53±5yrs, LVEF 29±4% NYHA Class II- III	12 weeks Aerobic
Stevens (2015)	RCT	n=28 randomised, n=22 analysed E: n=15 (67% male), 67±3yrs, LVEF 39±3% C: n=7 (86% male), 64±6yrs, LVEF 35±2% NYHA Class I-III	12 weeks Combined
Trippel (2017) *Ex-DHF Pilot study post hoc analysis*	RCT	n=67 randomised, n= 62 analysed for biomarkers E: n=44 (45% male), 64±8yrs, LVEF 68±7% C: n=20 (40% male), 65±6yrs, LVEF 67±7% NYHA Class II-III	12 weeks Combined
Wisloff (2007)	RCT	n=27 randomised, n=26 analysed E1: n=9 (78% male), 77±9yrs, LVEF 28±7% E2: n=9 (78% male), 74±12yrs, LVEF 33±5% C: n=9 (67% male), 76±13yrs, LVEF 26±8%	12 weeks Aerobic (E1: AIT, E2: MCT)
Yamamoto (2007)	Non-RCT Cohort with control group	n=18 enrolled & analysed E: n= 10 (90% male), 68(64-70)yrs, LVEF 40 (37-43)%* C: n= 8 (100% male), 70(66-73)yrs, LVEF 37 (35-38)% NYHA Class II-III	6 months Aerobic
Yeh (2004)	RCT	n=30 randomised & analysed E: n=15 (67% male), 66±12yrs, LVEF 24±7% C: n=15 (60% male), 61±14yrs, LVEF 22±8% NYHA Class I-IV	12 weeks Tai Chi
Yeh (2011)	RCT	n=100 randomised & analysed E: n=50 (56% male), 68±12yrs, LVEF 28±8% C: n=50 (72% male), 67±12yrs, LVEF 30±7% NYHA Class I-III	12 weeks Tai Chi

[(1)] Randomised between three exercise groups, but control group not randomised, [(2)] Excludes diet and diet and exercise group.
AIT: aerobic interval training, BNP: brain natriuretic peptide, CAE: continuous aerobic training, C: control, cTnT: cardiac troponin, CT-proAVP: copeptin, E: exercise, FES: functional electrical stimulation, Gal-3: galectin-3, IHF: Ischemic heart failure, IAE: aerobic interval training, IMT: inspiratory muscle training, LVEF: left ventricular ejection fraction, MCT: moderate continuous training, MR-proANP: mid-regional atrial natriuretic peptide, MR-proADM: mid-regional pro-adrenomedullin, NHF: non-ischemic heart failure, NT-proBNP: amino(N) portion of BNP, NYHA: New York Heart Association, ST2: suppression of tumorigenicity 2, ↓ statistically significant decrease, ↑statistically significant increase, ↔ no statistically significant change. * Median (IQR)

participants between exercise intervention groups, but the control group was not randomised, one[38] study was a retrospective analysis, all remaining studies were RCTs. Seven studies[30 31 39-43], representing six trials included participants with a mean Left Ventricular Ejection Fraction (LVEF) >50%, one[43] of which also included participants with LVEF <50%. Thirty six trials included participants with mean LVEF <50%, and the mean LVEF of at least three[44-46] studies indicates the inclusion of participants with a range of ejection fractions, reduced, mid-range and/or preserved ejection fraction. Baseline NT-proBNP and BNP levels are provided in Supplementary Table S2.

Intervention details

A detailed description of the interventions can be found in Supplementary Table S3. Thirty four studies utilised conventional exercise training, 8 studies utilised non-conventional exercise training or therapy, and one study combined non-conventional and conventional training. Intervention duration ranged from 4 weeks to 9 months.

Biomarker Assessment

Biomarker assay details are provided in Supplementary Table S4.

Outcome Measures

NT-proBNP Twenty studies reported on NT-proBNP. Two studies[32] [33] contained an overlap of some participants; to avoid possible duplication of data these studies are represented as one dataset in the meta-analysis.

Meta-analysis Overall exercise demonstrated a statistically significant improvement in NT-proBNP (pmol/L); MD -47.83 (95%CI -77.23, -18.43) p=0.001(Fig. 2a).

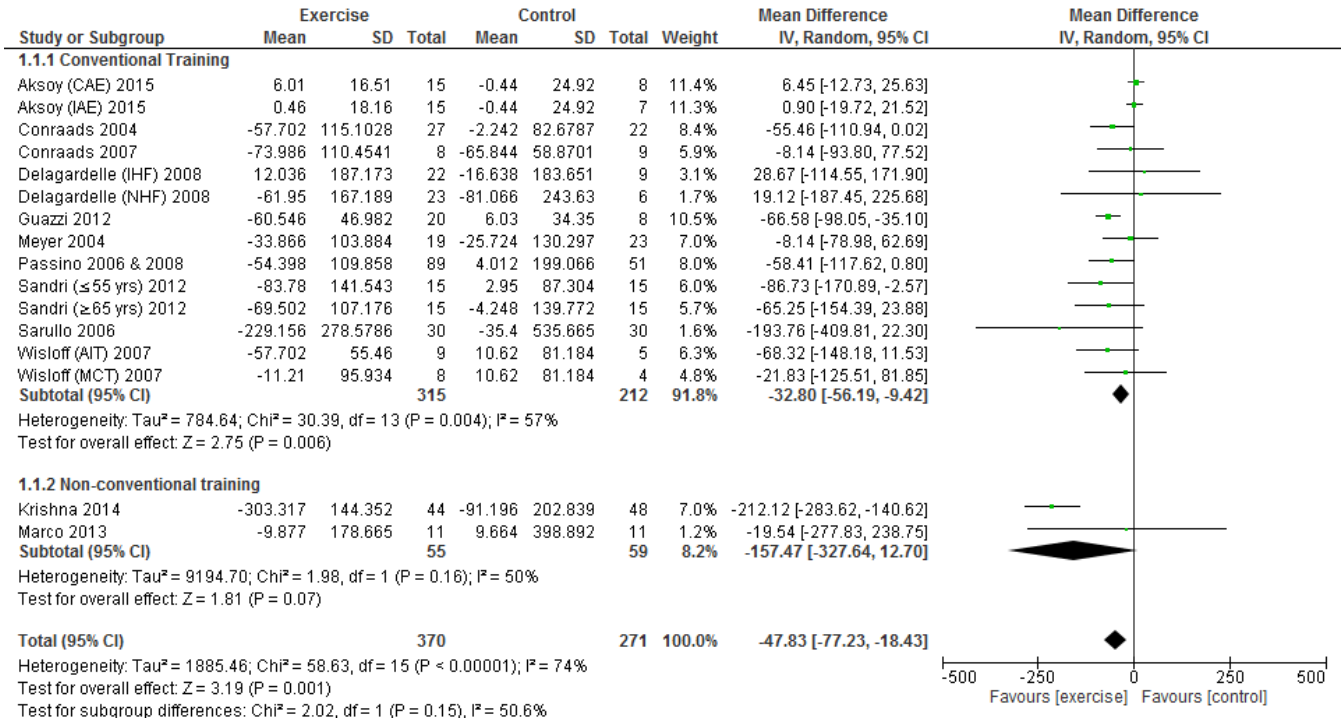


Fig. 2a Change (MD) in NT-proBNP (pmol/L) exercise vs. control.
For Conversion to pg/ml = pmol/L divided by 0.118.

Conventional training Pooled data from 10 studies[32 33 35 37 43 47-52] (14 intervention groups) (315 exercise participants, 212 controls) demonstrated a statistically significant improvement in favour of exercise, on NT-proBNP (pmol/L); MD -32.80 (95%CI -56.19, -9.42) p=0.006 (Fig. 2a). Removal of the two interventions groups from one[43] study, that included patients with a mean ejection fraction of 50%, improved the MD and statistical significance; MD -54.62 (95%CI -74.36, -34.87) pmol/L, p<0.00001(Supplementary table S5). Apart from the study of Aksoy et al. (2015), sensitivity analysis using the leave-one out approach revealed the results remained relatively stable (Fig. 2b). Sensitivity analyses conducted for different correlation coefficients for SD imputation, did not result in any significant variance in overall results.

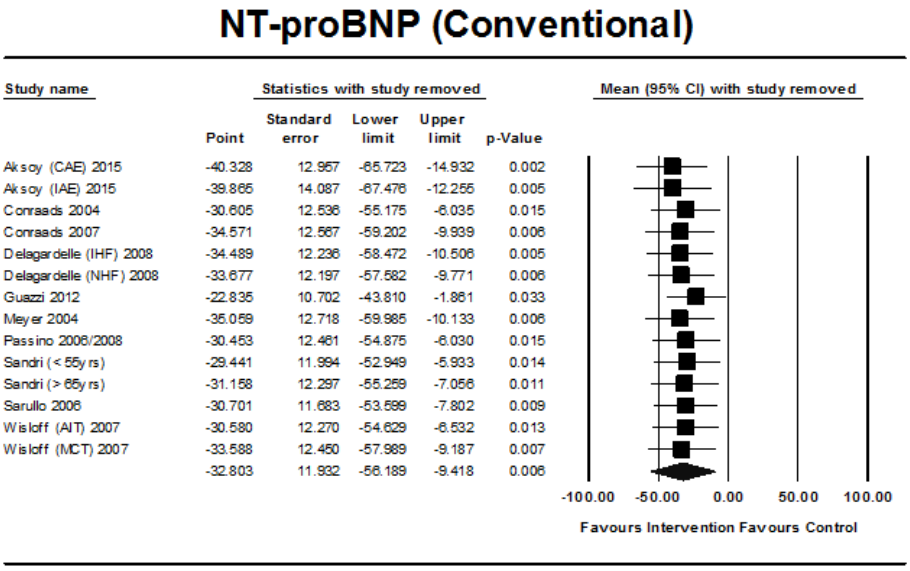


Fig. 2b Sensitivity analysis NT-proBNP (conventional training) with study removed

An additional six[30 34 53-56] studies (Table 2) could not be pooled due to differences in data reporting. Five studies presented data as median (IQR) or median (range) and one[30] study only included HFpEF patients. Two studies [34 54] reported pre to post intervention NT-proBNP changes in exercise participants, but only one[54] study reported a significant difference compared to control participants.

Non-conventional training Pooled data from two[45 57] studies (55 exercise participants, 59 controls) failed to demonstrate a statistically significant improvement in NT-proBNP (pmol/L); MD -157.47 (95%CI -327.64, 12.70) p=0.07 (Fig. 2a). Notably, the large size of the improvement was due to the inclusion of one study[45] (Fig. 2c).

One[42] additional study, in HFpEF patients, not pooled, failed to demonstrate any significant change (Table 2).

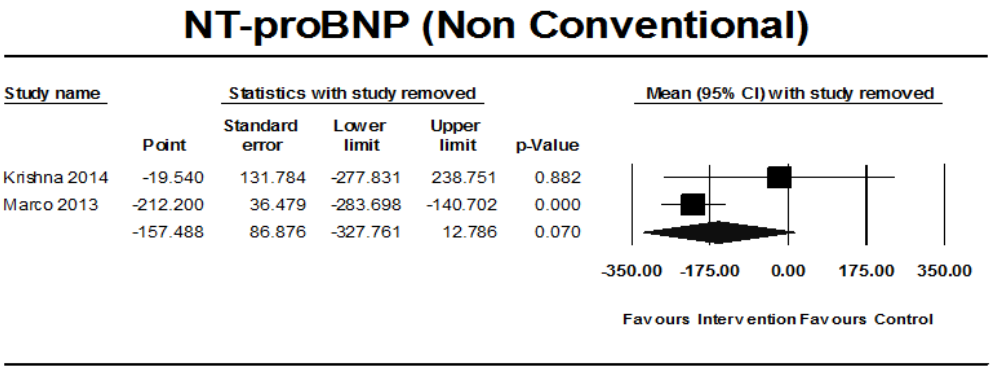


Fig. 2c Sensitivity analysis NT-proBNP (non-conventional training) with study removed

Table 2 Summary of findings of studies for NT-proBNP and BNP not pooled for meta-analysis

Study	Design	Intervention	Analysed E/C	Result
NT-proBNP				
Conventional Training				
Ahmad 2014	RCT	Aerobic	477/451	↔ between groups
Antonicelli 2016	RCT	Aerobic	170/173	↓ in E & significantly different to C
Berendoncks 2010	Controlled	Aerobic & Combined	46/34	↓ in E, but ↔ for Δ between E & C
Edelmann 2011	RCT	Combined	44/20	↔ in E or C
Eleuteri 2013	RCT	Aerobic	11/10	↔ in E or C
Nilsson 2010	RCT	Aerobic	37/33	↔ in E or C or between E & C
Non-Conventional				
Palau 2014	RCT	IMT	14/12	↔ in E or C or between E & C
BNP				
Conventional Training				
Billebeau 2017	Controlled	Aerobic	107/24	↓ in E, ↔ in C
Brubaker 2009	RCT	Aerobic	23/21	↔ between E & C
Kitzman 2010	RCT	Aerobic	26/27	↔ between E & C
Kitzman 2016	RCT	Aerobic	26/25	↔ in E or C
Yamamoto 2007	Controlled	Aerobic	10/8	↓ in E, ↔ in C
Non-Conventional				
Karavidas 2013	RCT	FES	15/15	↔ for Δ between E & C
Yeh 2011	RCT	Tai Chi	50/50	↔ for Δ between E & C

↓ statistically significant, ↔ no statistically significant change, C: control, E: exercise, FES: functional electrical stimulation, IMT: inspiratory muscle training, RCT: randomised controlled trial.

BNP Twenty two studies reported on BNP. Two[32 33] studies contained an overlap of some participants; to avoid duplication of data these studies are represented as one dataset in the meta-analysis.

Meta-analysis Overall exercise demonstrated a statistically significant improvement in BNP (pmol/L); MD -15.02 (95%CI -25.06, -4.99) p=0.003 (Fig. 3a).

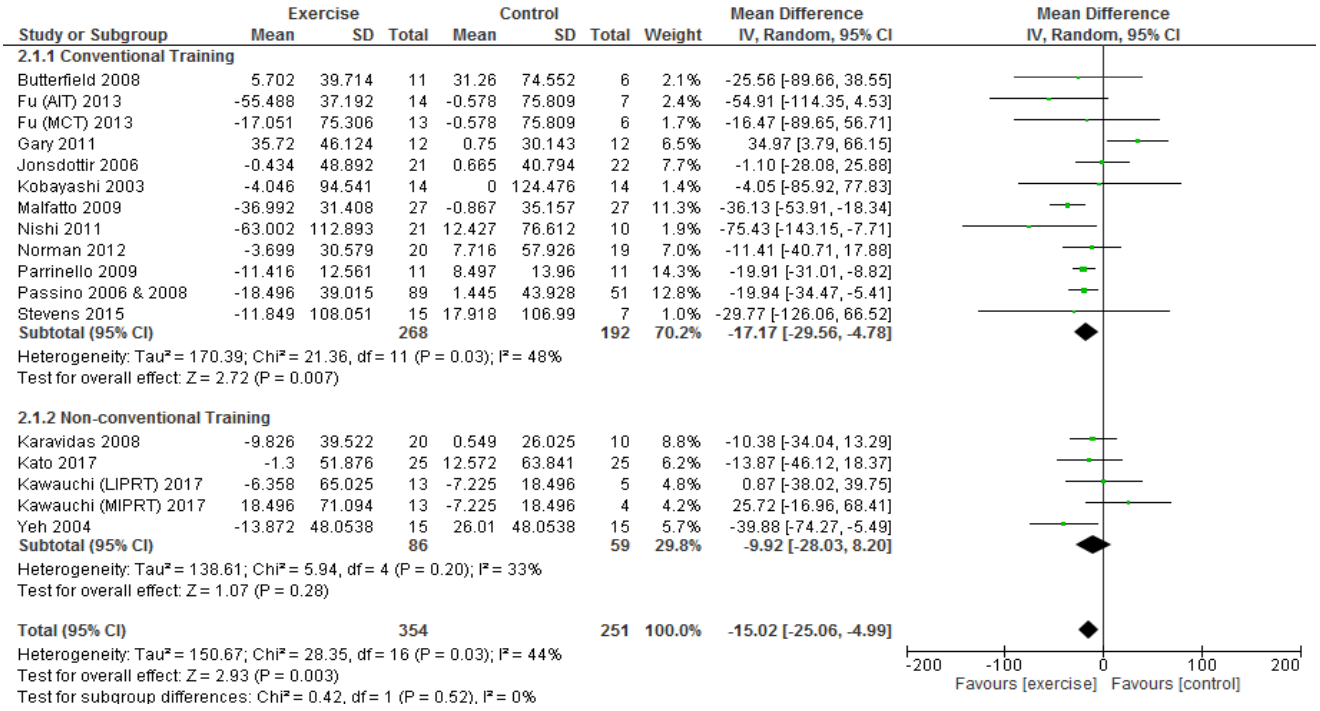


Fig. 3a Change (MD) in BNP (pmol/L) exercise vs. control.
For conversion to pg/ml = pmol/L divided by 0.289.

Conventional training Pooled data from 11 studies [32 33 38 46 58-65](12 intervention groups) (268 exercise participants, 192 controls) demonstrated a statistically significant improvement in BNP (pmol/L) in favour of exercise; MD -17.17 (95%CI -29.56, -4.78) p=0.007(Fig. 3a). Sensitivity analyses using the leave-one out approach revealed that the study of Gary et al. (2011)[66] impacted the size of the result, with an increase in MD and statistical significance with removal of this study (Fig. 3b).

An additional five[22 36 39 40 67] studies using conventional training (Table 2), reported on BNP concentrations, but were not pooled due to differences in data reporting. Two[22 36] studies reported data as median (IQR), two[39 40] studies were in participants with HFpEF and one[67] study did not provide post data but noted no change. Of the five studies, two[22 36] reported decreases post training in exercise participants with no change in controls. The two[39 40] studies with HFpEF patents failed to find any change.

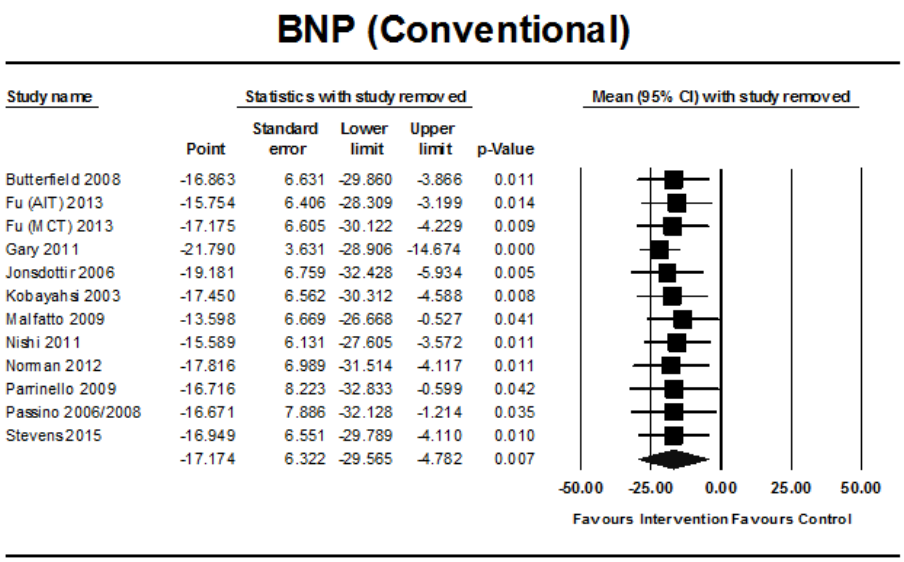


Fig. 3b Sensitivity analysis BNP (conventional training) with study removed

Non-conventional training Pooled data from 4 studies[68-71] (5 intervention groups) (86 exercise participants, 59 controls), failed to demonstrate a statistically significant improvement in BNP (pmol/L) exercise vs. control; MD -9.92 (95%CI -28.03, -8.20) p=0.28 (Fig. 3a). Sensitivity analysis indicated that the study of Kawauchi et al. (2017)[70] affected the magnitude of the result (Fig. 3c). Sensitivity analyses conducted for different correlation coefficients for SD imputation, did not result in any significant variance in overall results. Two[41 72] additional studies, utilising non-conventional training, were not pooled. One[72] reported data as median (IQR) and one[41] was in HFpEF patients, and both failed to demonstrate any significant change (Table 2).

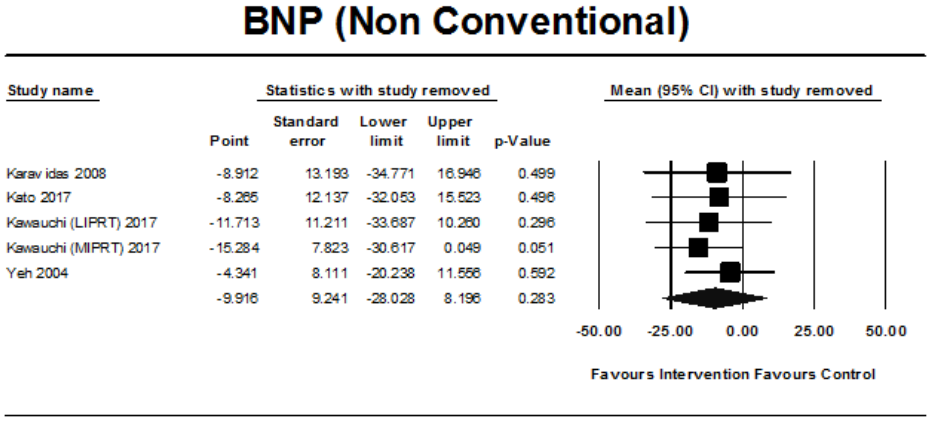


Fig. 3c Sensitivity analysis BNP (non-conventional training) with study removed

Cardiac Troponin (cTnT) Only a sub study of the HF ACTION trial reported on the effect of exercise training on cTnT levels compared to control participants, with no decreases in detectable levels of cTnT found in a cohort of participants from the trial[53].

Galectin-3 Two studies compared Gal-3 in exercising and control participants. However, differences in data reporting did not allow for data pooling. Billebeau et al. (2017)[22] observed a statistically significant ($p<0.001$) median decrease of 6.3% in the exercise group (n=107) with no change in control patients. While Fernandez-Silva et al. (2017)[23] reported no statistically significant difference in the mean change between exercise and control groups ($p=0.69$).

sST2 One study reported pre and post data in regard to the effect of exercise training on sST2 levels. A statistically significant ($p=0.035$) median decrease of 7.4% was observed post training (n=97) by Billebeau et al. (2017)[22], with no change in controls.

MR-proANP Two studies reported on post intervention MR-proANP concentrations. Billebeau et al. (2017)[22] observed a statistically significant ($p<0.001$) median decrease of 16% post training (n=105), with no changes in control participants. In contrast, the post hoc analysis of the Ex-DHF Pilot trial by Trippel et al. (2017)[31] noted no significant treatment effect in HFpEF patients.

MR-proADM Two studies reported on post intervention MR-proADM concentrations. Billebeau et al. (2017)[22] observed a statistically significant ($p=0.001$) 6.4% median decrease in MR-proADM (n=103), with no changes in control participants. In contrast, Trippel et al. (2017)[31] noted no significant treatment effect in HFpEF patients.

CT-proAVP One study by Trippel et al. (2017)[31] reported on CT-proAVP levels and failed to find any statistically significant change post training or compared to the control group in HFpEF patients.

Study quality and reporting

A median TESTEX score of 8.5 out of 15 was obtained (range 6-12) (Supplementary Table S6). Details of randomisation procedures, activity monitoring of control groups, adjustment of relative exercise intensity and provision of adequate details to calculate exercise energy expenditure were frequently lacking.

Heterogeneity and publication bias

Meta-analyses indicated a moderate level of heterogeneity. Visual inspection of the funnel plot showed slight asymmetry (Supplementary Figures 1a and 1b).

DISCUSSION

This systematic review and meta-analysis compiled evidence from a large volume of studies assessing the effect of exercise therapy on established and a selected number of emerging biomarkers in HF patients. Different to previous analyses both conventional and non-conventional modes of training were examined. When analysed separately, conventional training demonstrated a statistically significant improvement in NT-proBNP and BNP, while pooled analyses of non-conventional training failed to demonstrate any significance. While BNP and NT-proBNP are raised across the HF spectrum, as levels may be lower in HFpEF, and in some instances close to normal, we excluded studies from pooled analyses that only included HFpEF patients. However, it is highly likely that a number of other studies included in the analyses with mean ejection fractions >40% would have also included HFpEF patients and it is possible this could be reflected in the variability of the results.

The favourable result demonstrated in pooled analyses of conventional training are consistent with previous reviews[24 73] and a 2011 IPD meta-analysis[25]. However, in contrast to our pooled results, of studies unable to be pooled, only two of seven studies for BNP, and two of the seven studies for NT-proBNP, indicated any significant change post training or compared to controls. Furthermore, one of these studies was a sub analysis of a large cohort from the HF ACTION trial, which found that levels of plasma NT-proBNP did not significantly improve after 3 months of aerobic training[53], clearly contrasting with our result and previous analyses[24 25 73]. However, adherence and participant crossover issues may have confounded the results of the HF ACTION trial. It is also possible, that a longer intervention duration may have resulted in

significant changes, as seen after nine months by Passino et al. (2006)[32], although Sandri et al. (2012)[51] demonstrated significant decreases after only four weeks of endurance training.

Emerging Biomarkers While BNP/NT-proBNP remain the gold standard HF biomarkers, with proven prognostic value, there are limitations. Age, gender, arrhythmias, obesity, renal function, and comorbidities[10 12] may all affect concentrations; hence biomarkers less affected by these issues can provide valuable information. Furthermore, as biomarkers of myocardial stretch, BNP/NT-proBNP are only reflective of one pathophysiological pathway involved in HF, hence biomarkers reflecting other pathways may provide new and valuable information and complement BNP/NT-proBNP. Both Gal-3 and sST2 have been studied as emerging biomarkers in HF, and now have a class IIB recommendation for risk stratification by the ACC/AHA (2013) guideline for HF management[7]. Gal-3, a β-galactoside-binding lectin, plays a dominant role in inflammation, fibrosis and cardiac remodelling[10 12]. Soluble ST2, a member of the Interleukin (IL)-1 receptor family and defined as a ligand for IL-33, is considered a cardiovascular stress protein, associated with fibrosis, cardiac and vascular remodelling and inflammation[74]. Initial evidence also indicates that other novel biomarkers, such as CT-proAVP[20 75 76] and MR-proADM[77], both biomarkers of neurohormonal activation, also have prognostic value in HF.

Current evidence does not allow for any conclusion as to the effect of exercise training on emerging biomarkers. However, the recent studies of Fernandes-Silva et al. (2017)[23] and Billebeau et al. (2017)[22] provide an interesting and perhaps promising platform upon which future research can expand. Billebeau et al. (2017)[22], in a non-randomised trial, observed a significant decrease in BNP, MR-proANP, MR-proADM, Gal-3 and sST2 in exercise training participants with no change in controls. Analysis according to change in VO_{2peak}, demonstrated that patients with an increase in VO_{2peak} ≥14.5% (based on the median increase), experienced a significant decrease in Gal-3, sST2, MR-proADM and MR-proANP compared with no significant biomarker change in participants with change in VO_{2peak}<14.5%[22]. Furthermore, given that BNP improved regardless of the change in VO_{2peak} they concluded that the addition of the newer biomarkers improved the clinical follow-up of rehabilitation[22]. Overall, their results demonstrated that exercise training improves neurohormonal, inflammatory

and fibrotic processes[22]. Fernandes-Silva et al. (2017)[23] observed no significant difference between exercise and control patients for change in Gal-3 or the pro-inflammatory markers (IL-6 and TNF-a), however, VO_{2peak} significantly improved in participants with low baseline Gal-3 levels, compared to patients with high levels, with similar findings for the pro-inflammatory markers. These results suggesting biomarkers may predict a patient's response to training[23]. Interestingly, in a sub study of the HF ACTION trial, higher baseline ST2 levels were associated with a greater improvement in VO_{2peak} at 3 months[78].

Exercise Capacity Reduced exercise capacity is a major hallmark of HF, and NT-proBNP is a strong predictor of VO_{2peak}[79]. Changes in BNP and NT-proBNP have been correlated with changes in VO_{2peak} and suggested therefore as a possible surrogate for evaluating training responses[25]. Only a minimal number of studies included in the review reported associations between change in peak V_{O2peak} and biomarkers. Ahmad et al. (2014)[53], did however observe that in patients in whom NT-proBNP levels decreased there was an increase in VO_{2peak}, despite finding no significant change in NT-proBNP. While Passino et al. (2006)[32] observed that changes in VO_{2peak} correlated significantly with decreases in NT-proBNP and BNP. Recently, Billebeau et al. (2017) found that of all the biomarkers they tested, for predicting change in exercise capacity, MR-proADM best correlated with VO_{2peak}[22]. Given that adrenomedullin originates not only from the heart but from multiple organs, tissues and blood vessels[80] and that the mechanisms associated with improved exercise capacity in HF involve cardiac, vascular and skeletal muscle adaptations[81], a relationship between MR-proADM and improved exercise capacity makes sense.

Phenotype Levels of BNP and NT-proBNP are elevated irrespective of ejection fraction; albeit they are generally lower in HFpEF compared to HFrEF[82-84]. Patients also present with elevated levels of a number of other biomarkers reflective of different pathophysiological pathways. Currently there is limited data on the role of exercise training and biomarkers in HFpEF, and none of the HFpEF studies included in the review reported any significant changes in the biomarkers. Furthermore, it is likely that there exist different biomarker profiles for HFrEF and HFpEF[85 86]. Moving forward these different biomarker profiles may provide valuable information for treatment strategies, including exercise.

Exercise Prescription While moderate continuous training (MCT) has been the cornerstone of conventional HF training, over the past decade the interest in high-intensity interval training (HIIT) has grown[87]. Two studies included in the review that specifically incorporated HIIT and MCT groups for comparative purposes, observed significant improvements in BNP[88] and NT-proBNP[47] from HIIT, with no significant change from MCT. However, this is in contrast to the recent results of the larger, multicentre SMARTEX Heart Failure study, which failed to demonstrate any significant difference between HIIT and MCT after 12 weeks[89]. However, for comparisons, difficulty arises in regard to actual training intensities attained, and in SMARTEX both actual HIIT and MCT intensities attained may have impacted the results, with patients training at lower and higher intensities than prescribed[89].

To date the majority of HF training studies have utilised conventional modes of training, however, not all patients can or are willing to participate in these activities. Women for example, may be more likely to attend mind-body interventions, such as Tai Chi and Yoga, for cardiac rehabilitation purposes[90 91]. Furthermore, both FES and IMT offer alternative modes of physical therapy, particularly in patients unable to participate in more conventional modalities. Individually the included studies investigating FES and IMT failed to demonstrate any significant change in BNP or NT-proBNP compared to control groups. However, the combination of these non-conventional modes with conventional training may provide possible synergistic effects[92], as demonstrated by Caminiti et al. (2011)[93] with combined Tai Chi/Endurance training and Adamopoulos et al. (2014)[92] with combined IMT/AT. Furthermore, other modes of non-conventional exercise therapy, such as weight supported[94] and robot assisted[95] exercise training have demonstrated improvements in BNP and NT-proBNP in HF patients and may be beneficial in some subgroups.

Clinical Significance and Future Research Biomarkers are utilised in HF clinical trials for a number of reasons[10], including establishment of inclusion criteria, outcome measures, explaining therapeutic efficacy and as a target for therapy[96]. Biomarkers and biomarker panels may aid in identifying subgroups of HF patients who may have a more favourable response to exercise therapy, distinguishing responders and non-responders[21 23] in terms of specified outcomes including functional and long-term

outcomes. Different biomarkers may provide further insight into the downstream molecular mechanisms associated with improvements from exercise training[21]. It could be possible that different biomarker profiles respond differently to different intervention characteristics, such as intensity, perhaps allowing further tailoring of the exercise to the individual. Furthermore, biomarkers, with their prognostic utility, may provide useful post intervention information indicating improvements when other favourable outcomes may be absent. It remains premature to draw too many conclusions about the relationship between changes in emerging biomarkers and exercise training, and the utility of these biomarkers in HF is yet to be fully established, but it presents as an interesting and important area for future research.

Future research also needs to consider the clinical interpretation of changes in biomarkers given their biological variation[97]. While NT-proBNP is considered to have high biological variation, the newer markers of sST2 and Gal-3 demonstrate a lower variation and therefore add value to their use[97]. However, from an individual perspective in interpreting clinically meaningful changes in biomarkers, it is suggested that reference change values (RCVs) which indicate the percentage change necessary within an individual, reflective of a true change as opposed to biological variation, be utilised[97].

Strengths and Limitations in the systematic review and meta-analysis

To our knowledge this is the first meta-analysis of BNP and NT-proBNP to include training studies beyond the conventional aerobic and resistance training modalities, and the first review to consider exercise therapy and emerging biomarkers in HF. We aimed to provide a meta-analysis of studies reporting on a selected number of established and emerging biomarkers. However, as biomarker distributions can be skewed; study data may often be presented as median (IQR) or median (range), which precludes it from inclusion in meta-analyses. Valuable information may be ignored if a number of studies are excluded; therefore, upon initial review, and identification of a number of studies that had examined biomarkers and reported data as median or provided a descriptive result, we felt that the inclusion of these studies would enhance the value of the review and analysis. Therefore, we included results of studies reporting data that was considered inappropriate for pooling and only provided a descriptive analysis of these studies.

Studies in which biomarkers were assessed as secondary outcomes may not have been adequately powered to detect significant differences in biomarkers. Furthermore, the studies included in the review reported a wide range of intervention durations, training frequency, session times and intensity. In regard to data pooling, we measured the difference between pre-intervention and post-intervention means, however, in cases where exact p values within groups, or 95% CI were not available, we imputed the SD and hence statistical analysis depended on extrapolated data. However, our imputation was conservative and sensitivity analyses were conducted for different correlation coefficients. Abstracts and trials not reported in English were excluded and could have led to publication bias.

CONCLUSION

Pooled data of conventional training modalities indicated a favourable effect on the established HF biomarkers NT-proBNP and BNP, contrasting with information from a number of non-pooled studies. Limited evidence exists in regard to exercise training and emerging biomarkers. Given the complex pathways involved in the onset and progression of HF, more research is required to establish exactly how established and emerging biomarkers can be utilised in exercise training in this population. The use of multiple biomarkers is an area of active research in HF, and future studies utilising biomarker panels may prove beneficial in guiding non-pharmacological therapy such as exercise by facilitating a more precise approach to exercise for subgroups of patients.

Contributors MJP designed the review, conducted the literature search, extracted data, undertook data analysis and wrote the manuscript. NK assisted with preparation of study quality assessment and review of manuscript. NAS assisted in selecting eligible articles, review and editing of manuscript. All authors approved the final manuscript

Funding M.J Pearson is supported by an Australian Postgraduate Award Scholarship. This work received no other financial support and has no relationship to industry

Competing interests none

Data sharing statement No additional data are available

References

1. Taylor RS, Sagar VA, Davies EJ, et al. Exercise-based rehabilitation for heart failure. *The Cochrane Library* 2014
2. Ismail H, McFarlane JR, Nojoumian AH, et al. Clinical outcomes and cardiovascular responses to different exercise training intensities in patients with heart failure: a systematic review and meta-analysis. *JACC: Heart Failure* 2013;1(6):514-22.
3. Pearson M, Smart N. Exercise therapy and autonomic function in heart failure patients: a systematic review and meta-analysis. *Heart failure reviews* 2017:1-18.
4. Dieberg G, Ismail H, Giallauria F, et al. Clinical outcomes and cardiovascular responses to exercise training in heart failure patients with preserved ejection fraction: a systematic review and meta-analysis. *Journal of Applied Physiology* 2015;119(6):726-33.
5. Pearson M, Smart N. Effect of exercise training on endothelial function in heart failure patients: A systematic review meta-analysis. *International journal of cardiology* 2017;231:234-43.
6. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *European Heart Journal* 2016;37(27):2129-200m. doi: 10.1093/eurheartj/ehw128
7. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American college of cardiology foundation/american heart association task force on practice guidelines. *Journal of the American College of Cardiology* 2013;62(16):e147-e239. doi: 10.1016/j.jacc.2013.05.019
8. Senthong V, Kirsop JL, Tang WW. Clinical phenotyping of heart failure with biomarkers: current and future perspectives. *Current heart failure reports* 2017;14(2):106-16.
9. Cypen J, Ahmad T, Testani JM, et al. Novel Biomarkers for the Risk Stratification of Heart Failure with Preserved Ejection Fraction. *Current heart failure reports* 2017;14(5):434-43.
10. Chow SL, Maisel AS, Anand I, et al. Role of Biomarkers for the Prevention, Assessment, and Management of Heart Failure: A Scientific Statement From the American Heart Association. *Circulation* 2017;135(22):e1054-e91.
11. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure. *Journal of cardiac failure* 2017;23(8):628-51.
12. Berezin AE. Up-to-date clinical approaches of biomarkers' use in heart failure. *Biomedical Research and Therapy* 2017;4(6):1344-73. doi: 10.15419/bmrat.v4i06.178
13. Braunwald E. Heart Failure. *JACC: Heart Failure* 2013;1(1):1-20.
14. Aimo A, Vergaro G, Passino C, et al. Prognostic Value of Soluble Suppression of Tumorigenicity-2 in Chronic Heart Failure: A Meta-Analysis. *JACC: Heart Failure* 2017;5(4):280-86.
15. Miller WL, Saenger AK, Grill DE, et al. Prognostic value of serial measurements of soluble suppression of tumorigenicity 2 and galectin-3 in ambulatory patients with chronic heart failure. *Journal of cardiac failure* 2016;22(4):249-55.
16. Imran TF, Shin HJ, Mathenge N, et al. Meta-Analysis of the Usefulness of Plasma Galectin-3 to Predict the Risk of Mortality in Patients With Heart Failure and in the General Population. *The American Journal of Cardiology* 2017;119(1):57-64.
17. French B, Wang L, Ky B, et al. Prognostic value of galectin-3 for adverse outcomes in chronic heart failure. *Journal of cardiac failure* 2016;22(4):256-62.
18. Pascual-Figal DA, Ordoñez-Llanos J, Tornel PL, et al. Soluble ST2 for predicting sudden cardiac death in patients with chronic heart failure and left ventricular systolic dysfunction. *Journal of the American College of Cardiology* 2009;54(23):2174-79.
19. Ahmad T, Fiuzat M, Neely B, et al. Biomarkers of myocardial stress and fibrosis as predictors of mode of death in patients with chronic heart failure. *JACC: Heart Failure* 2014;2(3):260-68. doi: 10.1016/j.jchf.2013.12.004

20. Zhang P, Wu X, Li G, et al. Prognostic role of copeptin with all-cause mortality after heart failure: a systematic review and meta-analysis. *Therapeutics and clinical risk management* 2017;13:49.
21. Masterson Creber RM, Lee CS, Margulies K, et al. Identifying biomarker patterns and predictors of inflammation and myocardial stress. *Journal of Cardiac Failure* 2015;21(6):439-45. doi: 10.1016/j.cardfail.2015.02.006
22. Billebeau G, Vodovar N, Sadoune M, et al. Effects of a cardiac rehabilitation programme on plasma cardiac biomarkers in patients with chronic heart failure. *European Journal of Preventive Cardiology* 2017;24(11):1127-35. doi: 10.1177/2047487317705488
23. Fernandes-Silva MM, Guimarães GV, Rigaud VOC, et al. Inflammatory biomarkers and effect of exercise on functional capacity in patients with heart failure: Insights from a randomized clinical trial. *European Journal of Preventive Cardiology* 2017;24(8):808-17. doi: 10.1177/2047487317690458
24. Smart N, Steele M. Systematic review of the effect of aerobic and resistance exercise training on systemic brain natriuretic peptide (BNP) and N-terminal BNP expression in heart failure patients. *International journal of cardiology* 2010;140(3):260-65.
25. Smart NA, Meyer T, Butterfield JA, et al. Individual patient meta-analysis of exercise training effects on systemic brain natriuretic peptide expression in heart failure. *European journal of preventive cardiology* 2012;19(3):428-35.
26. Fu R, Vandermeer BW, Shamliyan TA, et al. Handling continuous outcomes in quantitative synthesis. 2013
27. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327(7414):557-60.
28. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315(7109):629-34.
29. Smart NA, Waldron M, Ismail H, et al. Validation of a new tool for the assessment of study quality and reporting in exercise training studies: TESTEX. *International Journal of Evidence-Based Healthcare* 2015;13(1):9-18.
30. Edelmann F, Gelbrich G, Düngen H-D, et al. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. *Journal of the American College of Cardiology* 2011;58(17):1780-91.
31. Trippel TD, Holzendorf V, Halle M, et al. Ghrelin and hormonal markers under exercise training in patients with heart failure with preserved ejection fraction: results from the Ex-DHF pilot study. *ESC Heart Failure* 2017;4(1):56-65.
32. Passino C, Severino S, Poletti R, et al. Aerobic training decreases B-type natriuretic peptide expression and adrenergic activation in patients with heart failure. *Journal of the American College of Cardiology* 2006;47(9):1835-39.
33. Passino C, Del Ry S, Severino S, et al. C-type natriuretic peptide expression in patients with chronic heart failure: effects of aerobic training. *European Journal of Cardiovascular Prevention & Rehabilitation* 2008;15(2):168-72.
34. Van Berendoncks AM, Beckers P, Hoymans VY, et al. Exercise training reduces circulating adiponectin levels in patients with chronic heart failure. *Clinical Science* 2010;118(4):281-89. doi: 10.1042/CS20090213
35. Conraads VM, Beckers P, Vaes J, et al. Combined endurance/resistance training reduces NT-proBNP levels in patients with chronic heart failure. *European Heart Journal* 2004;25(20):1797-805.
36. Yamamoto U, Mohri M, Shimada K, et al. Six-month aerobic exercise training ameliorates central sleep apnea in patients with chronic heart failure. *Journal of cardiac failure* 2007;13(10):825-29.

37. Delagardelle C, Feiereisen P, Vaillant M, et al. Reverse remodelling through exercise training is more pronounced in non-ischemic heart failure. *Clinical Research in Cardiology* 2008;97(12):865.
38. Nishi I, Noguchi T, Iwanaga Y, et al. Effects of exercise training in patients with chronic heart failure and advanced left ventricular systolic dysfunction receiving β-blockers. *Circulation Journal* 2011;75(7):1649-55.
39. Kitzman DW, Brubaker P, Morgan T, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. *Jama* 2016;315(1):36-46.
40. Kitzman DW, Hundley WG, Brubaker PH, et al. A randomized double-blind trial of enalapril in older patients with heart failure and preserved ejection fraction: Effects on exercise tolerance and arterial distensibility. *Circulation: Heart Failure* 2010;3(4):477-85. doi: 10.1161/CIRCHEARTFAILURE.109.898916
41. Karavidas A, Driva M, Parissis JT, et al. Functional electrical stimulation of peripheral muscles improves endothelial function and clinical and emotional status in heart failure patients with preserved left ventricular ejection fraction. *American heart journal* 2013;166(4):760-67.
42. Palau P, Domínguez E, Núñez E, et al. Effects of inspiratory muscle training in patients with heart failure with preserved ejection fraction. *European Journal of Preventive Cardiology* 2014;21(12):1465-73. doi: 10.1177/2047487313498832
43. Aksoy S, Findikoglu G, Ardic F, et al. Effect of 10-Week Supervised Moderate-Intensity Intermittent vs. Continuous Aerobic Exercise Programs on Vascular Adhesion Molecules in Patients with Heart Failure. *American journal of physical medicine & rehabilitation / Association of Academic Physiatrists* 2015;94(10):898-911. doi: 10.1097/PHM.0000000000000306
44. Antonicelli R, Spazzafumo L, Scalvini S, et al. Exercise: a "new drug" for elderly patients with chronic heart failure. *Aging (Albany NY)* 2016;8(5):860.
45. Krishna BH, Pal P, Pal GK, et al. A randomized controlled trial to study the effect of yoga therapy on cardiac function and N terminal Pro BNP in heart failure. *Integrative medicine insights* 2014;9:1.
46. Jónsdóttir S, Andersen KK, Sigurðsson AF, et al. The effect of physical training in chronic heart failure. *European journal of heart failure* 2006;8(1):97-101.
47. Wisløff U, Støylen A, Loennechen JP, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients. *Circulation* 2007;115(24):3086-94.
48. Conraads VM, Vanderheyden M, Paelinck B, et al. The effect of endurance training on exercise capacity following cardiac resynchronization therapy in chronic heart failure patients: a pilot trial. *European Journal of Cardiovascular Prevention & Rehabilitation* 2007;14(1):99-106.
49. Guazzi M, Vitelli A, Arena R. The effect of exercise training on plasma NT-pro-BNP levels and its correlation with improved exercise ventilatory efficiency in patients with heart failure. *International journal of cardiology* 2012;158(2):290-91.
50. Meyer T, Schwaab B, Görge G, et al. Can serum NT-proBNP detect changes of functional capacity in patients with chronic heart failure? *Zeitschrift fur Kardiologie* 2004;93(7):540-45.
51. Sandri M, Kozarez I, Adams V, et al. Age-related effects of exercise training on diastolic function in heart failure with reduced ejection fraction: the Leipzig Exercise Intervention in Chronic Heart Failure and Aging (LEICA) Diastolic Dysfunction Study. *European heart journal* 2012;33(14):1758-68. doi: 10.1093/eurheartj/ehr469
52. Maria Sarullo F, Gristina T, Brusca I, et al. Effect of physical training on exercise capacity, gas exchange and N-terminal pro-brain natriuretic peptide levels in patients with chronic heart failure. *Eur J Cardiovasc Prev Rehabil* 2006;13(5):812-7. doi: 10.1097/01.hjr.0000238396.42718.61 [published Online First: 2006/09/27]

53. Ahmad T, Fiuzat M, Mark DB, et al. The effects of exercise on cardiovascular biomarkers in patients with chronic heart failure. *American Heart Journal* 2014;167(2):193-202.e1. doi: 10.1016/j.ahj.2013.10.018
54. Antonicelli R, Spazzafumo L, Scalvini S, et al. Exercise: a "new drug" for elderly patients with chronic heart failure. *Aging* 2016; 8(5). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/824/CN-01426824/frame.html.
55. Eleuteri E, Mezzani A, Di Stefano A, et al. Aerobic training and angiogenesis activation in patients with stable chronic heart failure: a preliminary report. *Biomarkers* 2013;18(5):418-24. doi: 10.3109/1354750x.2013.805342 [published Online First: 2013/06/29]
56. Nilsson B, Westheim A, Risberg M, et al. No effect of group-based aerobic interval training on N-terminal pro- B-type natriuretic peptide levels in patients with chronic heart failure. *Scandinavian cardiovascular journal : SCJ* 2010; 44(4). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/682/CN-00759682/frame.html.
57. Marco E, Ramírez-Sarmiento AL, Coloma A, et al. High-intensity vs. sham inspiratory muscle training in patients with chronic heart failure: A prospective randomized trial. *European Journal of Heart Failure* 2013;15(8):892-901. doi: 10.1093/eurjhf/hft035
58. Fu T-c, Wang C-H, Lin P-S, et al. Aerobic interval training improves oxygen uptake efficiency by enhancing cerebral and muscular hemodynamics in patients with heart failure. *International journal of cardiology* 2013;167(1):41-50.
59. Butterfield JA, Faddy SC, Davidson P, et al. Exercise training in patients with stable chronic heart failure: effects on thoracic impedance cardiography and B-type natriuretic peptide. *J Cardiopulm Rehabil Prev* 2008;28(1):33-7. doi: 10.1097/01.HCR.0000311506.49398.6d [published Online First: 2008/02/19]
60. Gary RA, Cress ME, Higgins MK, et al. Combined aerobic and resistance exercise program improves task performance in patients with heart failure. *Arch Phys Med Rehabil* 2011;92(9):1371-81. doi: 10.1016/j.apmr.2011.02.022 [published Online First: 2011/09/01]
61. Malfatto G, Branzi G, Osculati G, et al. Improvement in left ventricular diastolic stiffness induced by physical training in patients with dilated cardiomyopathy. *J Card Fail* 2009;15(4):327-33. doi: 10.1016/j.cardfail.2008.10.032 [published Online First: 2009/04/29]
62. Kobayashi N, Tsuruya Y, Iwasawa T, et al. Exercise training in patients with chronic heart failure improves endothelial function predominantly in the trained extremities. *Circulation journal* 2003;67(6):505-10.
63. Norman J, Pozehl B, Duncan K, et al. Effects of Exercise Training versus Attention on Plasma B-type Natriuretic Peptide, 6-Minute Walk Test and Quality of Life in Individuals with Heart Failure. *Cardiopulmonary physical therapy journal* 2012; 23. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/337/CN-00870337/frame.html.
64. Parrinello G, Torres D, Paterna S, et al. Short-term walking physical training and changes in body hydration status, B-type natriuretic peptide and C-reactive protein levels in compensated congestive heart failure. *Int J Cardiol* 2010;144(1):97-100. doi: 10.1016/j.ijcard.2008.12.130 [published Online First: 2009/01/30]
65. Stevens AL, Hansen D, Herbots L, et al. Exercise training improves insulin release during glucose tolerance testing in stable chronic heart failure patients. *J Cardiopulm Rehabil Prev* 2015;35(1):37-46. doi: 10.1097/hcr.0000000000000092 [published Online First: 2014/12/24]
66. Gary R, Cress M, Higgins M, et al. Combined aerobic and resistance exercise program improves task performance in patients with heart failure. *Archives of physical medicine and rehabilitation* 2011; 92(9). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/277/CN-00798277/frame.html.
67. Brubaker PH, Moore JB, Stewart KP, et al. Endurance Exercise Training in Older Patients with Heart Failure: Results from a Randomized, Controlled, Single-Blind Trial. *Journal of the American Geriatrics Society* 2009;57(11):1982-89.

68. Karavidas A, Parissis J, Arapi S, et al. Effects of functional electrical stimulation on quality of life and emotional stress in patients with chronic heart failure secondary to ischaemic or idiopathic dilated cardiomyopathy: a randomised, placebo-controlled trial. *European journal of heart failure* 2008; 10(7). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/607/CN-00668607/frame.html.
69. Kato Y, Suzuki S, Uejima T, et al. Impact of BNP level and peak VO2 on future heart failure events: comparison between sinus rhythm and atrial fibrillation. *Heart Vessels* 2017;32(4):428-35. doi: 10.1007/s00380-016-0887-x [published Online First: 2016/08/24]
70. Kawauchi TS, Umeda IIK, Braga LM, et al. Is there any benefit using low-intensity inspiratory and peripheral muscle training in heart failure? A randomized clinical trial. *Clinical Research in Cardiology* 2017;106(9):676-85.
71. Yeh G, Wood M, Lorell B, et al. Effects of tai chi mind-body movement therapy on functional status and exercise capacity in patients with chronic heart failure: a randomized controlled trial. *American journal of medicine* 2004; 117(8). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/881/CN-00491881/frame.html.
72. Yeh GY, McCarthy EP, Wayne PM, et al. Tai chi exercise in patients with chronic heart failure: A randomized clinical trial. *Archives of Internal Medicine* 2011;171(8):750-57. doi: 10.1001/archinternmed.2011.150
73. Cipriano G, Cipriano VT, Da Silva VZM, et al. Aerobic exercise effect on prognostic markers for systolic heart failure patients: a systematic review and meta-analysis. *Heart failure reviews* 2014;19(5):655-67.
74. Pascual-Figal DA, Januzzi JL. The biology of ST2: the international ST2 consensus panel. *American Journal of Cardiology* 2015;115(7):3B-7B.
75. Zhong Y, Wang R, Yan L, et al. Copeptin in heart failure: Review and meta-analysis. *Clinica Chimica Acta* 2017
76. Balling L, Gustafsson F. Copeptin as a biomarker in heart failure. *Biomarkers in medicine* 2014;8(6):841-54.
77. Yuyun MF, Narayan HK, Ng LL. Prognostic significance of adrenomedullin in patients with heart failure and with myocardial infarction. *The American journal of cardiology* 2015;115(7):986-91.
78. Felker GM, Fiuzat M, Thompson V, et al. Soluble ST2 in Ambulatory Patients with Heart Failure Association with Functional Capacity and Long-Term Outcomes. *Circulation: Heart Failure* 2013;6(6):1172-79. doi: 10.1161/CIRCHEARTFAILURE.113.000207
79. Felker GM, Whellan D, Kraus WE, et al. N-terminal pro-brain natriuretic peptide and exercise capacity in chronic heart failure: Data from the Heart Failure and a Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study. *American Heart Journal* 2009;158(4 SUPPL.):S37-S44. doi: 10.1016/j.ahj.2009.07.011
80. Nishikimi T, Nakagawa Y. Adrenomedullin as a Biomarker of Heart Failure. *Heart failure clinics* 2018;14(1):49-55.
81. Tucker WJ, Lijauco CC, Hearon Jr CM, et al. Mechanisms of the Improvement in Peak VO2 with Exercise Training in Heart Failure with Reduced or Preserved Ejection Fraction. *Heart, Lung and Circulation* 2018;27(1):9-21.
82. Komajda M, Carson PE, Hetzel S, et al. Factors associated with outcome in heart failure with preserved ejection fraction: findings from the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE). *Circulation: Heart Failure* 2010:CIRCHEARTFAILURE. 109.932996.
83. Masson S, Latini R, Anand IS, et al. Direct comparison of B-type natriuretic peptide (BNP) and amino-terminal proBNP in a large population of patients with chronic and symptomatic heart failure: the Valsartan Heart Failure (Val-HeFT) data. *Clinical chemistry* 2006;52(8):1528-38.

84. van Veldhuisen DJ, Linssen GC, Jaarsma T, et al. B-type natriuretic peptide and prognosis in heart failure patients with preserved and reduced ejection fraction. *Journal of the American College of Cardiology* 2013;61(14):1498-506.
85. Tromp J, Khan MA, Klip IT, et al. Biomarker Profiles in Heart Failure Patients With Preserved and Reduced Ejection Fraction. *Journal of the American Heart Association* 2017;6(4):e003989.
86. Sanders-van Wijk S, van Empel V, Davarzani N, et al. Circulating biomarkers of distinct pathophysiological pathways in heart failure with preserved vs. reduced left ventricular ejection fraction. *European journal of heart failure* 2015;17(10):1006-14.
87. Pearson M, Smart N. Aerobic Training Intensity for Improved Endothelial Function in Heart Failure Patients: A Systematic Review and Meta-Analysis. *Cardiology research and practice* 2017;2017
88. Fu TC, Wang CH, Lin PS, et al. Aerobic interval training improves oxygen uptake efficiency by enhancing cerebral and muscular hemodynamics in patients with heart failure. *International Journal of Cardiology* 2013;167(1):41-50. doi: 10.1016/j.ijcard.2011.11.086
89. Ellingsen Ø, Halle M, Conraads V, et al. High-Intensity Interval Training in Patients With Heart Failure With Reduced Ejection FractionClinical Perspective. *Circulation* 2017;135(9):839-49.
90. Salmoirago-Blotcher E, Wayne PM, Dunsiger S, et al. Tai chi is a promising exercise option for patients with coronary heart disease declining cardiac rehabilitation. *Journal of the American Heart Association* 2017;6(10):e006603.
91. Liu T, Chan AW, Liu YH, et al. Effects of Tai Chi-based cardiac rehabilitation on aerobic endurance, psychosocial well-being, and cardiovascular risk reduction among patients with coronary heart disease: A systematic review and meta-analysis. *European Journal of Cardiovascular Nursing* 2017:1474515117749592.
92. Adamopoulos S, Schmid JP, Dendale P, et al. Combined aerobic/inspiratory muscle training vs. aerobic training in patients with chronic heart failure. *European journal of heart failure* 2014;16(5):574-82.
93. Caminiti G, Volterrani M, Marazzi G, et al. Tai chi enhances the effects of endurance training in the rehabilitation of elderly patients with chronic heart failure. *Rehabilitation research and practice* 2011;2011
94. Jiao D-D, Zhang W-Y, Xu J, et al. Effect of weight support exercise therapy on the cardiac function in patients with chronic heart failure. *Journal of Hainan Medical University* 2016;22(20):21-23.
95. Schoenrath F, Markendorf S, Brauchlin A, et al. Robot-assisted training for heart failure patients - a small pilot study. *Acta cardiologica* 2015; 70(6). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/533/CN-01168533/frame.html.
96. Ibrahim NE, Gaggin HK, Konstam MA, et al. Established and emerging roles of biomarkers in heart failure clinical trials. *Circulation: heart failure* 2016;9(9):e002528.
97. Meijers WC, van der Velde AR, Muller Kobold AC, et al. Variability of biomarkers in patients with chronic heart failure and healthy controls. *European journal of heart failure* 2017;19(3):357-65.

Online supplementary material

Supplementary Material

Appendix 1

Effect of exercise therapy on established and emerging biomarkers in heart failure patients: a systematic review and meta-analysis

Melissa J. Pearson, Nicola King and Neil A. Smart

Supplementary Table S1 Excluded studies

Study	Reason for Exclusion
Adamopoulos (2014)	Comparison to two different training modalities (aerobic/IMT vs. aerobic/sham IMT), no usual care/no exercise control group
Arad (2008)	Single group pre-post study, no usual care/no exercise control group
Braith (1999)	Biomarker outcome (ANP) does not meet inclusion criteria
Beckers (2008)	Comparison of two different training modalities (CT vs. ET), no usual care/no exercise control group
Besson (2013)	Comparison of Eccentric ergometer training to Concentric(standard ergometer) training
Caminiti (2011)	Comparison of two different training modalities (Tai Chi vs. Tai Chi/ET), no usual care/no exercise control group
Casillas (2016)	Comparison of Eccentric ergometer training to Concentric(standard ergometer) training
Ellingsen (2011) SMARTEX	Comparison of three training modalities (HIIT vs. MCT vs. RRE), no usual care/no exercise control group
Giallauria (2006)	Authors do not note a specific chronic heart failure diagnosis
Giallauria (2008)	Authors do not note a specific chronic heart failure diagnosis
Hagglund (2017)	Comparison of two different training modalities (Yoga vs. Hydrotherapy), no usual care/no exercise control group
Haseba (2016)	Comparison of exercise with exercise/sauna therapy, no separate usual care/no exercise control group
Jiao (2016)	Exercise did not fit inclusion criteria – weight supported training
Karavidas (2010)	Comparison of FES in NYHA Class II to NYHA Class III/IV
Kiilavuori (1999)	Biomarker outcome (proANP) did not meet inclusion criteria
Laoutaris (2008)	Comparison of two different training protocols (HITG IMT vs. LITG IMT), no usual care/no exercise control group
Legallois (2016)	Single group pre-post study, no usual care/no exercise control group
Lima (2010)	Patients with Chagas cardiomyopathy
Municino (2006)	Single group pre-post study, no usual care/no exercise control group
Nakanishi (2017)	Single group pre-post study, no usual care/no exercise control group
Ozasa (2011)	Machine assisted cycling vs. conventional ET, no usual care/no exercise control group
Prescott (2009)(a)	Single group pre-post study, no usual care/no exercise control group
Prescott (2009)(b)	All participants previously participated in an exercise rehabilitation program
Pritchett (2012)	The exercise group also consisted of dietary changes, no separate exercise only group
Radi (2017)	Patients had been hospitalised for acute HF, intervention 1 month
Reda (2017)	Patients had decompensated heart failure and intervention < 4 weeks
Rengo (2014)	Single group pre-post study, no usual care/no exercise control group
Schoenrath (2015)	Single group pre-post study, no usual care/no exercise control group
Stout (2012)	Comparison of Exercise + Testosterone vs. Exercise, no usual care/no exercise control group
Svealv (2009)	Crossover trail, no separate control group
Takagawa (2017)	Single group pre-post study, no usual care/no exercise control group
Van Buuren (2017)	Comparison of two different training protocols (EEMS vs. LEMS), no usual care/no exercise control group
Yamauchi (2016)	Single group pre-post study, no usual care/no exercise control group
Yeh (2013)	Comparison of two different training modalities (Tai Chi vs. Aerobic) no usual care/no exercise control group

Supplementary Table S2 Baseline Levels NT-proBNP (pg/ml) & BNP (pg/ml)

Study	Baseline NT-proBNP (pg/ml)	
	Exercise	**Control**
Ahmad 2014	693.7 (276.1, 1725) *	778.5 (296.7, 1825) *
Aksoy 2015 [(1)]	203.4±154.8 176.2±152.9	262.3±215.2
Antonicelli 2015	1236 (2038)**	618 (520)**
Berendoncks 2010	1216 (530–2887)*	833 (373–2477)*
Conraads 2004	2124±397 (SE)	1228±240 (SE)
Conraads 2007	2325±785 (SE)	1269±296 (SE)
Delagardelle 2008	1145±1185 1431±1537	1143±1793 1971±2379
Edelmann 2011	157±17	172±110
Eleuteri 2013	853 (87–3772)***	545.6 (62–3312)***
Guazzi 2012	1088.1±447.1	1110±312.9
Krishna 2014	3965.48±1365.08	5495.47±1382.5
Nilsson 2010 [(2)]	1412 (753, 2486) *	1987 (1108, 3315)*
Marco 2013	1677.4±1658.4	2212.9±3155.5
Meyer 2004	1092±980	1075±1067
Passino 2006/2008[(3)]	1382±1478	1708±1680
Palau 2014	983 (325–1932)*	1314 (255–1868)*
Sandri 2012	1675±354 (SE) 1426±189 (SE)	1426±189 (SE) 1509±327 (SE)
Sarullo 2006	3376±3133	3285±3012
Wisloff 2007	1305±714 1521±1281	1321±148
	Baseline BNP (pg/ml)	
	Exercise	**Control**
Billebeau 2017	293 (158,757)*	137 (44, 148)* (n=12)
Brubaker 2009	NR	NR
Butterfield 2008	355±352	646±348
Fu 2013 [(4)]	405± 453±	483±
Gary 2011	184.4±151.6	105.8±159.1
Jonsdottir 2006	173.2±180.4	122.2±121.8
Karavidas 2008	563.5±136.2	521.7±9.5
Karavidas 2013	646±188	668±209
Kato 2017	185.6±178.6	224.7±180.4
Kawauchi 2017	339±291 303±301	168±108
Kitzman 2010	45±56	72±122
Kitzman 2016	23.6 (19.4, 39.4)*	21.9 (18.2, 26.5)*
Kobayashi 2003	281±92 (SE)	383±89 (SE)
Malfatto 2009	293±115	318±125
Nishi 2011	432±451	238±130
Norman 2012	103.2±108.5	175.1±182.1
Parrinello 2009	205.2±46.5	210.4±51.5
Passino 2006/2008[(3)]	193±199	194±180
Stevens 2015	281±95 (SE)	285±117 (SE)
Yamamoto 2007	273.9 (108.1, 658)*	177.8 (161.5, 241.7)*
Yeh 2004	329±377	285±340
Yeh 2011	102 (47, 212)*	106 (42, 493)*

Mean±SD unless otherwise noted, * Median (IQR), **Median (interval), ***Median (range)
[(1)] Converted from fmol/ml [(2)] converted from pmol/l, [(3)] Data from Passino 2006 and 2008 consolidated into one dataset.
[(4)] extracted from graph

Supplementary Table S3 Detailed Exercise Intervention Characteristics

Study	Modality	Duration	Sessions/week	Total Time per session	Intensity
Ahmad 2014	Aerobic (group based walking, treadmill or cycling)	3 months	3	15-30 min	60%HRR and ramped up
Aksoy 2015	Aerobic (Cycle) 2 groups: Interval & Continuous	10 weeks	3	35 min (includes 5 min WU & 5 min CD)	Starting power @50%VO_{2peak}, ↑every 2 weeks to power @ 75% VO_{2peak} @ week 10. Interval group - 60s work to 30s recovery (17 cycles)
Antonicelli 2016	Aerobic (cycle) 3 months supervised, 3 months home	6 months	3	50 min (includes 10min WU & CD)	20 min @ 60-70%HR_{max}
Berendoncks 2010	Aerobic and Combined Training	4 months	3	60 min (includes 5 min WU & CD)	AT intensity 90%HR @ ANT. Initial RM intensity 50% 1RM with an increase to 60% after 2 months
Billebeau 2017	Aerobic (cycle, treadmill or rowers)	4-6 months	2		Workload @ VAT
Brubaker 2009	Aerobic (walking & cycle)	16 weeks	3	60 min (includes WU & CD)	40-50% HRR (weeks 1-2), increased to 60-70% HRR
Butterfield 2008	Combined Training. 1 x groups session @ hospital (65 min) (45 min circuit) plus daily home-based walking (45 min)	12 weeks	7	>45 min	
Conraads 2007	Aerobic (cycle & waking)	4 months	3	60 min (includes 5 min WU & CD)	HR @ 90%VT
Conraads 2004	Combined	4 months	3	60 min (includes WU & CD)	AT intensity - HR @ 90%VT, RT intensity - 50% 1RM, increased to 60% after 2 months
Delagardelle 2008	Aerobic (cycle & treadmill), Strength, Combined (3 groups)	13.3 weeks	3	45 min (includes 5 WU)	AT intensity – 60% VO_{2peak} increased to 75%VO_{2peak} RT intensity – 60% 1RM, increased to 70% 1RM
Rx-DHF Pilot Edelmann 2011 & Trippel 2017	Combined Training, initially aerobic (cycling) weeks 1-4 (20-40 min), with addition of RT @ week 5	12 weeks	2-3 (AT) 2 (RT)	40 min +	AT: HR @ 50-60% VO_{2peak} (weeks 1-4) ↑HR @ 70% VO_{2peak} 2 week 5, RT @ 60-65%1RM (15 reps)
Eleuteri 2013	Aerobic (cycle)	3 months	5	40 min (includes 5 min WU & 5 min CD)	Power & HR @ VAT
Fernandez-Silva 2017	Aerobic (cycle) 2 groups, Interval (1 min: 2 min) and Continuous	12 weeks	3	40 min (includes 5 min WU & 5 min CD)	Interval: THR= 1 min @ HR @ RCP, 2 min @ HR @ AT, Continuous: THR = [HR @ RCP + 2 (HR @ AT)]/3 (NB: both groups same average workload @ end 30 min)
Fu 2013	Aerobic (cycle) 2 groups, Intervals 5 x 3 with 3 min recovery (30 min), Continuous (30 min), both programs isocaloric. Supervised	12 weeks	3	30 min (+ 3 min WP & 3 min CD)	Interval: 5 x 3 @ 80% VO_{2peak}, 3 min recovery @ 40% VO_{2peak} between each interval Continuous @ 60% VO_{2peak}
Gary 2011	Combined Training (walking and RT)	12 weeks	3 (AT) 2-3 (RT)	30-60 min 45-60 min	AT intensity- started 50% HRR, increased 70%HRR RT started @ 2 x 12-15 reps. Increased to 3 x 12-15 reps
Guazzi 2012	Aerobic	24 weeks	4	40 min	80% HRR (60% for first 2 weeks)

Jonsdottir 2006	Combined (Cycle and circuit RT)	5 months	2	45 min (includes 10 min WU)	Initial cycle workload @ 50% peak WL, then increased. RT intensity started @20-25%1RM, increased to 35-40%1RM.
Karavidas 2008	FES	6 weeks	5	30 min	Intensity for visible muscle contraction- 25Hz for 5s than 5s rest
Karavidas 2013	FES	6 weeks	5	30 min	Intensity for visible muscle contraction- 25Hz for 5s than 5s rest
Kato 2017	Stretching	4 weeks	7	20 min	Low intensity
Kawauchi 2017	IMT + RT. 2 groups LIPRT & MIPRT	8 weeks	7	30 min (IMT)	LIPRT - IMT @15% MIP and RT with 0.5 kg. MIPRT - IMT @ 30% MIP and RT @ 50%1RM RT - 1 x10, then increased to 2x10 reps
Kitzman 2010	Aerobic (walking & cycling)	16 weeks	3	60 min (includes WU & CD)	40-50% HRR (weeks 1-2), increased to 60-70% HRR
Kitzman 2016	Aerobic (primarily walking)	20 weeks	3	60 min	Individualised intensity based on HRR progressed as tolerated
Kobayashi 2003	Aerobic (cycle)	12 weeks	4-6 (2-3 per week x 2 per day)	15 min (30 min/day)	HR @ VT
Krishna 2014	Yoga. Supervised 3 days, 3 days home	12 weeks	6	60 min	-
Malfatto 2009	Aerobic (cycle or treadmill)	12 weeks	3	60 min (includes 15-20 min WU)	60% VO_{2peak}
Marco 2013	IMT	4 weeks	14 (daily x 2)	-	5 x 10 breaths (100% of their RM) then 1–2 min of unloaded recovery breathing,
Meyer 2004	Aerobic (cycle)	12 weeks	4	45 min	ANT
Nilsson 2010	Aerobic/Strength (group-based)	4 months	2	50 min	Included - 3 High intensity intervals @ RPE 15-18 for 5-10 minutes.
Nishi 2011	Aerobic (walking, cycling, callisthenics)	3 months	3-5	40-60 min	30-50% HRR
Norman 2012	Combined (AT + RT)	24 weeks	3 x AT, 2 x RT	30 min AT (+15 min WU& CD)	AT: 40- 70% HRR of (RPE 11-14), RT: 8 -10 exercises 1 x 10-15 reps.
Palau 2014	IMT	12 weeks	14 (Daily x 2)	20 min	Started breathing @ 25–30% MIP for 1 week, resistance modified each session according to 25–30% MIP measured.
Parrinello 2009	Aerobic (walking)	10 weeks	5	30 min	Mild to moderate
Passino 2006	Aerobic (cycle)	9 months	3	30 min	65% VO_{2peak}
Passino 2008	Aerobic (cycle)	9 months	3	30 min	65% VO_{2peak}
Sandri 2012	Aerobic (cycle)	4 weeks	20 (5 days of 4 sessions per day)	20 min (80 min/day)	70% symptom limited VO_{2peak}
Sarullo 2006	Aerobic (cycle)	12 weeks	3	30 min	60-70% VO_{2peak}
Stevens 2015	Combined: Aerobic 4 x 6-8 (2 min rest), ↑8-12 min @ wk. 6 + RT	12 weeks	5 x fortnight	>30 min	Aerobic @ HR@ 2nd VT, RT @ 50-70% 1RM (2 x 15, ↑2-3 reps)
Wisloff 2007	Aerobic (treadmill walking), 2 supervised, 1 home per week, 2 groups: AIT & MCT	12 weeks	3	38 min (AIT) (includes 10 min	Interval: 4x4 @ 90-95%HR_{peak}, 3 min recovery @ 50-70%HR_{peak} between intervals

				WU) 47 min (MCT)	Continuous @ 70-75%HR_{peak}
Yamamoto 2007	Aerobic (cycle and walking)	6 months	3	60 min	HR and WL @ VAT and 1 minute before ANT
Yeh 2004	Tai Chi	12 weeks	2	60 min	NR
Yeh 2011	Tai Chi	12 weeks	2	60 min	NR

ANT: anaerobic threshold, AIT: aerobic interval training, AT: aerobic training, CD: cool-down, FES: functional electrical stimulation, HR: heart rate, HRR: heart rate reserve, IMT: inspiratory muscle training, LIPRT: low intensity inspiratory muscle training and peripheral resistance training, MCT: moderate continuous training, MIPRT: moderate intensity inspiratory muscle training and peripheral resistance training, MIP: maximal inspiratory pressure, RM: repetition maximum, RT: resistance training, VAT, ventilatory anaerobic threshold, VT: ventilatory threshold, WL: workload, WU: warm-up,

Supplementary Table S4 Biomarker Assessment

Study	Plasma/ Serum	Assay/Supplier
BNP		
Brubaker 2009	Plasma	Commercially available radioimmunoassay
Billebeau 2017	Plasma	ARCHITECT BNP assay, Abbott Laboratories, Abbot Park, Il, USA
Butterfield 2008	Whole Blood/Plasma	Fluorescence immunoassay, Triage BNP, Biosite Diagnostics Inc., San Diego California
Fu 2013	Plasma	ELISA, USCN Life Science Inc., Burlington, NC
Gary 2011	?	BNP test, Triage assay
Jonsdottir 2006	Plasma	Immunoradiometric assay (IRMA) kits
Karavidas 2008	Plasma	Immunoassay technique, Triage BNP assay, Biosite Inc., San Diego, California, USA
Karavidas 2013	Plasma	Immunoassay technique, Triage BNP assay; Biosite Inc., San Diego, CA
Kato 2017	Plasma	?
Kawauchi 2017	?	Immunoassay, Biosite Diagnostics Inc., San Diego, CA, USA
Kitzman 2010	Plasma	Radioimmunoassay, Phoenix Pharmaceuticals Inc.; Mountain View, Calif.
Kitzman 2016	Plasma	Radioimmunoassay, Phoenix Pharmaceuticals
Kobayashi 2003	?	Radioimmunoassay
Malfatto 2009	Serum	Triage BNP test, Biosite Ltd, Belfast, United Kingdom
Nishi 2011	Plasma	Immunoradiometric assay for human BNP using a commercial kit, Shionoria
Norman 2012	Plasma	Commercially available immunoflurometric assay , Triage BNP, Biosite Diagnostics, San Diego CA
Parrinello 2009	Plasma	Immunoradiometric assay, Triage; Biosite Diagnostics
Passino 2006	Plasma	BNP was measured by a two-site Immunoradiometric Assay, Shionogi, Japan
Passino 2008	Plasma	BNP was measured by a two-site Immunoradiometric Assay, Shionogi, Japan
Stevens 2015	Plasma	ADVIA Centaur, Siemens Medical Solutions Diagnostics, Munich, Germany
Yamamoto 2007	?	?
Yeh 2004	Whole Blood	Fluorescence immunoassay, Biosite Triage BNP Test; San Diego, California
Yeh 2011	Whole Blood	Fluorescence immunoassay, Biosite Triage BNP Test, Biosite Diagnostics, San Diego, California
NT-proBNP		
Ahmad 2014	Plasma	ELISA, Roche Diagnostics, Indianapolis, IN
Aksoy 2015	Serum	Enzyme immunoassay kits, Biomedica, Bratislava, Slovakia
Antonicelli 2016	Serum	ElectroChemiLuminescence Immunoassay, ECLIA-Cobas, Roche Diagnostics, Rotkreutz, CH
Berendoncks 2010	Plasma	Sandwich immunoassay on Elecsys 2010, Roche Diagnostics
Conraads 2004	Plasma	Sandwich immunoassay on an Elecsys 2010, Roche diagnostics, Mannheim, Germany
Conraads 2007	Plasma	Sandwich immunoassay on an Elecsys 2010, Roche Diagnostics GmbH, Mannheim, Germany
Delagardelle 2008	Serum	Sandwich immunoassay using electro-Chemiluminescence detection on a Modular E170, Roche Diagnostics, Mannheim, Germany
Edelmann 2011	Serum	Commercially available Elecsys proBNP sandwich immunoassay, Elecsys 2010 analyser, Roche Diagnostics, Mannheim, Germany
Eleuteri 2013	Serum	Modular Analytics, Roche Diagnostics
Guazzi 2012	Plasma	?
Krishna 2014	Serum	Commercially available ELISA kit , Uscn Life Science Inc.
Meyer 2004	Serum	ElectroChemiLuminescence using the automated assay of Roche Diagnostics (Elecsys®proBNP).
Nilsson 2010	Plasma	Elecsys proBNP sandwich immunoassay on Elecsys 2010, Roche Diagnostics, Indianapolis, IN, USA.

Palau 2014	Serum	?
Passino 2006	Plasma	Measured with an automated electro chemiluminescent immunoassay.
Sandri 2012	Serum	ElectroChemiLuminescence Immunoassay, ECLIA, Roche Diagnostics, Mannheim, Germany)
Sarullo 2006	Plasma	Immunoassay, Roche Diagnostics, Branchburg, New Jersey, USA, was determined on an Elecsys 2010.
Wisloff 2007	Plasma	enzyme immunoassays, Roche Diagnostics, Indianapolis, Ind.
Galectin-3		
Billebeau 2017	Plasma	ARCHITECT Galectibn-3 assay, Abbott Laboratories, Abbot Park, Il, USA
Fernandes-Silva 2017	Serum	Milliplex MAP kits using Luminex TM xMAP technology, EMD Millipore Corporation, Germany.
sST2		
Billebeau 2017	Plasma	Test Presage ST2, Critical Diagnostics, San Diego CA, USA
MR-proANP & MT-proADM		
Billebeau 2017	Plasma	B.R.A.H.M.S. MR-proADM and MR-proANP KRYPTOR, Thermo Fisher Scientific
Trippel 2017	Serum	BRAHMS Kryptor Assays, Thermo Fisher Scientific Clinical Diagnostics B · R · A · H ·M· S GmbH, Hennigsdorf, Germany
CT-proAVP		
Trippel 2017	Serum	BRAHMS Kryptor Assays, Thermo Fisher Scientific Clinical Diagnostics B · R · A · H ·M· S GmbH, Hennigsdorf, Germany

Supplementary Table S5 Sensitivity Analysis using the leave-one-out approach

Study removed	MD (95% CI)	*p*-value
BNP (pmol/L)		
Conventional	**-17.17 (-29.56, -4.78)**	**0.007**
Butterfield 2008	-16.86 (-29.86, -3.87)	0.01
Fu 2013	-15.64 (-28.79, -2.50)	0.02
Gary 2011	-21.79 (-28.91, -14.67)	<0.00001
Jonsdottir 2006	-19.18 (-32.43, -5.94)	0.005
Kobayashi 2003	-17.45 (-30.31, -4.59)	0.008
Malfatto 2009	-13.60 (-26.67, -0.53)	0.04
Nishi 2011	-15.59 (-27.61, -3.57)	0.01
Norman 2012	-17.82 (-31.51, -4.12)	0.01
Parrinello 2009	-16.72 (-32.83, -0.60)	0.04
Passino 2006/2008	-16.67 (-32.13, -1.22)	0.03
Stevens 2015	-16.95 (-29.79, -4.11)	0.01
Non-conventional	**-9.92 (-28.03, 8.20)**	**0.28**
Karavidas 2008	-8.91 (-34.77, 16.95)	0.50
Kato 2017	-8.26 (-32.05, 15.52)	0.50
Kawauchi 2017	-18.28 (-35.05, -1.52)	0.03
Yeh 2004	-4.34 (-20.24, 11.56)	0.59
NT-proBNP (pmol/L)		
Conventional	**-32.80 (-56.19, -9.42)**	**0.006**
Aksoy 2015	-54.62 (-74.36, -34.87)	<0.00001
Conraads 2004	-30.60 (-55.17, -6.03)	0.01
Conraads 2007	-34.57 (-59.20, -9.94)	0.006
Delagardelle 2008	-35.45 (-59.97, -10.93)	0.005
Guazzi 2012	-22.84 (-43.81, -1.86)	0.03
Meyer 2004	-35.06 (-59.98, -10.13)	0.006
Passino 2006/2008	-30.45 (-54.87, -6.03)	0.01
Sandri 2012	-27.53 (-51.75, -3.32)	0.03
Sarullo 2006	-30.70 (-53.60, -7.80)	0.009
Wisloff 2007	-31.28 (-56.44, -6.12)	0.01
Non-conventional	**-157.47 (-327.64, 12.70)**	**0.07**
Krishna 2014	-19.54 (-277.83, 238.75)	0.88
Marco 2013	-212.12 (-283.62, -140.62)	<0.00001

Supplementary Table S6 Assessment of study quality and reporting using TESTEX

Study	Eligibility Criteria specified	Randomisation details specified	Allocation concealed	Groups similar at baseline	Assessors blinded	Outcome measures assessed >85% participants#	ITT	Reporting between group statistical comparison*	Point measures & measures of variability	Activity monitoring in control group	Relative exercise intensity reviewed	Exercise volume & EE	Overall TESTEX (/15)
RCTs													
Ahmad (2014)[1]	1	1	1	1	1	2	0	2	1	0	1	0	11
Aksoy (2015)	1	1	0	1	0	0	0	2	1	0	0	1	7
Antonicelli (2016)	1	1	0	1	0	3	0	2	1	0	0	0	9
Brubaker (2009)	1	0	0	1	1	2	0	2	1	0	0	1	9
Butterfield (2008)	0	0	0	1	0	2	0	2	1	0	0	0	6
Conraads (2007)	1	0	0	1	0	2	0	2	1	0	1	0	8
Delagardelle (2008)	1	0	0	1	0	2	1	2	1	0	0	0	8
Edelmann (2011)	1	1	1	1	0	3	0	2	1	0	1	0	11
Eleuteri (2013)	1	0	0	1	0	3	1	2	1	0	1	1	11
Fernandes-Silva (2017)	1	1	1	1	0	0	0	2	1	0	1	0	8
Fu (2013)	1	0	0	1	0	2	0	2	1	0	1	1	9
Gary (2011)	1	1	0	1	0	3	1	2	1	0	1	1	12
Guazzi (2012)	1	1	0	1	0	1	1	0	1	0	1	0	7
Jonsdottir (2006)	1	0	0	1	0	2	0	2	1	0	0	0	7
Karavidas (2008)	1	1	1	1	1	2	1	2	1	0	0	0	11
Karavidas (2013)	1	1	1	1	1	2	1	2	1	0	0	0	11
Kawauchi (2017)	1	1	1	1	0	1	0	2	1	0	0	0	8
Kitzman (2010)	1	0	0	1	1	3	1	2	1	0	0	1	11
Kitzman (2016)	1	1	1	1	1	3	0	2	1	0	0	0	11
Kobayashi (2003)	1	0	0	1	0	3	1	2	1	0	0	0	9
Krishna (2014)	1	1	1	1	1	0	0	2	1	0	0	0	8
Malfatto (2009)	1	0	0	1	0	1	1	2	1	0	1	0	8
Marco (2013)	1	1	1	1	1	2	1	2	1	0	0	0	11
Meyer (2004)	1	0	0	1	0	1	0	2	1	0	1	0	7
Nilsson (2010)	1	1	0	1	0	2	0	1	1	0	0	0	7
Norman (2012)	1	0	0	1	0	3	0	2	1	0	0	0	9
Palau (2014)	1	0	0	1	1	2	0	2	1	0	0	0	8
Parrinello (2009)	1	0	0	1	0	1	1	2	1	0	0	0	7
Passino (2006)	1	0	0	1	1	1	0	2	1	0	1	0	8
Passino (2008)	1	0	0	1	1	2	0	2	1	0	1	0	9
Sandri (2012)	1	1	0	1	0	3	1	2	1	0	0	0	10
Sarullo (2006)	1	1	1	1	1	3	0	2	1	0	0	0	11
Stevens (2015)	1	0	0	1	0	2	0	2	1	0	0	0	7
Trippel (2016) [2]	1	1	1	1	0	3	0	2	1	0	0	0	10
Wisloff (2007)	1	1	1	1	0	3	0	2	1	0	1	0	11
Yeh (2004)	1	1	1	1	0	2	1	2	1	1	0	0	11

Yeh (2011)	1	1	1	1	1	3	1	2	1	0	0	0	12
Non-Randomised/Retrospective													
Berendoncks (2010)	1	0	0	1	1	1	0	2	1	0	0	0	7
Billebeau (2017)	1	0	0	1	0	1	0	2	1	0	1	0	7
Conraads (2004)	1	0	0	1	0	1	0	2	1	0	0	0	6
Nishi (2011)	1	0	0	1	0	2	0	2	1	0	0	0	7
Yamamoto (2007)	1	0	0	1	0	2	0	2	1	1	0	0	8

Key: total out of 15 points. Legend: #three points possible—one point if adherence >85%, one point if adverse events reported, one point if exercise attendance is reported. *Two points possible—one point if primary outcome is reported, one point if all other outcomes reported. TESTEX, Tool for the assessment of Study quality and reporting in Exercise. 0 awarded if no mention was made of this criteria or if it was unclear whether criteria was meet. If ITT was not specifically mentioned, but it was noted that no participants withdrew and all analysed 1 point was awarded.

Fig. S1a Funnel Plot NT-proBNP

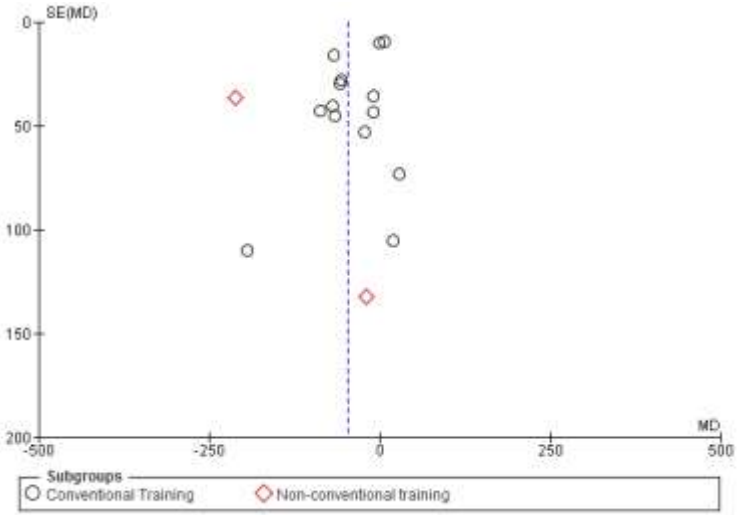
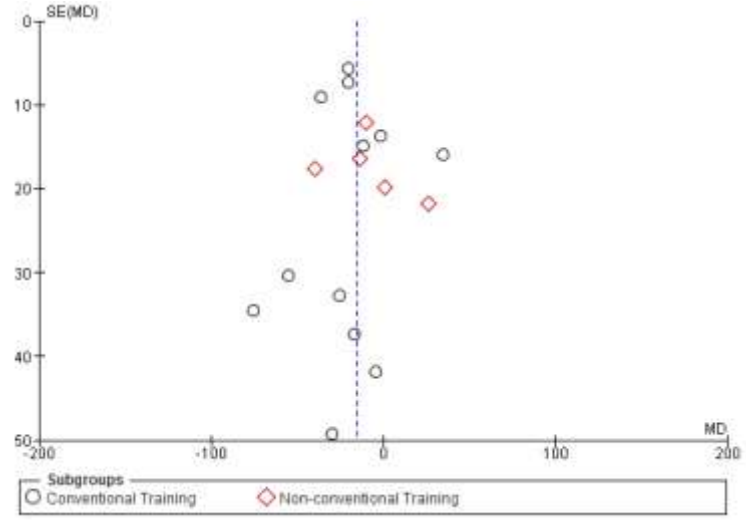


Fig. S1b Funnel Plot BNP



Example Search Strategy

EMBASE	
1	‘heart failure’: ab, ti, kw
2	‘exercise’: ab, kw
3	‘exercise’/exp OR ‘exercise’
4	‘aerobic exercise’/exp OR ‘aerobic exercise’
5	‘endurance training’/exp OR ‘endurance training’
6	‘resistance training’/exp OR ‘resistance training’
7	‘tai chi’/exp OR ‘tai chi’
8	‘yoga’/exp OR ‘yoga’
9	‘functional electrical stimulation’/exp OR ‘functional electrical stimulation’
10	‘neuromuscular electrical stimulation’/exp OR ‘neuromuscular electrical stimulation’
11	‘inspiratory muscle training’/exp OR ‘inspiratory muscle training’
12	‘respiratory muscle training’/exp OR ‘respiratory muscle training’
13	‘kinesiotherapy’/exp OR ‘kinesiotherapy’
14	‘physiotherapy’/exp OR ‘physiotherapy’
15	‘heart rehabilitation’/exp OR ‘heart rehabilitation’
16	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
17	‘biological marker’: kw
18	‘biological marker’/exp OR ‘biological marker’
19	‘natriuretic factor’/exp OR ‘natriuretic factor’
20	‘brain natriuretic peptide’/exp OR ‘brain natriuretic peptide’
21	‘amino terminal pro brain natriuretic peptide’/exp OR ‘amino terminal pro brain natriuretic peptide’
22	‘atrial natriuretic peptide’/exp OR ‘atrial natriuretic peptide’
23	‘suppression of tumorigenicity 2’/exp OR ‘suppression of tumorigenicity 2’
24	‘soluble ST2 protein’/ exp OR ‘soluble ST 2 protein’
25	‘galectin 3’/exp OR ‘galectin 3’
26	‘troponin’/exp OR ‘troponin’
27	‘copeptin’/exp OR ‘copeptin’
28	‘adrenomedullin’/exp OR ‘adrenomedullin’
30	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28
31	#1 AND #16 AND #30

8 Chapter 8 - Peer reviewed publication: Effect of exercise on diastolic function in heart failure patients: a systematic review and meta-analysis

8.1 Manuscript Information

Pearson, M. J., Mungovan, S. F., & Smart, N. A. (2017). Effect of exercise on diastolic function in heart failure patients: a systematic review and meta-analysis. *Heart Failure Reviews, 22(2), 229-242*. https://doi.org/10.1007/s10741-017-9600-0

Submitted 30th November 2016, Submitted in revised form 22nd January 2017, Accepted 25th January 2017, Available Online 23rd February 2017

[redacted] 20th June 2018

Candidate

[redacted]

Principal Supervisor 20th June 2018

8.2 Statement of author's contribution

Higher Degree Research Thesis by Publication

University of New England

STATEMENT OF AUTHORS' CONTRIBUTION

We, the PhD candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated in the *Statement of Originality*.

	Author's Name (please print clearly)	**% of contribution**
Candidate	Melissa Pearson	70%
Other Authors	Neil Smart	20%
	Sean Mungovan	10%

Name of Candidate: Melissa Jane Pearson

Name/title of Principal Supervisor: Professor Neil Smart

[redacted]

Candidate

20th June 2018
Date

[redacted]

Principal Supervisor

20th June 2018
Date

8.3 Statement of originality

Higher Degree Research Thesis by Publication

University of New England

STATEMENT OF ORIGINALITY

We, the PhD candidate and the candidate's Principal Supervisor, certify that the following text, figures and diagrams are the candidate's original work.

Type of work	Page number(s)
Systematic Review & Meta-analysis	221-242

Name of Candidate: Melissa Jane Pearson

Name/title of Principal Supervisor: Professor Neil Smart

[redacted]

Candidate

20th June 2018

Date

[redacted]

Principal Supervisor

20th June 2018

Date

8.4 Full manuscript as published

Heart Fail Rev (2017) 22:229–242
DOI 10.1007/s10741-017-9600-0

Effect of exercise on diastolic function in heart failure patients: a systematic review and meta-analysis

M. J. Pearson[1] · S. F. Mungovan[2,3] · N. A. Smart[1]

Published online: 23 February 2017

Abstract Diastolic dysfunction contributes to the development and progression of heart failure. Conventional echocardiography and tissue Doppler imaging are widely utilised in clinical research providing a number of indices of diastolic function valuable in the diagnosis and prognosis of heart failure patients. The aim of this meta-analysis was to quantify the effect of exercise training on diastolic function in patients with heart failure. Exercise training studies that investigate different indices of diastolic function in patients with heart failure have reported that exercise training improves diastolic function in these patients. We sought to add to the current literature by quantifying, where possible, the effect of exercise training on diastolic function. We conducted database searches (PubMed, EBSCO, EMBASE, and Cochrane Trials Register to 31 July 2016) for exercise based rehabilitation trials in heart failure, using the search terms 'exercise training, diastolic function and diastolic dysfunction'. Data from six studies, with a total of 266 heart failure with reduced ejection fraction (HFrEF) participants, 144 in intervention groups and 122 in control groups, indicated a significant reduction in the ratio of early diastolic transmitral velocity (E) to early diastolic tissue velocity (E′) (E/E′ ratio) with exercise training, exercise vs. control mean difference (MD) of −2.85 (95% CI −3.66 to −2.04, $p < 0.00001$). Data from five studies in heart failure with preserved ejection fraction (HFpEF) patients, with a total of 204 participants, 115 in intervention groups and 89 in control groups, also demonstrated a significant improvement in E/E′ in exercise vs. control MD of −2.38 (95% CI −3.47 to −1.28, $p < 0.0001$).

Keywords Heart failure · Exercise · Diastolic function · Cardiac function

The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Electronic supplementary material The online version of this article (doi:10.1007/s10741-017-9600-0) contains supplementary material, which is available to authorized users.

✉ N. A. Smart
nsmart2@une.edu.au

[1] School of Science and Technology, University of New England, Armidale, NSW 2351, Australia

[2] Westmead Private Physiotherapy Services and The Clinical Research Institute, Sydney, Australia

[3] Department of Physiotherapy, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Melbourne, Australia

Introduction

Left ventricular diastolic dysfunction exists to varying degrees within the community [1] and is associated with the development and progression of heart failure (HF) [2]. While most frequently referred to in the context of HF with preserved ejection fractions (HFpEF) due to its central role in its pathophysiology [3], impaired diastolic function (DF) or diastolic dysfunction (DD) often coexists with systolic dysfunction [3–6]. Diastolic dysfunction is defined by abnormal left ventricular (LV) relaxation and LV stiffness, leading to increased filling pressures [7] and is associated with reduced exercise capacity [8] a hallmark symptom of HF.

Exercise training improves DF in healthy subjects [9] and may assist in preventing the reduction of DF associated with ageing [8, 10]; however, whether exercise actually improves DF in HF patients is not as clear. In heart failure with reduced ejection fraction (HFrEF) patients, DF has been demonstrated to be a predictor of exercise capacity [4, 11] and in HFpEF

patients greater than one third of the improvement in VO_{2peak} has been explained by improved DF [12].

Whereas LV systolic function is generally quantified by measuring ejection fraction, there is no single non-invasive measure that quantifies left ventricular diastolic function (LVDF) [7, 13]. Instead, a number of indices based on cardiac imaging are utilised and current recommendations include the use of algorithm based decision trees in the diagnosis and grading of DD [7]. In most patients, a combination of conventional echocardiography and tissue Doppler imaging (TDI) can determine if DF is normal or impaired [13]. Diastolic dysfunction occurs on a continuum and conventional echocardiographic, and TDI measures are combined to grade the severity of DD, with individuals classified as having either grade 1 (impaired relaxation), which commonly occurs as part of the ageing process, grade II (pseudonormal filling) or grade III (restrictive filling), which can be further categorised as reversible or non-reversible. Both pseudonormal and restrictive filling patterns have been shown to be associated with poorer outcomes than impaired relaxation [14].

From a clinical perspective, the basis for the measurement of DF in HF patients differs based on ejection fraction. In HFpEF patients, E/E′, the ratio of early diastolic transmitral velocity (E) to early diastolic tissue velocity (E′), is a key variable in diagnosis, while in HFrEF patients, both conventional echocardiography and TDI quantify LV filling pressure and grade DD [7, 15], with both E′ and E/E′ providing valuable prognostic information [16, 17] and guiding medical therapy [18] in both phenotypes. E/E′ is a surrogate measure of filling pressure with an E/E′ < 8 considered normal and an average E/E′ > 14 (>13 lateral or >15 septal) abnormal and a strong indicator of DD [7], with values between 8 and 15 a grey zone in which other indices of DF are required for the diagnosis of DD [19]. Additionally, as the effects of increased filling pressure over time are reflected in the volume of the left atrium (LA) [13], LA maximal volume index (LAVI) is also recommended as an important marker of diastolic function and is recommended as one of several indices to be evaluated in determining and grading of DD [7, 13]; however, to date, minimal exercise training studies in HF patients have reported on LA volume [12, 20] or size [6].

Improvements in LVDF following exercise training were first reported by Belardinelli and colleagues [5] in patients with reduced ejection fractions, and a number of HF exercise studies have now measured DF as either a primary or a secondary outcome. Previously, three meta-analyses [21–23] with differing inclusion criteria, in HFpEF patients, have reported on DF indices after exercise interventions. The aim of this meta-analysis is to quantify the effects of exercise training on DF in HF patients. To our knowledge, this work is the first to examine DF in both HFrEF and HFpEF patients.

Methods

Search strategy

Potential studies were identified by conducting systematic searches of PubMed, EBSCO, EMBASE and the Cochrane Library of Controlled Trials up to 31 July 2016. Searches included a mix of MeSH and free-text terms related to the key concepts of heart failure, exercise training and diastolic dysfunction. Additionally, systematic reviews, meta-analyses and reference lists of papers were hand searched for additional studies. One reviewer (MJP) conducted the search. One author was contacted to provide additional information but was unable to supply any further details.

Study selection

Randomised and non-randomised controlled trials of exercise training in HFrEF and HFpEF patients were included. Only studies that specifically referred to the participants as having HFrEF and HFpEF were included. Studies in which authors did not specifically state that patients had HF were excluded, e.g. studies that only refer to patients as post acute myocardial infarction with no additional statement to classify participants as having HF were excluded. Where non-randomised controlled trials (RCTs) were included, additional sensitivity analyses were conducted. Exercise was defined to allow for inclusion of a broad range of structured physical activities and included aerobic, resistance, combined training (aerobic and resistance), hydrotherapy, yoga, Pilates and Tai Chi. Additionally, the physical therapies of functional electrical stimulation/neuromuscular electrical stimulation (FES/NMES) and inspiratory muscle training (IMT) were included in the definition of exercise for the purpose of this review. Studies included in the review compare an exercise intervention to a usual care control group. Non-English language papers and animal studies were excluded.

Data extraction and outcome measures

Data were extracted by two reviewers (MJP and SFM). The primary outcome measure was the E/E′ ratio, a widely accepted surrogate of left ventricular filling pressure. Where E/E′ lateral and E/E′ septal were reported, the average was calculated for data pooling. The secondary outcome measures were the E/A ratio, the ratio of peak early to late diastolic filling velocity, and DT, deceleration time of early ventricular filling.

Data synthesis

Statistical analyses were performed using Revman 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark). The individual meta-analyses were completed for continuous data by using

the change in the mean and standard deviation (SD). Where the change in mean and SD were not reported, the change in mean was calculated by subtracting the pre-intervention mean from the post intervention mean, and Revman 5.3 enabled calculations of SD using number of participants in each group and within group p values or 95% CI. In cases were exact p values were not provided, we used default values, e.g. $p < 0.05$ becomes $p = 0.049$, $p < 0.01$ becomes $p = 0.0099$ and p = not significant becomes $p = 0.051$. Where a study included multiple intervention groups and a control group, the sample size of the control group was divided by the number of intervention groups to eliminate over inflation of the sample size. A fixed effects inverse variance was used with a measure of mean difference (MD). We used a 5% level of significance and a 95% CI to report change in outcome measures. Where data was considered not appropriate for pooling, a descriptive analysis was undertaken.

Heterogeneity and publication bias

Heterogeneity was quantified using the I^2 test [24]. Values range from 0% (homogeneity) to 100% (heterogeneity) [24]. Funnel plots [25] were provided to assess the risk of publication bias.

Study quality

Study quality was assessed by using the tool for assessment of study quality and reporting in exercise training studies (TESTEX) [26]. This is a 15-point scale that assesses study quality (maximum 5 points) and reporting (maximum 10 points). Two reviewers (MJP and SFM) conducted the assessment. A third reviewer (NAS) was consulted on any discrepancies.

Results

Studies included in the review

The initial search yielded 1011 articles. After removal of duplicates and exclusion of articles based on abstract and title, 39 full-text articles remained for screening. Full screening resulted in 22 articles meeting the stated inclusion criteria (PRISMA flow diagram; Fig. 1). The characteristics of the 22 studies are included in Table 1. Details of full-text articles reviewed but excluded are provided, with reasons, in Supplementary Table S1.

The average age of patients ranged between 49 ± 5 and 76.5 ± 9 years, and sex distribution was predominantly male, with only six studies [12, 20, 37, 40, 42, 43] including ≥50% of females (Table 1). Intervention duration varied from 4 weeks to 7 months and training frequency ranged from 2 days per week to daily. Aerobic training was utilised in 15 [5, 6, 27–31, 34–36, 38, 39, 42, 43, 45] studies, resistance training in one [40] study, a combination of aerobic and resistance training was utilised in four [12, 32, 41, 44] studies, one [37] study utilised FES and one [20] study utilised IMT.

Outcome measures—diastolic indices

All included studies measured one or more diastolic indices using conventional echocardiography or TDI. Only one study [5] specifically assigned patients to one of three subgroups based on the assessment of mitral inflow values (abnormal relaxation, "normal" or restrictive filling) and reported results separately on each group with a comparison to the corresponding control group. Baseline diastolic indices are provided in Supplementary Table S2.

E/E′—exercise vs. control HFrEF

Pooled data from six [6, 30, 32, 35, 44, 45] studies with nine intervention groups demonstrated a significant reduction in E/E′, MD −2.85 (95% CI −3.66 to −2.04, $p < 0.00001$) (Fig. 2). Sensitivity analysis to remove the one non-RCT [30] did not significantly impact the result, MD −2.59 (95% CI −3.49 to −1.69, $p < 0.00001$).

E/E′—exercise vs. control—HFpEF

Pooled data from five [12, 20, 35, 37, 42] studies indicated a significant improvement in E/E′, MD −2.38 (95% CI −3.47 to −1.28, $p < 0.0001$) (Fig. 3).

E/A

E/A was the most common DF index reported. Twenty [5, 6, 12, 27–32, 35–45] studies reported changes in the E/A ratio, providing a total of 1022 participants diagnosed with HF (583 exercising participants and 439 controls). Sixteen [5, 6, 27–32, 35, 36, 38–41, 44, 45] studies had 727 HFrEF participants (415 exercising and 312 control), while six [12, 27, 35, 37, 42, 43] studies had 295 HFpEF participants (168 exercising and 127 control). Of the 20 studies, two [27, 35] included participants with both HFrEF and HFpEF as separate intervention and control groups. One [27] of the studies that included both HFrEF and HFpEF also classified patients with mildly reduced ejection fractions into a separate training group with a corresponding control group.

Mitral inflow E/A data were not pooled for analysis due to the non-uniformity in values as the disease changes. Instead, a descriptive analysis was conducted. Of the 20 studies [5, 6, 12, 27–32, 35–45] that measured and reported E/A, only eight studies [5, 6, 27, 28, 32, 38, 39, 45] reported a significant improvement in E/A (Table 2). One [5] study with groups classified by type of DD, however, only reported an

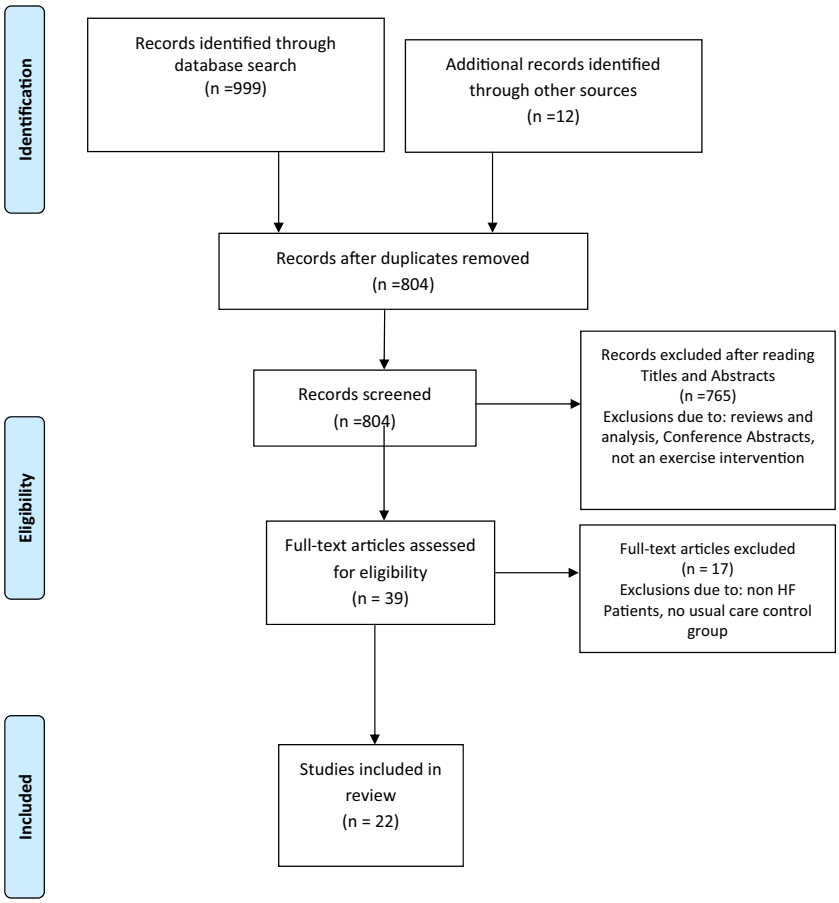


Fig. 1 PRISMA flow diagram

improvement in patients with abnormal relaxation. Of the six [12, 27, 35, 37, 42, 43] studies that included HFpEF patients, only one [27] reported a significant improvement in E/A ratio post intervention. Only eight [5, 6, 27, 28, 32, 38, 39, 45] of the 17 included studies with HFrEF patients noted improvement in the E/A ratio.

DT

Deceleration time data was reported in nine [5, 6, 12, 27, 34, 41–44] studies, providing a total of 423 participants (248 exercise and 175 controls). Four [12, 27, 42, 43] studies had 206 participants with preserved ejection fractions (123 exercise and 83 controls) and six [5, 6, 27, 34, 41, 44] studies had 217 participants with reduced ejection fractions (125 exercise and 92 controls). A baseline DT < 140 m/s was reported in one of three intervention groups in one study [5]. One study [27] noted that one intervention group, composed of HFrEF patients, included patients with DT < 140 m/s and patients with DT > 200 ms. Four [5, 27, 34, 44] studies included at least one intervention group with a DT > 140 and <220 m/s. Nine intervention groups from seven studies [5, 6, 12, 27, 41–43] reported baseline DT > 220 m/s (Supplementary Table S2).

Mitral Inflow DT data was not pooled for analysis due to the non-uniformity in values as the disease changes. Instead, a descriptive analysis was conducted. Of the nine [5, 6, 12, 27, 34, 41–44] studies to report DT data, only three studies [5, 6, 27] reported a significant improvement (Table 2). One [5] of the studies, however, only reported an improvement in patients with abnormal relaxation. One additional study [45] noted no change in DT but did not report data. Of the four [12, 27, 42, 43] studies that included HFpEF patients, only one [27] reported a significant improvement in DT post intervention. Only three [5, 6, 27] of the seven [5, 6, 27, 34, 41, 44, 45] studies which included HFrEF patients reported improvements in DT.

Grade of diastolic dysfunction

Only three [6, 38, 39] studies, all in HFrEF patients, reported post intervention data changes in diastolic grade/category. All three studies noted an improvement in all DD grades post intervention (Supplementary Table S3).

Intervention adherence and adverse events

Twelve studies [6, 12, 27, 29–31, 34, 40, 42–45] reported on session attendance and five [35–38, 41] studies failed to report adverse events (Supplementary Table S4).

Table 1 Characteristics of included studies

Study	Study duration	Participant characteristics	Exercise intervention				Major findings E/E′, E/A and DT
			Type	Frequency (per week)	Session duration	Intensity	
Alves [27]	6 months	*n* = 103 randomised, *n* = 98 completed Ex(p): *n* = 20, Con(p): *n* = 11, age 63 ± 10.2 years, 71% male, LVEF 56.3 ± 2.5%, NYHA classes I, II and III Ex(m): *n* = 23, Con(m): *n* = 10, age 63 ± 10.9 years, 73% male, LVEF 49.3 ± 1.9%, NYHA classes I, II and III Ex(s): *n* = 22, Con(s): *n* = 12, age 62 ± 9.9 years, 79% male, LVEF 37.3 ± 7.9%, NYHA classes I, II, III and IV, aetiology: DCM (*n* = 12%)	A (T/C)	3	15 min (month 1) (+10 min warm-up and 10 min cool-down) ↑35 min (months 2–6)	Interval training at 70–75% HR_{max} (5 × 3 min), with 1 min recovery at 45–55% $HR_{max.}$ ↑7 × 5 min intervals at month 2	*Preserved EF*: improved E/A (↑) and improved DT (↓) training group *Mild EF*: ↑E/A (improved) and improved DT (↓) training *Mod-severe EF*: ↔E/A or ↔ DT, but, sub-analysis: RF patients improved E/A (↓) and improved (↑) DT, IR patients improved E/A (↑) and improved DT (↓)
Belardinelli [5]	8 weeks	*n* = 55 randomised *n* = 55 completed Ex(RF): *n* = 17, age 54 ± 8 years, 88% male, LVEF 28 ± 4%, Con(RF): *n* = 8, age 55 ± 8 years, 75% male, LVEF 27.5 ± 6% Ex("N"): *n* = 7, age 54 ± 8 years, 86% male, LVEF 25 ± 8%, Con("N"): *n* = 4, age 51 ± 7 years, 100% male, LVEF 27.1 ± 6% Ex("AR"): *n* = 12, age 56 ± 5 years, 86% male, LVEF 28.9 ± 6%, Con(AR): *n* = 7, age 58.5 ± 7 years, 83% male, LVEF 27.8 ± 2% All NYHA classes II and III, aetiology: DCM and ICM	A (C)	3	40 min (+15–20 min stretching)	60% VO_{2peak}	*RF*: ↔ E/A training, ↔ DT training "*N*": ↔ E/A training, ↔ DT training *AR*: Improved E/A (↑70%) and improved DT (↓21%) training
Belardinelli [28]	8 weeks	*n* = 52 randomised, *n* = 52 completed Ex1: (ICD + CRT) *n* = 15, Ex2: *n* = 15 55 ± 14 years, 100% male, LVEF 30.2 ± 7% Con1: (ICD + CRT) *n* = 12, Con2 (ICD) *n* = 10 53 ± 1 years, 100% male, LVEF 33.6 ± 8% NYHA classes II and III, aetiology: previous MI, PTCS/stent, CABG	A (C)	3	40 min (+15–20 min stretching)	60% VO_{2peak}	Improved E/A (↓) (ICD + CRT) training group ↔ E/A (ICD) training group
Belardinelli [29]	8 weeks	*n* = 130 randomised, *n* = 128 completed Ex.(A): *n* = 43, age 59 ± 10 years, 86% male, LVEF 35 ± 8% Ex. (D): *n* = 43, age 60 ± 11 years, 86% male, LVEF 36 ± 7% Con: *n* = 42, age 58 ± 10 years, 83% male, LVEF 37 ± 8% NYHA classes II and III, aetiology: previous MI, PTCS/stent, CABG	A (C/T) D	3 3	30 min (+10 warm up) 21 min	70% VO_{2peak} ~70% VO_{2peak} (Waltz: 5 min slow, 3 min fast, 5 min slow, 3 min fast, 5 min slow)	↔ E/A aerobic groups ↓ E/A dance group
Benda [30]	12 weeks	*n* = 33 randomised, *n* = 29 completed Ex(HIIT): *n* = 10, age 63 ± 8 years, 90% male, LVEF 37 ± 6%, Ex(CT): *n* = 10, age 64 ± 8 years, 100% male, LVEF 38 ± 6%	A (C)	2	35 min (HIIT) 30 min (CT) (+10 min warm-up, 5 min cooldown each group)	HIIT: 10 × 1 min at 90% max. WL (RPE 15–17) separated by 2.5 min at 30% max. WL CT: at 60–75% max. WL (RPE 12–14)	↔ E/E-L′ or E/E′-S in either training group ↔ E/A in either training

Table 1 (continued)

Study	Study duration	Participant characteristics	Exercise intervention				Major findings E/E′, E/A and DT
			Type	Frequency (per week)	Session duration	Intensity	
		Con: n = 9, age 67 ± 7 years, 56% male, LVEF 40 ± 11% All NYHA classes II and III, aetiology: ischaemic and non-ischaemic				Warm-up at 40% max. WL and cooldown at 30% max WL	
Brubaker [31]	16 weeks	n = 59 randomised, n = 44 completed Ex: n = 23, age 70 ± 5.3 years, 64% male, LVEF 30.7 ± 9.0% Con: n = 21, age 70 ± 6.3 years, 69% male, LVEF 30.4 ± 8.8% All NYHA classes II and III	A (W and C)	3	30 to 40 min	40–50% HRR ↑60–70% HRR	↔E/A training group
Chrysohoou [32]	12 weeks	n = 100 randomised, n = 72 completed Ex: n = 33, age 63 ± 9 years, 88% male, LVEF 31% Con: n = 39, age 56 ± 11 years, 82% male, LVEF 32% All NYHA classes I, II and III, aetiology: ischaemic (70%) and non-ischaemic	CT (C + RT)	3	45 min	HIIT:30s at 80% WR_{peak}, 60 RPM, 30 s rest RT: ↑90% 1RM at week 7 (initially at 30–50% 1RM)	↔ E/E′ training ↓ E/A training
Edelmann [12] and Nolte [33]—Ex-DHP Study	3 months	n = 67 randomised, n = 64 completed Ex: n = 44, age 64 ± 8 years, 45% male, LVEF 68 ± 7%, All NYHA classes II and III, DD grades I (75%) and II (25%) Con: n = 20, age 65 ± 6 years, 40% male, LVEF 67 ± 7%, All NYHA classes II and III, DD grade I (65%) and II (35%)	CT (C + RT)	2 ↑3× at week 5 + RT 2× a week	20 min ↑40 min at week 5 + RT	C: 50–60% VO_{2peak} with ↑ @ week 5 to70% VO_{2peak} RT: 60–65% 1RM (15 reps)	↑E/E′ training, ↑E/E′ correlated with VO_{2peak} ↔ E/A training ↔ DT training
Eleuteri [34]	3 months	n = 21 randomised, n = 21 completed Ex: n = 11, 66 ± 2 years, 100% male, LVEF 28 ± 2.1% Con: n = 10, 63 ± 2 years, 100% male, LVEF 30 ± 1.8% All participants NYHA class II HF aetiology: IHD and idiopathic CM	A (C)	5	30 min (+5 min warm-up, 5 min cooldown)	HR and power at VAT (cycle at 60 RPM)	↔ DT training
Fu [35]	12 weeks	n = 120 randomised, n = 117 completed Ex(P): n = 30, age 61 ± 2.7 years, 67% male, LVEF 57.6 ± 1.9%, Con(p): n = 29, age 62 ± 2.4 years, 62% male, LVEF 56.5 ± 2.2% Ex(R): n = 30, age 60 ± 2.8 years, 70% male, LVEF 28.1 ± 1.1%, Con(r): n = 28, age 59 ± 2.2 years, 64% male, LVEF 28.1 ± 1.4%	A (C)	3	30 min	HIIT—5 × 3 min intervals at 80% VO_{2peak}, with 3 min recover at 40%	*P*: ↓E/E′ in training (↓21 ± 2.2%) *R*: ↔ E/E′ training ↔ E/A in either P or R training groups
Giannattasio [36]	8 weeks	n = 22 randomised, n = 22 completed Ex: n = 11, age 61 ± 1.5 years, 82% male, LVEF 32.9 ± 3.4% Con: n = 11, age 61 ± 1.5 years, 82% male, LVEF 32.2 ± 0.7%	A (C)	3	30 min	NR	↔ E/A training
Karavidas [37]	6 weeks	n = 30 randomised, n = 30 completed	FES	5	30 min		↔ E/E′ in FES group ↔ E/A in FES group

Table 1 (continued)

Study	Study duration	Participant characteristics	Exercise intervention				Major findings E/E′, E/A and DT
			Type	Frequency (per week)	Session duration	Intensity	
		Ex: n = 15, 69 ± 8.6 years, 40% male, LVEF 63.6 ± 7.6% Con: n = 15, 69 ± 7.9 years, 40% male, LVEF 62.6 ± 4.5% All participants NYHA classes II and III	(lower limb)			Intensity for visible muscle contraction—25 Hz for 5 s than 5 s rest	
Kitzman [43]	16 weeks	n = 63 randomised, n = 54* completed Ex: n = 24, 70 ± 7 years, 28% male, LVEF 58 ± 6%, DD: 44% Impaired relaxation, 53% pseudonormal, 3% restrictive filling Con: n = 28, 70 ± 7 years, 20% male, LVEF 56 ± 5%, DD: 52% Impaired relaxation, 41% pseudonormal, 7% restrictive filling All participants NYHA classes II and III	A (W/C and AER-G)	3	40 min (+5–10 min warm-up and recovery)	70% HRR for 20 min each of W and C/ERG	↔ E/A training ↔ DT training
Malfatto [38]	12 weeks	n = 54 randomised, n = 54 completed Ex: n = 27, 65 ± 11 years, 70% male, LVEF 31 ± 6%, 70% abnormal filling Con: n = 27, 67 ± 9 years, 74% male, LVEF 33 ± 6%, All NYHA classes I and II, aetiology: ischaemic and non-ischaemic	A (C/T)	3	40 min (+15–20 min stretching)	60% VO_{2peak}	Improvement E/A (↓) in training group 11 of 19 patients recovered to normal parameters
Mehani [39]	7 months	n = 40 randomised, n = 30 completed Ex: n = 15, 56 ± 5.8 years, 100% male, LVEF 35.8 ± 6.8%, grade 1 DD n = 11, grade II n = 2, grade III n = 2 Con: n = 15, 54 ± 9 years, 100% male, LVEF 33.09 ± 4.8%, grade 1 DD n = 7, grade II n = 4, grade III n = 4	A (circuit)	3	24 min ↑45 min (by end month 7) (+5–10 min warm-up and 10 min cool down)	55% ↑80% HRR (by end month 7)	Improvement in E/A ratio Post training 8/15 patients returned to normal E/A ratio type, normal DD classification
Palau[20]	12 weeks	n = 27 randomised, n = 26 completed Ex: n = 14, age 68 years, 50% male, LVEF 69% Con: n = 12, age 74 years, 50% male, LVEF 76%	IMT	2× daily	20 min	25–30% MIP	↔ E/E′ in IMT group
Parnell [41]	8 weeks	n = 21 randomised, n = 21 completed Ex: n = 11, age 57 ± 15 years, 91% male, LVEF 25 ± 2%, Con: n = 10, age 53 ± 11 years, 90% male, LVEF 24 ± 3% All NYHA classes II and III, aetiology: ischaemic and non-ischaemic	CT (C/-W + RT)	3 ↑ to 5–7× a week	30 ↑ 60 min	50–60% HR_{max}	↔ E/A training ↔DT training
Pu [40]	10 weeks	n = 16 randomised, n = 16 completed Ex: n = 9, age 77 years, 0% male, LVEF 36% Con: n = 7, age 77 years, 0% male, LVEF 36% All NYHA classes I, II and III, aetiology: IHD, idiopathic and valvular	RT	3	60 min	80% of 1RM (3 sets × 8 reps)	↔ E/A training
Sandri [6]	4 weeks	n = 60 randomised, n = 60 completed Ex(<55): n = 15, 50 ± 5 years, 80% male,		5 (4× per weekday)	15–20 min/session	70% of symptom limited VO_{2max}	↓ E/E′ in both <55 years and >65 years training groups

Table 1 (continued)

Study	Study duration	Participant characteristics	Exercise intervention				Major findings E/E′, E/A and DT
			Type	Frequency (per week)	Session duration	Intensity	
		LVEF 27 ± 6% Con(<55): *n* = 15, 49 ± 5 years, 87% male, LVEF 28 ± 5% Ex(>65): *n* = 15, 72 ± 4 years, 80% male, LVEF 29 ± 6% Con (>65): *n* = 15, 72 ± 3 years, 80% male, LVEF 28 ± 6%. All participants NYHA classes II and III, DD grades I and II, HF aetiology: IHD and DCM	A (C) + 1 × -GS*		(~60 min/day total) (+ 1 × 60 min GS per/week)		Improvement E/A (↑) in both <55 and >65 years training groups Improvement DT (↓) in both <55 years (↓20%) and >65 years (↓15%) training groups Significant correlation between ΔE/E′ and ΔVO_{2max} in training groups
Smart 42] [43]	16 weeks	*n* = 30 randomised, *n* = 15 completed Ex: *n* = 12, age 67 ± 5.8 years, 46% male, LVEF 58.9 ± 11.9 Con: *n* = 13, age 62 ± 6.9 years, 46% male, LVEF 56.7 ± 7.7% All NYHA classes I and II, DD: moderate *n* = 21, severe *n* = 9	A (C)	3	30 min	HR at 60–70% VO_{2peak}	↔ E/E′ training ↔ E/A training ↔ DT training
Stevens [44]	12 weeks	*n* = 28 randomised, *n* = 22 completed Ex: *n* = 15, age 67 ± 3.1 years, 67% male, LVEF 39 ± 3% Con: *n* = 7, age 64 ± 6.3 years, 86% male, LVEF 35 ± 2% NYHA classes I, II and III, aetiology: IHD (*n* = 10)	CT (C/-W+ RT)	5× every 2 weeks	24–32 min ↑ 32–48 min A+ RT	C: HR at 2nd VT—4 × 6–8 min (2 min rest periods) ↑8–12 min at week 6 + RT: 50–70% 1RM (2 sets × 10 ↑ 3 x 15 reps)	↔ E/E′ training ↔E/A training ↔ DT training
Wisloff [45]	12 weeks	*n* = 27 randomised, *n* = 26 completed Ex1: AIT *n* = 9, 77 ± 9 years, 78% male, LVEF 28.0 ± 7.3% Ex2: MCT *n* = 8, 74 ± 12 years, 78% male, LVEF 32.8 ± 4.8% Con: *n* = 9, 76 ± 13 years, 67% male, LVEF 26.2 ± 8% aetiology: ischaemic post infarct on β-blockers	A (W)	3	HIIT: 38 min (includes 10 min warm-up) MCT: 47 min	HIIT: 4 min × 4 at 90–95% HR_{max}, separated by 3 min at 50–70% HR_{max} MCT: at 70–75% HR_{max}	↓ E/E′ AIT group (26%) ↓ E/E′ MCT group (15%) Improvement E/A (↑) (AIT group), ↔E/A (MCT) ↔ DT (data not provided)

↔ non-significant change, ↑ significant increase, ↓ significant decrease, *A* aerobic, *AERG* arm ergometer, *AIT* aerobic interval training, *AR* abnormal relaxation, *Con* control, *C* cycle, *CM* cardiomyopathy, *CT* combined training, *DCM* dilated cardiomyopathy, *DD* diastolic dysfunction, *DT* deceleration time, *E/A* peak early mitral inflow velocity to the peak mitral atrial velocity contraction, *E/E′* ratio of transmitral flow velocity to annular velocity, *Ex* exercise training, *Ex(P)* exercise group preserved ejection fraction, *Ex(m)* mild ejection fraction, *Ex(s)* severely reduced ejection fraction, *GS* group session, *FES* functional electrical stimulation, *HIIT* high-intensity interval training, *HR* heart rate, HR_{max} maximum heart rate, HR_{peak} peak heart rate, *HRR* heart rate reserve, *IHD* ischaemic heart disease, *IMT* inspiratory muscle training, *LVEF* left ventricular ejection fraction, *MCT* moderate continuous training, *MIP* maximal inspiratory pressure, *NYHA* New York Heart Association, *non-RCT* non-randomised controlled trial, "*N*" pseudonormal filling pattern, *RF* restrictive filling, *RT* resistance training, *RPM* revolutions per minute, *T* treadmill, *VAT* ventilatory anaerobic threshold, VO_{2peak} peak oxygen uptake, VO_{2max} maximal oxygen uptake, *W* walking, *WL* workload

*n = 54 completed study, but n = 52 only available for analysis of diastolic function outcomes

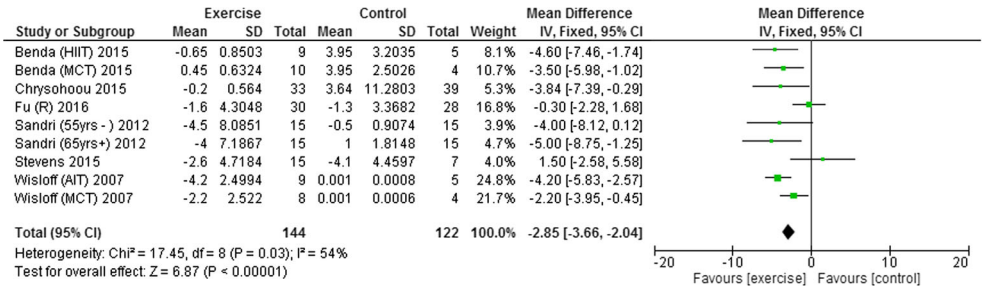


Fig. 2 Change in E/E′—exercise vs. control—HFrEF

Quality assessment

The median TESTEX score was 10 (Supplementary Table S5). While most studies reported on the randomisation of participants, only eight [5, 6, 12, 29, 32, 39, 42, 45] noted specific methods such as random numbers or computer generated blocks. Studies scored poorly in activity monitoring of the control group and in providing sufficient information that would allow for accurate calculation of exercise energy expenditure.

Heterogeneity and publication bias

Our analysis in HFrEF and HFpEF demonstrated moderate heterogeneity (I^2 = 54 and 52%, respectively). Funnel plots demonstrated little evidence of publication bias in HFrEF (see Supplementary Data).

Discussion

This work analysed the effects of exercise training on indices of DF in HF patients. Our primary finding shows that exercise training significantly improves E/E′ in HF patients, indicating reduced filling pressure and suggestive of improved DF [18]. E/E′ is considered advantageous as a measure of DF as E′ is a less load dependent index of LV relaxation [13, 46], it reduces the influence of age and heart rate [8] and it can be used in patients with atrial fibrillation [7], an important consideration given AF commonly coexists with cardiac conditions.

While a number of exercise studies have now reported on diastolic indices, as TDI is a relatively new method, only the more recent studies have assessed E/E′. To our knowledge, this is the first time E/E′ data has been pooled in HFrEF patients. While it is not always considered necessary or critical to measure E/E′ in patients with reduced ejection fractions [19], tissue Doppler annular velocity (E′) [45] and E/E′ [47] are considered to be more sensitive and accurate than the E/A ratio for the measurement of ventricular relaxation and DD. Additionally, in the situation where E/A falls between 0.8 and 2, other criteria including E/E′ are recommended in the evaluation of DF [7]. While Belardinelli et al. [5] were the first to report improved DF in HFrEF, only conventional echocardiography (not TDI) was utilised. The most comprehensive study to date to have measured DF in HFrEF patients, the age stratified LEICA study by Sandri and colleagues [6], not only confirmed that DF is significantly impaired in HFrEF patients, independent of age, but that 4 weeks of aerobic training significantly reduces E/E′ in these patients. They also noted a significant inverse correlation between the ΔE/E′ and exercise capacity (ΔVO_{2max}). While a number of factors are considered to limit exercise capacity in HF patients [48], in patients with reduced ejection fractions, DD is more strongly associated with reduced exercise capacity than ejection fraction [4, 11].

In HFpEF, the reduction, hence, improvement in E/E′ is consistent with results of a previous meta-analysis [22] in this population. Our analysis includes one more recent study [35] since the previous analysis was undertaken. While our overall result indicated a significant improvement, only two [12, 35] of the five studies in our analysis reported a significant improvement pre- to post intervention in training groups. The positive findings of E/E′ in the first large randomised multicentre trial in HFpEF patients by Edelmann and colleagues [12] are supported by the more recent study of Fu et al. [35]. Fu et al. [35] reported that 15% of HFpEF patients normalised their E/E′ ratio (<8) post intervention and the percentage of patients with a baseline E/E′ > 15 was reduced. Our pooled data is in contrast to an earlier pre-post study [49] that failed to find a change in E/E′ after 16 weeks of aerobic training. While the exact reasons for the contrasting results between studies are not entirely clear, a number of potential explanations can be proposed. While

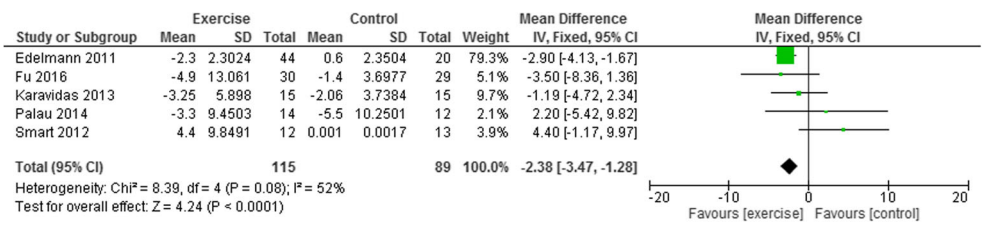


Fig. 3 Change in E/E′—exercise vs. control—HFpEF

Table 2 Summary of diastolic indices E/A and DT pre vs. post intervention

Study	E/A ratio	DT (ms)
HFrEF		
Alves [27]	*Mildly reduced EF*: ↑ training (0.83 to 0.93, $p < 0.001$), ↔ control *Moderate to severely reduce EF*: ↔ training (0.98 to 0.98, p = NS) Sub-analysis based on type DD - Restrictive filling—↓ E/A (1.58 ± 0.11 to 1.24 ± 0.22, $p = 0.02$) - Impaired relaxation—↑E/A (0.79 ± 0.11 to 0.9 ± 0.08, $p < 0.001$) ↔ Control	*Mildly reduced EF*: ↓ training (248.2 to 233.1, $p < 0.001$), ↔control *Moderate to severely reduce EF*: ↔ (216.4 to 208.4, p = NS) Sub-analysis based on type of DD: - Restrictive filling—↑DT (129.8 ± 6.1 to 166.6 ± 11.8, $p < 0.001$) - Impaired relaxation—↓ DT (243.5 ± 37 to 221.5 ± 19, $p < 0.001$) ↔Control
Belardinelli [5]	*Diastolic filling pattern groups* *Restrictive filling*: ↔ training (2 ± 0.4 to 2.1 ± 0.5, p = NS), ↔control *Normal*: ↔ training (1.3 ± 0.2 to 1.2 ± 0.3, p = NS), ↔control *Abnormal relaxation*: ↑ training (↑70%, 0.7 ± 0.2 to 1.2 ± 0.4, $p < 0.005$), ↔ control	*Diastolic filling pattern groups* *Restrictive filling* ↔ training (140 ± 20 to 130 ± 28), ↔ control *Normal*: ↔ training (160 ± 20 to 158 ± 50), ↔ control *Abnormal relaxation*: ↓ (↓21%) training (239 ± 30 to 190 ± 32), ↔control
Belardinelli [28]	↓ ICD + CRT training group (1.82 ± 0.9 to 0.93 ± 0.1, $p < 0.001$) ↔ ICD training group (no data reported) ↔ Control	NR
Belardinelli [29]	↔ Aerobic (0.92 ± 0.8 to 0.64 ± 0.8, p = NS) ↓Dance (0.98 ± 0.9 to 0.56 ± 1.1, $p < 0.05$) ↔control	NR
Benda [30]	↔ HIIT (1.53 ± 1.42 to 1.6 ± 1.53, p = NS) ↔ MICT (1.15 ± 0.71 to 1.17 ± 0.89, p = NS) ↔ Control	NR
Brubaker [31]	↔ Training (0.9 ± 0.1 to1.2 ± 0.2, p = NS) ↔ Control * ±SE	NR
Chrysohoou [32]	↓ Training (24%) (1.04 ± 0.79 to 0.78 ± 0.38, $p = 0.004$), ↔Control (1.77 ± 1.45 to 1.45 ± 1.17, p = NS)	NR
Eleuteri [34]	NR	↔ Training (189 ± 14 to 183 ± 15, $p = 0.31$) ↔ Control
Fu [35]	↔ HFrEF (1.1 ± 0.3 to 0.9 ± 0.1, p = NS) ↔ Control * ±SEM	NR
Giannattasio [36]	↔ (1.5 ± 0.8 to 1.4 ± 0.7, p = NS) ↔ Control * ±SE	NR
Malfatto [38]	↓ Training (1.59 ± 0.08 to 1.11 ± 0.59, $p < 0.02$)	NR
Mehani [39]	Improvement in E/A ratio (individual data not provided)	NR
Parnell [41]	↔ Training (1.96 ± 0.38 to 1.77 ± 0.36, p = NS) ↔ Control * ±SEM	↔ Training (219.4 ± 21.8 to 225.8 ± 18.6, p = NS) ↔ Control * ±SEM
Pu[40]	↔ Training (0.95 ± 0.17 to 0.94 ± 0.15, p = NS) ↔ Control * ±SE	NR
Sandri [6]	↑ Both training groups pre vs. post	↓ In both training groups

Table 2 (continued)

Study	E/A ratio	DT (ms)
	- <55 years: (0.7 ± 0.1 to 1.1 ± 0.1, p = 0.002), 38%↑ - >65 years: (0.8 ± 0.1 to 1.2 ± 0.1, p = 0.001), ↑35% ↔ Control * ±SEM	- <55 years (↓20%) (274 ± 9 to 231 ± 8, p = 0.03) - >65 years (↓15%) (282 ± 6 to 245 ± 4, p = 0.02) ↔ Control * ±SEM
Stevens [44]	↔ Training (1.2 ± 0.1 to 1.4 ± 0.2, p = NS) ↔ Control * ±SE	↔ Training (189 ± 16 to 192 ± 14, p = NS) ↔ Control * ±SE
Wisloff [45]	↑ AIT (0.7 ± 0.1 to 0.9 ± 0.2, p = 0.05, ↑15%) ↔ MCT (0.8 ± 0.1 to 0.8 ± 0.3, p = NS) ↔ Control	↔ (Data not provided)
HFpEF		
Alves [27]	*Preserved EF*: ↑ training (0.93 to 1.05, p < 0.001) ↔ control	*Preserved EF*: ↓ training (236.7 to 222.7, p < 0.001) ↔ Control
Edelmann [12] and Nolte [33]—Ex-DHP Study	↔ In training (0.89 ± 0.34 to 0.88 ± 0.35, p = 0.81) ↔ Control	↔ Training (225 ± 62 to ±225 ± 42, p > 0.99) ↔ Control
Fu [35]	↔ In HFpEF training (1.1 ± 0.2 to 0.9 ± 0.1, p = NS) * ±SEM	NR
Karavidas [37]	↔ In FES (0.7 ± 0.4 to 0.6 ± 0.1, p = NS) ↔ Control	NR
Kitzman [43]	↔ Training (1.03 ± 0.94 to 0.99 ± 0.59, p = NS) ↔ Control	↔ Training (225 ± 48 to 219 ± 51, p = NS) ↔ Control
Smart [42]	↔ Training (0.87 ± 0.13 to 0.82 ± 0.17, p = 0.31) ↔ Control	↔ Training (276 ± 50 to 281 ± 54, p = 0.78) ↔ Control

All data mean ± SD except those noted *

↔ non-significant change, ↑ significant increase, ↓ significant decrease, *AIT* aerobic interval training, *AR* abnormal relaxation, *DT* deceleration time, *E/A* peak early mitral inflow velocity to the peak mitral atrial velocity contraction, *E/E'* mitral peak early filling velocity to early diastolic mitral annular velocity, *EF* ejection fraction, *HIIT* high-intensity interval training, *HFpEF* heart failure preserved ejection fraction, *HFrEF* heart failure reduced ejection fraction, *ICD* implantable cardio-defibrillator, *CRT* cardiac synchronisation therapy, *IVRT* isovolumic relaxation time, *M* mildly reduced ejection fraction, *MCT* moderate continuous training, *NR* not reported, *NS* not significant, *P* preserved ejection fraction, *RF* restrictive filling

differing aetiologies, comorbidities, gender and pharmacological interventions may contribute to different results between studies, the studies by Edelmann [12] and Fu [35] were double the sample size of the other three [20, 37, 42] studies and all utilised a different exercise mode, protocol and duration, all of which cannot be discounted in contributing to the contrasting results. Interestingly, Fu [35] utilised a high-intensity interval training (HIIT) protocol, and an earlier comparative HIIT/moderate-intensity continuous training (MICT) study by Angadi et al. [50] found that DD grade was reduced after HIIT training compared to MICT, similar to findings of improved E/E′ from HIIT in type 2 diabetic patients [51]. While our pooled result indicates improved E/E′, one additional study by Kitzman and colleagues [52] in obese HFpEF patients, not included in our analysis, due to differences in data reporting, did not report any significant change in E/E′ in an exercise only training group compared to controls. Our result of improved E/E′ in HFpEF patients is in contrast to those reported in acute post MI patients [53, 54] (EF% >50%), which failed to find a significant change in E/E′. While our understanding of the mechanisms for reduced exercise tolerance in HFpEF is still evolving, Edelmann et al. [12] also reported that the improvement in E/E′ correlated with the ΔVO_{2peak} and quality of life. However, in HFpEF patients, given the heterogeneity within this phenotype, our result may not be generalizable to this population.

We also conducted a descriptive analysis of both E/A and DT as we did not feel it was appropriate to pool data due to the non-uniform changes in these diastolic indices between DD categories. Despite some studies reporting an improved E/A ratio and DT, our descriptive analysis failed to find enough evidence to indicate conclusively that exercise training improves these diastolic indices. Previous meta-analyses [21–23] have reported pooled data for the change in E/A ratio and DT in HFpEF patients, with contrasting results.

Given that no one diastolic index should be considered in isolation in evaluating DD [7], reporting on the change in DD grade may provide a more comprehensive and robust interpretation of the effect of an intervention. All three studies in our review that reported pre- and post DD grade/category by patient numbers found improvements in DD grade post intervention. We did not conduct an analysis of the effect of exercise training on LAVI, an important index in determination of DD [7], as minimal HF exercise studies to data have reported on this index. Edelmann et al. [12] reported a significant decrease in LAVI ($p < 0.001$) in their training group, while Palau et al. [20] reported no change in LAVI after IMT and Sandri et al. [6] failed to find a significant change in LA size after 4 weeks of training. Future studies should look to include measurement and reporting of this parameter.

Several factors may influence the effects of exercise training on cardiac structure and function. The criteria utilised in evaluating and grading DF, which has evolved considerably over the years and between study periods, baseline DF, underlying HF aetiology/comorbidities and exercise intervention characteristics such as the type of exercise [55], could all have influenced results. Additionally, some patients in the early stages of DD may have been missed, with evidence for DD only identified during exercise testing [15, 56] particularly, in HFpEF. Hence, improvements in DD may have occurred in patients that presented with and were graded as having normal DF. Overall, the wide variation in study characteristics and exercise prescription in HF makes comparison between studies difficult.

Our primary outcome measure of DF was E/E′, which is now extensively utilised in cardiac research and clinical practice [19], although recent studies [57, 58] have raised questions as to its accuracy in estimating LV filling pressure in some populations and situations. Therefore, while we can conclude from our data that exercise training improves the diastolic E/E′ index in HF patients and is strongly suggestive of improved DF, it would be inaccurate to say that this is conclusive evidence of improved DF as not one non-invasive index is a perfect marker of DF. Future studies should consider not only categorising and assigning patients to an intervention group based on DD grade but also reporting post intervention changes in grade to provide a more robust measure of the effect of intervention on DF.

Limitations in the systematic review and meta-analysis

The major limitation of this review is that although studies measured DF, early studies in HFrEF patients that measured and reported on changes in DF did not identify the number of participants with DD or the category/grade of DD. Additionally, only one study [5] separated intervention and control groups into the grade or type of DD and reported results based on each group. It is therefore not possible to draw a conclusion on the effect of exercise based on the grade of DD. We were unable to conduct meta-analysis of the effect of exercise training on LAVI, an important measure, as minimal studies have reported on this outcome.

In regard to data pooling, we measured the difference between pre-intervention and post intervention means; however, in cases where exact p values of 95% CI within groups were not available, default values for p were utilised and this may introduce errors.

Conclusion

This systematic review and meta-analysis found that exercise training improves E/E′ in patients with heart failure, which is suggestive of improved diastolic function. The improvements occur in patients irrespective of the degree of systolic function.

Compliance with ethical standards This work received no financial support and has no relationship to industry.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ (2003) Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 289(2):194–202
2. Kane GC, Karon BL, Mahoney DW et al (2011) Progression of left ventricular diastolic dysfunction and risk of heart failure. JAMA 306(8):856–863
3. Atherton JJ, Bauersachs J, Carerj S et al (2016) 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 18(8):891–975
4. Gardin JM, Leifer ES, Fleg JL et al (2009) Relationship of Doppler-echocardiographic left ventricular diastolic function to exercise performance in systolic heart failure: the HF-ACTION study. Am Heart J 158(4):S45–S52
5. Belardinelli R, Georgiou D, Cianci G, Berman N, Ginzton L, Purcaro A (1995) Exercise training improves left ventricular diastolic filling in patients with dilated cardiomyopathy clinical and prognostic implications. Circulation 91(11):2775–2784
6. Sandri M, Kozarez I, Adams V et al (2012) Age-related effects of exercise training on diastolic function in heart failure with reduced ejection fraction: the Leipzig Exercise Intervention in Chronic Heart Failure and Aging (LEICA) Diastolic Dysfunction Study. Eur Heart J 33(14):1758–1768
7. Nagueh SF, Smiseth OA, Appleton CP et al (2016) Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 29(4):277–314
8. Barmeyer A, Müllerleile K, Mortensen K, Meinertz T (2009) Diastolic dysfunction in exercise and its role for exercise capacity. Heart Fail Rev 14(2):125–134
9. Levy WC, Cerqueira MD, Abrass IB, Schwartz RS, Stratton JR (1993) Endurance exercise training augments diastolic filling at rest and during exercise in healthy young and older men. Circulation 88(1):116–126
10. Takemoto KA, Bernstein L, Lopez JF, Marshak D, Rahimtoola SH, Chandraratna PAN (1992) Abnormalities of diastolic filling of the left ventricle associated with aging are less pronounced in exercise-trained individuals. Am Heart J 124(1):143–148
11. Ohara T, Iwano H, Thohan V et al (2015) Role of diastolic function in preserved exercise capacity in patients with reduced ejection fractions. J Am Soc Echocardiogr 28(10):1184–1193
12. Edelmann F, Gelbrich G, Düngen H-D et al (2011) Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. J Am Coll Cardiol 58(17):1780–1791
13. Flachskampf FA, Biering-Sørensen T, Solomon SD, Duvernoy O, Bjerner T, Smiseth OA (2015) Cardiac imaging to evaluate left ventricular diastolic function. J Am Coll Cardiol Img 8(9):1071–1093
14. Somaratne JB, Whalley GA, Poppe KK, Gamble GD, Doughty RN (2009) Pseudonormal mitral filling is associated with similarly poor prognosis as restrictive filling in patients with heart failure and coronary heart disease: a systematic review and meta-analysis of prospective studies. J Am Soc Echocardiogr 22(5):494–498
15. AlJaroudi WA, Thomas JD, Rodriguez LL, Jaber WA (2014) Prognostic value of diastolic dysfunction: state of the art review. Cardiol Rev 22(2):79–90
16. Acil T, Wichter T, Stypmann J et al (2005) Prognostic value of tissue Doppler imaging in patients with chronic congestive heart failure. Int J Cardiol 103(2):175–181
17. Olson JM, Samad BA, Alam M (2008) Prognostic value of pulse-wave tissue Doppler parameters in patients with systolic heart failure. Am J Cardiol 102(6):722–725
18. Little WC, Oh JK (2009) Echocardiographic evaluation of diastolic function can be used to guide clinical care. Circulation 120(9):802–809
19. Nagueh SF, Appleton CP, Gillebert TC et al (2009) Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 22(2): 107–133
20. Palau P, Domínguez E, Núñez E et al (2014) Effects of inspiratory muscle training in patients with heart failure with preserved ejection fraction. Eur J Prev Cardiol 21(12):1465–1473
21. Taylor RS, Davies EJ, Dalal HM et al (2012) Effects of exercise training for heart failure with preserved ejection fraction: a systematic review and meta-analysis of comparative studies. Int J Cardiol 162(1):6–13
22. Dieberg G, Ismail H, Giallauria F, Smart NA (2015) Clinical outcomes and cardiovascular responses to exercise training in preserved ejection fraction heart failure patients: systematic review & meta-analysis. J Appl Physiol
23. Pandey A, Parashar A, Kumbhani DJ et al (2015) Exercise training in patients with heart failure and preserved ejection fraction meta-analysis of randomized control trials. Circulation: Heart Failure. 8(1):33–40
24. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414): 557–560
25. Egger M, Smith GD, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315(7109):629–634
26. Smart NA, Waldron M, Ismail H et al (2015) Validation of a new tool for the assessment of study quality and reporting in exercise training studies: TESTEX. International Journal of Evidence-Based Healthcare 13(1):9–18
27. Alves AJ, Ribeiro F, Goldhammer E et al (2012) Exercise training improves diastolic function in heart failure patients. Med Sci Sports Exerc 44(5):776–785
28. Belardinelli R, Capestro F, Misiani A, Scipione P, Georgiou D (2006) Moderate exercise training improves functional capacity, quality of life, and endothelium-dependent vasodilation in chronic heart failure patients with implantable cardioverter defibrillators and cardiac resynchronization therapy. Eur J Cardiovasc Prev Rehabil 13(5):818–825
29. Belardinelli R, Lacalaprice F, Ventrella C, Volpe L, Faccenda E (2008) Waltz dancing in patients with chronic heart failure new form of exercise training. Circulation: Heart Failure. 1(2):107–114
30. Benda NM, Seeger JP, Stevens GG et al (2015) Effects of high-intensity interval training versus continuous training on physical fitness, cardiovascular function and quality of life in heart failure patients. PLoS One 10(10):e0141256
31. Brubaker PH, Moore JB, Stewart KP, Wesley DJ, Kitzman DW (2009) Endurance exercise training in older patients with heart failure: results from a randomized, controlled, single-blind trial. J Am Geriatr Soc 57(11):1982–1989
32. Chrysohoou C, Angelis A, Tsitsinakis G et al (2015) Cardiovascular effects of high-intensity interval aerobic training combined with strength exercise in patients with chronic heart failure. A randomized phase III clinical trial. Int J Cardiol 179:269–274

33. Nolte K, Herrmann-Lingen C, Wachter R et al (2015) Effects if exercise training on different quality of life dimensions in heart failure with preserved ejection fraction: the Ex-DHF-P trial. European Journal or Preventive Cardiology 22(5):582–593
34. Eleuteri E, Mezzani A, Di Stefano A et al (2013) Aerobic training and angiogenesis activation in patients with stable chronic heart failure: a preliminary report. Biomarkers 18(5):418–424
35. Fu T-C, Yang N-I, Wang C-H et al (2016) Aerobic interval training elicits different hemodynamic adaptations between heart failure patients with preserved and reduced ejection fraction. American Journal of Physical Medicine & Rehabilitation 95(1):15–27
36. Giannattasio C, Achilli F, Grappiolo A et al (2001) Radial artery flow-mediated dilatation in heart failure patients effects of pharmacological and nonpharmacological treatment. Hypertension 38(6): 1451–1455
37. Karavidas A, Driva M, Parissis JT et al (2013) Functional electrical stimulation of peripheral muscles improves endothelial function and clinical and emotional status in heart failure patients with preserved left ventricular ejection fraction. Am Heart J 166(4):760–767
38. Malfatto G, Branzi G, Osculati G et al (2009) Improvement in left ventricular diastolic stiffness induced by physical training in patients with dilated cardiomyopathy. J Card Fail 15(4):327–333
39. Mehani SH (2013) Correlation between changes in diastolic dysfunction and health-related quality of life after cardiac rehabilitation program in dilated cardiomyopathy. J Adv Res 4(2):189–200
40. Pu CT, Johnson MT, Forman DE et al (2001) Randomized trial of progressive resistance training to counteract the myopathy of chronic heart failure. J Appl Physiol 90(6):2341–2350
41. PARNELL MM, HOLST DP (2002) Exercise training increases arterial compliance in patients with congestive heart failure. Clin Sci 102(1):1–7
42. Smart NA, Haluska B, Jeffriess L, Leung D (2012) Exercise training in heart failure with preserved systolic function: a randomized controlled trial of the effects on cardiac function and functional capacity. Congestive Heart Failure 18(6):295–301
43. Kitzman DW, Brubaker PH, Herrington DM et al (2013) Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. J Am Coll Cardiol 62(7):584–592
44. Stevens AL, Hansen D, Herbots L et al (2015) Exercise training improves insulin release during glucose tolerance testing in stable chronic heart failure patients. Journal of Cardiopulmonary Rehabilitation and Prevention 35(1):37–46
45. Wisløff U, Støylen A, Loennechen JP et al (2007) Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients a randomized study. Circulation 115(24):3086–3094
46. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quiñones MA (1997) Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 30(6):1527–1533
47. Arques S, Roux E, Luccioni R (2007) Current clinical applications of spectral tissue Doppler echocardiography (E/E′ ratio) as a noninvasive surrogate for left ventricular diastolic pressures in the diagnosis of heart failure with preserved left ventricular systolic function. Cardiovascular Ultrasound 5(1):1
48. Haykowsky MJ, Tomczak CR, Scott JM, Paterson DI, Kitzman DW (2015) Determinants of exercise intolerance in patients with heart failure and reduced or preserved ejection fraction. J Appl Physiol 119(6):739–744
49. Smart N, Haluska B, Jeffriess L, Marwick TH (2007) Exercise training in systolic and diastolic dysfunction: effects on cardiac function, functional capacity, and quality of life. Am Heart J 153(4):530–536
50. Angadi SS, Mookadam F, Lee CD, Tucker WJ, Haykowsky MJ, Gaesser GA (2015) High-intensity interval training vs. moderate-intensity continuous exercise training in heart failure with preserved ejection fraction: a pilot study. J Appl Physiol 119(6):753–758
51. Hollekim-Strand SM, Bjørgaas MR, Albrektsen G, Tjønna AE, Wisløff U, Ingul CB (2014) High-intensity interval exercise effectively improves cardiac function in patients with type 2 diabetes mellitus and diastolic dysfunction: a randomized controlled trial. J Am Coll Cardiol 64(16):1758–1760
52. Kitzman DW, Brubaker P, Morgan T et al (2016) Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. JAMA 315(1):36–46
53. Fontes-Carvalho R, Azevedo AI, Sampaio F et al (2015) The effect of exercise training on diastolic and systolic function after acute myocardial infarction: a randomized study. Medicine 94(36)
54. Korzeniowska-Kubacka I, Bilińska M, Michalak E, Kuśmierczyk-Droszcz B, Dobraszkiewicz-Wasilewska B, Piotrowicz R (2010) Influence of exercise training on left ventricular diastolic function and its relationship to exercise capacity in patients after myocardial infarction. Cardiol J 17(2):136–142
55. Haykowsky MJ, Liang Y, Pechter D, Jones LW, McAlister FA, Clark AM (2007) A meta-analysis of the effect of exercise training on left ventricular remodeling in heart failure patients: the benefit depends on the type of training performed. J Am Coll Cardiol 49(24):2329–2336
56. Guazzi M (2015) Stress echocardiography combined with cardiopulmonary exercise testing: opening a new window into diagnosis of heart failure with preserved ejection fraction. Eur J Prev Cardiol. doi:10.1177/2047487315607076
57. Santos M, Rivero J, McCullough SD et al (2015) E/e′ ratio in patients with unexplained dyspnea lack of accuracy in estimating left ventricular filling pressure. Circulation: Heart Failure 8(4):749–756
58. Sharifov OF, Schiros CG, Aban I, Denney TS, Gupta H (2016) Diagnostic accuracy of tissue Doppler index E/e′ for evaluating left ventricular filling pressure and diastolic dysfunction/heart failure with preserved ejection fraction: a systematic review and meta-analysis. J Am Heart Assoc 5(1):e002530

Online supplementary material 10741_2017_9600_MOESM1_ESM.docx

Supplementary Table S1. Studies reviewed but excluded from meta-analysis with reasons

Author (ref)	**Reasons for Exclusion**
Angadi (2014)	Comparison of two different training protocols, no control group
Freimark (2005)	No non-exercising control group
Fontes-Carvalho (2015)	Does not meet inclusion criteria
Giallauria (2008)	Does not meet inclusion criteria
Giallauria (2009)	Does not meet inclusion criteria
Giallauria (2006)	Does not meet inclusion criteria
Karapolat (2009)	Comparison of home based and hospital based exercise, no non-exercise control group
Kitzman (2010)	Data already included as part of Kitzman 2013
Kitzman (2016)	Follow up data presented as Least Square Mean (LS Mean), baseline reported as mean
Korzeniowska-Kubacka (2009)	Does not meet inclusion criteria
Myers (2002)	No relevant E/E', DT or E/A data
Nolte (2014)	Compared HFpEF to patients with Diastolic dysfunction
Ritzel (2014)	Comparison of two heart failure groups and analysis of parameters based on weight loss in two groups, no control group
Rustaad (2014)	Heart transplant patients only
Smart (2007)	Comparison of HFpEF to HFrEF, no non-exercise control group
Teffaha (2011)	Comparison of exercise training on land to exercise training in water and no control group
Yeh (2013)	Comparison of Tai Chi to aerobic exercise and no control group

DT: deceleration time, E/A: the ratio of peak early to late diastolic filling velocity, E/E': the ratio of early diastolic transmitral velocity to early diastolic tissue velocity, HFpEF: heart failure preserved ejection fraction, HFrEF: heart failure reduced ejection fraction

Supplementary Table S2. Baseline Diastolic Indices in exercise training intervention groups

Study	**Mitral Inflow**			**Tissue Doppler**	
	E/A (m/s)	**D_T (m/s)**	**IVRT (m/s)**	**E' (cm/s)**	**E/E'**
Alves (2011)	0.93 (P) 0.83 (M) 0.98 (Mod-S)	236.7 (P) 248.2 (M) 216.4 (Mod-S)	NR	NR	NR
Benda (2015)	1.53±1.42 (HIIT) 1.15±0.71 (MCT)	NR	142±27 (Lateral) (HIIT) 164±41 (Septal) (HIIT) 145±32 (Lateral) (MCT) 160±36 (Septal) (MCT)	NR	10.3±4 (L) (HIIT) 12.6±9.8 (S) (HIIT) 6.8±1.9 (L) (MCT) 10.1±4.1 (S) (MCT)
Belardinelli (1995)	2.0±0.4 (RF) 1.3±0.2 ("N") 1.2±0.4 (AR)	140±20 (RF) 160±20 ("N") 239±39 (AR)		NR	NR
Belardinelli (2006)	1.82±0.9 (ICD+CRT group) No Data CRT group	NR	NR	NR	NR
Belardinelli (2008)	0.92±0.8 (A) 0.98±0.9 (D)	NR	NR	NR	NR
Brubaker (2009) *±SE*	0.9±0.1	NR	NR	NR	NR
Chrysohoou (2015)	1.04±0.79	NR	NR	NR	9.2±4.2
Edelmann (2011)	0.89±0.34	225±62	NR	5.4±1.2	12.8±3.2
Eleuteri (2013)	NR	189±14	NR	NR	NR
Fu (2016) *±SEM*	1.1±0.2 (HFpEF) 1.1±0.3 (HFrEF)	NR	NR	NR	21.0±2.2 (HFpEF) 20.3±2.8 (HFrEF)
Giannattasio (2001) *±SE*	1.5±0.8	NR	NR	NR	NR
Karavidas (2013)	0.7±0.4	NR	NR	NR	11.1±2.5
Kitzman (2013)	1.03±0.94	225±48	80±24	NR	NR
Malfatto (2009)	1.59±0.08	NR	NR	NR	NR
Mehani (2013)	Median 0.53	NR	NR	NR	NR
Palau (2014)	NR	NR	NR	5.2 (3.8-6.9)	16.2 (10.5-21.6)
Parnell (2002) *±SEM*	1.96±0.68	219.4±21.8	NR	NR	NR
Pu (2001)	0.95±0.17 *±SE*	NR	NR	NR	NR
Sandri (2012) *±SEM*	0.7±0.1 (<55yrs) 0.8±0.1 (>65yrs)	274±9 (<55yrs) 282±6 (>65yrs)	158±5 (<55yrs) 163±7 (>65yrs)	4.2±1.1 (Septal) (<55yrs) 5.3±1.5 (Lateral) (<55yrs) 3.8 ±0.8 (Septal) (>65yrs) 5.3±1.4 (Lateral) (>65yrs)	13±1 (Septal) (<55yrs) 15±2 Lateral) (<55yrs) 14±2 (Septal) (>65yrs) 15±2 (Lateral) (>65yrs)

Smart (2012)	0.87±0.13	276±50	NR	4.4±1.5	20.7±12.8
Stevens (2015) *±SE*	1.2 ± 0.1	184 ± 16	97 ± 4	NR	19.8 ± 3.2
Wisloff (2007	0.7±0.1 (AIT) 0.8±0.1 (MCT)	NR	100.7±18.9 112.4±23.4	4.5±1.3 4.6±0.8	16.0±3.5 15.1±5.4

All data mean ± SD, except those studies noted. AIT: aerobic interval training, AR: abnormal relaxation, DT: deceleration time, E/A: peak early mitral inflow velocity to the peak mitral atrial velocity contraction, E/E': mitral peak early filling velocity to early diastolic mitral annular velocity, HIIT: High intensity interval training, HFpEF: heart failure preserved ejection fraction, HFrEF: heart failure reduced ejection fraction, IVRT: isovolumic relaxation time, M: mildly reduced ejection fraction, MCT: moderate continuous training, "N": pseudonormal, NR: not reported, P: preserved ejection fraction, RF: restrictive filling, Mod-S: moderate to severely reduced ejection fraction.

Supplementary Table S3. Change in Diastolic Grade

Study	Grade/Category	Pre	Post	Change
Malfatto (2009)	Grade 0 (Normal)	8	19	↑11
	Grade I (Abnormal Relaxation)	6	4	↓2
	Grade II (Pseudonormal)	4	3	↓1
	Grade III (Restrictive)	9	1	↓8
Mehani (2013)	Grade 0 (Normal)	0	8	↑8
	Grade I (Abnormal Relaxation)	11	5	↓6
	Grade II (Pseudonormal)	2	1	↓1
	Grade III (Restrictive)	2	1	↓1
Sandri (2012) (<55yrs)	Grade 0 (Normal)	0	1	↑1
	Grade I (Abnormal Relaxation)	6	8	↑2
	Grade II (Pseudonormal)	9	6	↓3
Sandri (2012) (>65yrs)	Grade 0 (Normal)	0	0	↑0
	Grade I (Abnormal Relaxation)	5	9	↑4
	Grade II (Pseudonormal)	10	6	↓4

Supplementary Table S4. Intervention Compliance and Adverse Events

Study	Session Attendance	Adverse Events
Alves (2011)	>80% for patients analysed (patients who completed less were excluded from analysis)	No adverse events registered
Belardinelli (1995)	NR	No significant cardiovascular events during training. n=1 self-limited episode of AD during cycling, spontaneously converting to sinus rhythm after 10 mins rest. Sporadic ventricular extra systoles n=11 during cycling and n=5 during recovery. n=2 hypotension at end of cycling, promptly resolved.
Belardinelli (2006)	NR	Nil Adverse events in trained patients during intervention
Belardinelli (2008)	Exercise group = 77±8%, Dance group 91±8%	Sporadic ventricular premature contractions (n=14: n=8 dancing group, n=6 exercise training group), dizziness (n=3: n=2 dancing group, n=1 exercise training group), hypotension during recovery (n=2 dancing group)
Benda (2015)	100% sessions attended	Musculoskeletal complaints n=2 (n= 1 from both training groups), Progression of heart failure n=2 (n= 1 from both training groups)
Brubaker (2009)	Mean adherence 94% (range 83%-100%)	No deaths, hospitalisation or cardiac events related to the intervention or testing procedures
Chrysohoou (2015)	NR	No serious adverse events including cardiac, musculoskeletal or hospitalization related to the exercise
Edelmann (2011)	Sessions: n=34% >90%, n=52% 70-90%, n=14%<70%	No deaths or hospitalisation, 5 cardiac events (palpitations) in exercise group
Eleuteri (2013)	Non-Adherence <1%	No deaths, hospitalisation or cardiac events
Fu (2016)	NR	NR
Giannattasio (2001)	NR	NR
Karavidas (2013)	NR	NR
Kitzman (2013)	88% of exercise training sessions attended	n=1 transient hypoglycaemia, no other protocol-related events
Malfatto (2009)	NR	NR
Mehani (2013)	NR	Training group n= 3 worsening HF, n=2 decompensated HF & hospitalised, n=2 Control group n=2 SCD
Palau (2014)	NR	No deaths or hospitalisations
Parnell (2002)	NR	NR
Pu (2001)	Average attendance at exercise session 98%	No deaths or hospitalisations
Sandri (2012)	100% sessions attended	No serious adverse events
Smart (2012)	87.6% sessions attended	No deaths, adverse events or hospitalisation
Stevens (2015)	Average attendance at exercise session 93% (Range 73%-100%)	n=1 cardiac and renal failure in training group, no details on whether this was directed related to the training
Wisloff (2007)	Average attendance 92±2% for aerobic interval training group and 95±3% moderate continuous training group	1 death in the moderate continuous training group due to cardiac causes unrelated to the training

NR: not reported or noted

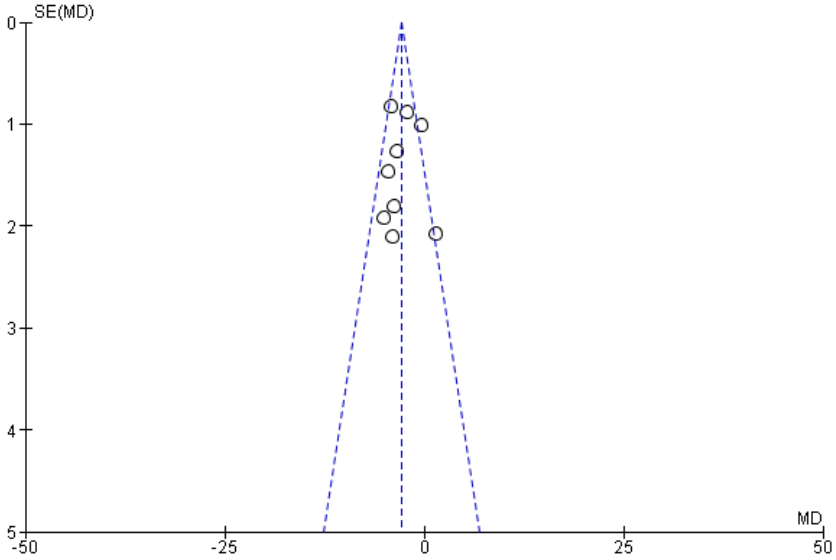
Supplementary Table S5. Assessment of study quality using TESTEX scale

Study Ref	Eligibility Criteria Specified	Randomization Specified	Allocation Concealed	Groups Similar at baseline	Blinding of Assessors	Outcome measures in >85% Participants *	Intention to treat analysis	Between-group statistical comparisons reported**	Point measures & measures of variability reported	Activity monitoring in control group	Relative Exercise intensity reviewed	Exercise Volume and Energy Expended	Overall TESTEX
Alves (2011)	1	0	0	1	1	3/3	0	2/2	1	0	1	0	9
Belardinelli (1995)	1	1	0	1	0	2/3	1	2/2	1	0	1	0	10
Belardinelli (2006)	1	0	0	1	0	2/3	1	2/2	1	0	0	0	8
Belardinelli (2008)	1	1	1	1	0	3/3	1	2/2	1	0	0	0	11
Benda (2015)	1	0	0	1	0	2/3	0	1/2	1	0	1	1	8
Brubaker (2009)	1	0	0	1	1	2/3	0	2/2	1	0	1	1	10
Chrysohoou (2015)	1	1	1	1	0	1/3	1	2/2	1	0	0	0	9
Edelmann (2011)	1	1	0	1	1	3/3	1	2/2	1	0	1	0	12
Eleuteri (2013)	1	0	0	1	1	3/3	1	0/2	1	0	1	1	10
Fu (2016)	1	0	0	1	1	1/3	0	2/2	1	0	1	1	9
Giannattasio (2001)	1	0	0	1	1	1/3	1	0/2	1	0	0	0	6
Karavidas (2013)	1	0	0	1	1	1/3	1	2/2	1	0	1	0	9
Kitzman (2013)	1	0	0	1	1	3/3	0	2/2	1	0	1	1	11
Malfatto (2009)	1	0	0	1	0	1/3	0	0/2	1	0	1	0	5
Mehani (2013)	1	1	0	1	1	1/3	0	2/2	1	1	1	0	10
Palau (2014)	1	0	0	1	1	2/3	0	2/2	1	0	1	1	10
Parnell (2002)	1	0	0	1	1	1/3	1	0/2	1	0	1	0	7
Pu (2001)	1	0	0	1	1	3/3	1	2/2	1	0	1	0	11
Sandri (2012)	1	1	1	1	1	3/3	1	2/2	1	0	0	0	12
Smart (2012)	1	1	1	1	0	3/3	1	2/2	1	0	1	1	13
Stevens (2015)	1	0	0	1	0	2/3	0	2/2	1	0	1	0	8
Wisloff (2007)	1	1	1	1	1	3/3	0	2/2	1	0	1	0	12

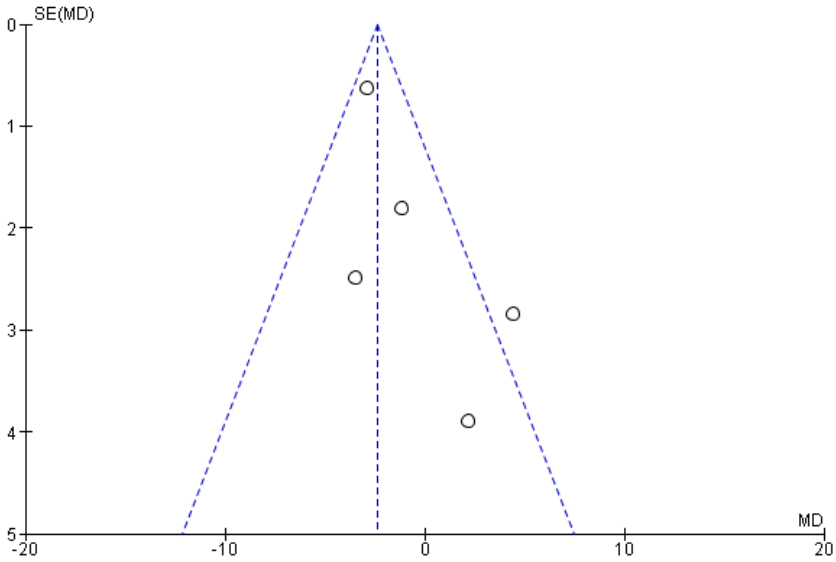
TESTEX total out of 15 points. * Three points possible, ** Two points possible. A score of Zero (0) was allocated if it was unclear. If ITT was not specifically mentioned, but it was noted that no participants withdrew and all analysed 1 point was awarded.

Funnel Plots

E/E'- Exercise vs. control – HFrEF



E/E'- Exercise vs. control – HFpEF



9 Chapter 9 - Peer reviewed publication: Reported methods for handling missing change standard deviations in meta-analyses of exercise therapy interventions in patients with heart failure: a systematic review

9.1 Manuscript Information

Pearson, M.J., & Smart, N.A. (2018). Reported methods for handling missing change standard deviations in meta-analyses of exercise therapy interventions in patients with heart failure: a systematic review

Submitted to PLOS ONE 25th May 2018 - Under Review

20th June 2018

Candidate

Principal Supervisor 20th June 2018

9.2 Statement of author's contribution

Higher Degree Research Thesis by Publication

University of New England

STATEMENT OF AUTHORS' CONTRIBUTION

We, the PhD candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated in the *Statement of Originality*.

	Author's Name (please print clearly)	**% of contribution**
Candidate	Melissa Pearson	90%
Other Authors	Neil Smart	10%

Name of Candidate: Melissa Jane Pearson

Name/title of Principal Supervisor: Professor Neil Smart

[redacted]

20th June 2018

Candidate Date

[redacted]

20th June 2018

Principal Supervisor Date

9.3 Statement of originality

Higher Degree Research Thesis by Publication

University of New England

STATEMENT OF ORIGINALITY

We, the PhD candidate and the candidate's Principal Supervisor, certify that the following text, figures and diagrams are the candidate's original work.

Type of work	Page number(s)
Systematic Review	247-274

Name of Candidate: Melissa Jane Pearson

Name/title of Principal Supervisor: Professor Neil Smart

[redacted]

20th June 2018

Candidate Date

[redacted]

20th June 2018

Principal Supervisor Date

9.4 Full manuscript - As submitted to peer- reviewed journal

Reported methods for handling missing change standard deviations in meta-analyses of exercise therapy interventions in patients with heart failure: a systematic review

Melissa J Pearson[1]*, Neil A Smart [1]

[1] School of Science and Technology, University of New England, Armidale, NSW, Australia 2351

* Corresponding author

Email: mpears23@myune.edu.au

ABSTRACT

Background Well-constructed systematic reviews and meta-analyses are key tools in evidenced-based healthcare. However, a common problem with performing a meta-analysis is missing data, such as standard deviations (SD). An increasing number of methods are utilised to calculate or impute missing SDs, allowing these studies to be included in analyses. The aim of this review was to investigate the methods reported and utilised for handling missing change SDs in meta-analyses, using the topic of exercise therapy in heart failure patients as a model.

Methods A systematic search of PubMed, EMBASE and Cochrane Library from 1 January 2014 to 31st March 2018 was conducted for meta-analyses of exercise based trials in heart failure. Studies were eligible to be included if they performed a meta-analysis of change in exercise capacity in heart failure patients after a training intervention.

Results Twenty publications performed a meta-analysis on the effect of exercise therapy on exercise capacity in heart failure patients. Nine (45%) publications did not directly report the approach for dealing with missing change SDs. Approaches reported and utilised to deal with missing change SDs included imputation, actual and approximate algebraic recalculation using study level summary statistics and exclusion of studies.

Conclusion Authors need to clearly report the approach to be utilised for missing change SD, and where data is imputed, sensitivity analysis should be conducted.

Keywords Heart Failure, Meta-analysis, Missing data, Standard Deviation, Imputation

INTRODUCTION

Systematic reviews (SRs) and meta-analyses (MAs) serve key purposes; identifying, synthesizing and critically reviewing evidence, answering a specific question[1, 2]. Well-constructed SRs and MAs play a key role in evidenced-based healthcare helping inform clinical guidelines and practice[3, 4]. Furthermore, and as importantly, they assist in identifying knowledge gaps and research needs[4, 5]. When feasible, systematic reviews use meta-analysis, the statistical method for combining two or more studies to provide an estimate of the overall effect[2].

For meta-analysis of continuous variables, the standard approach requires information on the mean, standard deviation (SD) or standard error (SE) and sample size, in order to calculate an effect size[6]. There are multiple ways to calculate the effect size including change score from baseline and follow-up scores. However, a common situation that arises when the change score method is utilised is that change SD may not be reported[7]. While the best approach is to obtain any missing data from the original study authors, this is not always feasible or possible. The absence of and inability to obtain data from authors may result in the omission of studies from the review and analysis. However, omission of studies from a meta-analysis may reduce statistical power and potentially cause bias[7]. For this reason, meta-analysts utilise a range of methods to estimate SDs [6-8].

The Cochrane Handbook provides guidelines on a number of methods that can be utilised to calculate missing change SDs[6]. Reported summary statistics such as confidence intervals (CIs), t-values and p-values can be used for algebraic recalculation of SDs[6]. In instances when exact levels of significance are not reported, but significance is represented by an

upper or lower limit, i.e., $p<0.05$, then a conservative approach using the limit provided, is often utilised[6]. Where reported data does not allow for algebraic recalculation, SDs may be imputed[6]. Recently, fifteen methods were identified for dealing with missing SDs in meta-analyses[8]. This is in addition to the methods previously identified by Wiebe and colleagues in 2006[7].

Heart failure remains a leading cause of morbidity and mortality worldwide. One of the primary symptoms of heart failure is reduced exercise tolerance. As cardiorespiratory fitness is linked to heart failure prognosis [9, 10], therapies that improve exercise capacity are of interest to clinicians, patients and researchers. Results of primary research and secondary level research via SRs and MAs of exercise therapy in heart failure, have led to exercise therapy being a Class 1A recommendation for stable heart failure patients, due in part to its ability to improve exercise tolerance[11]. Therefore, changes in exercise capacity from baseline to post intervention represent a continuous outcome frequently measured and analysed in this population and therefore is a suitable model upon which to investigate methodological approaches utilised. The primary aim of this review was to investigate what approaches were reported by meta-analysts for handling missing change SDs in the analysis of exercise capacity after exercise therapy interventions in heart failure patients.

METHODS

Search Strategy

Potential studies were identified by conducting systematic searches of PubMed, EMBASE, and the Cochrane Library from 1st January 2014 to 31st March 2018. Searches included a mix of MeSH and free text terms related to the key concepts of heart failure, exercise and meta-

analysis. One reviewer (MJP) conducted the search and full articles were assessed for eligibility by two reviewers (MJP and NAS).

Inclusion criteria

Publications were included if they were published in English between 1st January 2014 and 31st March, 2018. The search period was limited as there are numerous meta-analyses in this field and new methods have been introduced, so we wished to provide a contemporary approach. Meta-analyses were included if they analysed continuous variables of either $VO_{2peak,}$ 6MWT, peak power, exercise time or combined exercise capacity, in heart failure patients undertaking exercise training. As the issue of missing SDs is generally more of a problem when the MA is conducted using the mean difference or standardised mean difference for change (pre-post intervention) between an intervention and control group, for the purpose of this review we only included MAs that conducted statistical analysis using the change score method; hence MAs that utilised follow-up methods for analysis were excluded. Exercise training included any form of exercise therapy, including physical therapy modalities of functional electrical stimulation and inspiratory muscle training. Meta-analyses included studies of any design. Meta-analyses in which other interventions were analysed, i.e., pharmacological therapy or diet, were only included if exercise was analysed separately. Publications which identified themselves as a meta-regression analysis were included only if they provided the methods, results and details of the associated meta-analysis.

Exclusion criteria

For the purpose of this review we excluded publications that focused solely on heart failure patients supported by left ventricular assist devices or implantable cardioverter-defibrillators. Meta-analyses were also excluded if they included populations in addition to heart failure patients, even if heart failure patients were included and a separate analysis and/or a sub analysis were provided on heart failure patients. Abstracts or articles not available as full-text and non-English publications were excluded. Meta-analyses were excluded if they did not analyse the specified outcomes.

Data extraction

Data extraction was performed by one reviewer (MJP). For each meta-analysis the following information was extracted: 1) author, year of publication and Journal, 2) study designs included in analyses, 3) type of intervention, 4) exercise capacity outcome measure, 5) statistical methods applied for meta-analysis, and 6) details of methods reported and utilised to handle missing SDs.

Data Analysis

The primary outcome to be assessed in the review was identification of the reported approach in meta-analyses for dealing with missing change SDs. Meta-analyses, including supplementary files were individually reviewed and categorised based on the approach reported in the publications to handle missing change SDs. Meta-analyses were allocated to one of four categories 1) No clear approach reported, 2) Algebraic or approximate algebraic recalculation of SD, 3) Imputed SD, and 4) No imputation. Where no approach for handling missing change SDs was reported, our secondary aim was to examine, where possible, a

random selection of studies in the identified meta-analysis in an attempt to ascertain what approach may have been adopted by the meta-analyst.

RESULTS

The initial search generated a total of 779 articles. After removal of duplicates and exclusion of articles based on abstract and title, 37 full-text articles remained for screening. Full screening resulted in 20[12-31] articles meeting the stated inclusion criteria (Fig. 1). Details of MAs reviewed, but excluded are provided in Supplementary Table S1.

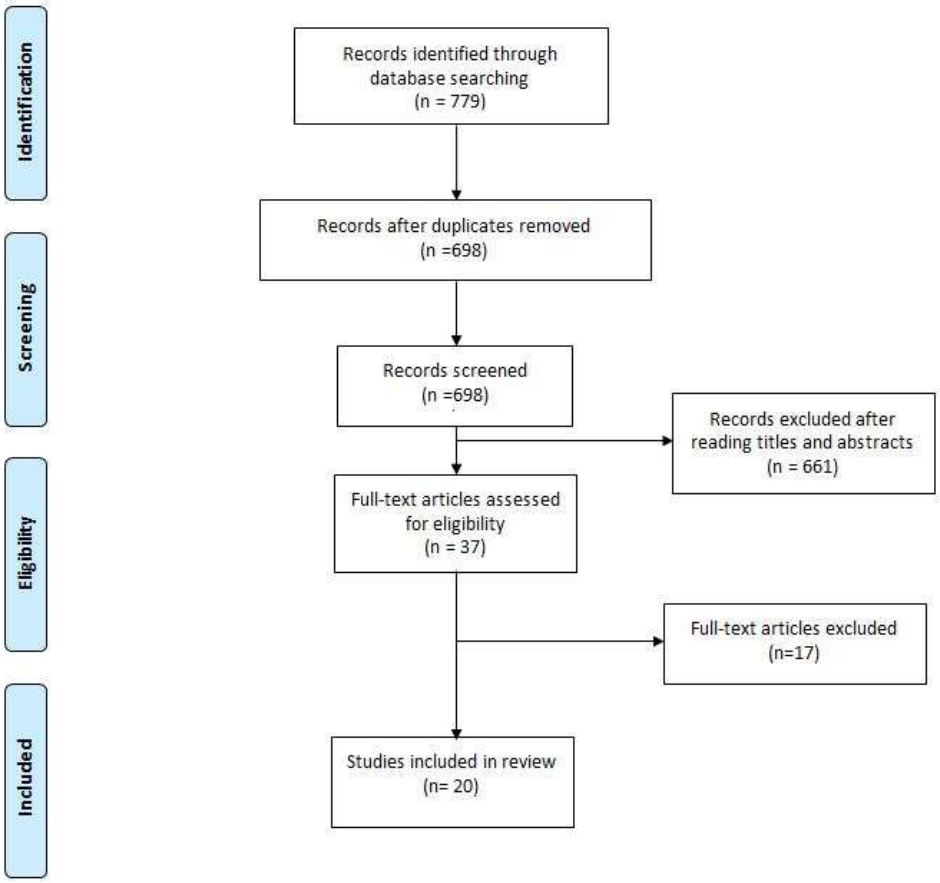


Fig. 1 PRISMA Study flow diagram

Characteristics of included Meta-analyses

A general description of included analyses is provided in Table 1. Twenty [12-31] MAs reported on change in exercise capacity. Meta-analysis of VO_{2peak} was performed in 19 publications[12-16, 18-31], 6MWD was analysed in 11 publications[12-17, 19, 20, 22, 25, 28] peak power in two[12, 21] and exercise time in one[26] publication. Analyses examined a range of exercise modalities across heart failure phenotypes, and Review Manager (Revman) was the most popular software package utilised. Supplementary Table S2 and S3 provide additional details of included publications. The publications were spread across 13 journals.

Table 1. Summary of characteristics of meta-analyses included in review

Characteristics	Number
Meta-analyses included in review	20
Associated Journals	13
Study Designs included in Meta-analysis	
• RCTs only	18
• RCTs & Controlled Trials	2
Year Meta-analysis published	
• 2014	4
• 2015	4
• 2016	7
• 2017	3
• 2018	2
Exercise Training/Therapy Modalities included in MAs	
• Aerobic only	3
• Resistance only	2
• Aerobic, Resistance and/or Combined Training	3
• Mixed modalities (aerobic, resistance, combined, yoga, tai chi, NMES and/or IMT)	4
• Tai Chi only	2
• Yoga only	1
• Hydrotherapy/Aquatic only	2
• IMT only	1
• NMES and other Exercise	2
Exercise Capacity Outcome Measures in MAs	
• VO_{2peak}	19
• 6MWT	11
• Peak Power/Workload	2
• Exercise Time	1

6MWT: 6-minute walk test, IMT: inspiratory muscle training, MAs: meta-analysis, NMES: neuromuscular electrical stimulation, RCTs: randomised controlled trials

Reported approaches for handling missing change SDs

A number of publications note contacting authors for missing and raw data; however, no MA reported the specific details on any SD data requested, and if the requested information was provided. A number of MAs within the review adopted more than one approach for dealing with missing change SDs. Only one MA quantified the number of studies with missing SDs, and how each of these studies was dealt with[21]. This was specifically in regard to the pre and/or post SD required to calculate a change SD[21]. Two MAs [12, 29] report the exclusion of studies if suitable data was not available, however, this appears to be only in the case where both mean and SD were missing. Only one MA[21], specifically reported excluding a study due to missing pre/post SD required to impute a change SD, and no other MA utilising change values for meta-analysis made reference to the possibility of missing pre or post SDs and how this would be handled. Table 2 provides a summary of approaches as reported in the MAs to deal with missing change SDs.

Table 2. Summary of approaches to deal with missing change SDs as reported in the Meta-analyses

Approach	Method reported in Publication	Number of Publications
No details reported/Unclear	No clear method for handling missing change SDs reported in the paper	9
Algebraic or approximate algebraic recalculation	SD calculated using SE, t or F- statistics, 95% CI, actual p-values or default p-values using upper or lower bound p-values and non-significant p-values	6
	Data extracted from figures/visual analysis	1
Imputation	Imputation using a correlation value	4
	Directly substituted SD – Baseline SD used as change SD	1
	Imputation of mean±SD from non-parametric data	4
No Imputation	Studies excluded from meta-analysis if data not available to impute a SD	1

1) No method of handling missing change SD reported

Overall nine [12, 17, 22, 23, 25-27, 29, 31] MAs failed to report anywhere within the publication any clear approach to deal with missing change SDs. Further examination of the nine MAs revealed a range of methods were utilised in these analyses, including actual and approximate algebraic recalculations using actual or default p-values, post-intervention SDs and imputed SDs using correlation values (Table 3).

Table 3. Summary of approaches utilised to deal with missing change SDs from the nine publications where no approach was reported

Approach	Method utilised	Number of Publications
Approach still unclear	Approach still unclear after examination of a random selection of individual studies included in MAs	3
Algebraic or approximate algebraic recalculation	SD calculated using SE, t or F- statistics, 95% CI, actual p-values or default p-values using upper or lower bound p-values and non-significant p-values	1
Imputation	Imputation using a correlation value	2
	Directly substituted SD – Follow-up SD used as change SD	4

2) Algebraic or approximate algebraic recalculation of SD

One MA[28] noted that the *t*- value was utilised to calculate SD change. Five MAs [13, 14, 18, 19, 24] report utilising CIs, actual p-values or default p-values when an exact p-value was not available. Hence, in the case of default p-values the SD value becomes an approximate algebraic recalculation. Further individual examination of 4 MAs [13, 14, 18, 19] that noted using actual or approximate p-values revealed that both actual and default p-values were utilised. Further review of one MAs[24] indicated that while the CI was reported as being utilised, the post intervention SD was directly substituted for the change SD in the analysis. One[21] MA noted the extraction of data from one included study using visual analysis.

3) Imputation of SD

Three MAs[15, 16, 30] reported utilising a specific correlation value to calculate the change SD. Values of 0.8[16], 0.5[15] and 0.7[30] were utilised, however, only the study that utilised 0.5 noted why, stipulating it was a conservative value[15]. One additional MA[21] noted using the change score method to calculate the SD of each study; however, the correlation value was not reported. Direct substitution was only reported in one MA[20], with the baseline SD utilised. Four MAs [17, 24, 28, 29] noted the conversion of mean±SD when non-parametric data was provided. Of these, one[17] calculated the SD using IQR/1.35, one[24] stipulated using the method of Wan et al. (2014), one[29] utilised a formula provided in the paper, while one MA[28] notes using a formula, but provided no details.

4) No Imputation

One MA[21] reported the exclusion of studies if SDs were not available to calculate the change score SD.

Sensitivity analysis

No meta-analysis reported performing a sensitivity analysis specifically in relation to imputed SDs in order to examine the impact of different imputed values. Three MAs[14, 18, 19] that adopted the approach of utilising default p-values when actual values were not available, did however note that this approach was a limitation, which could “introduce errors” into the analysis.

DISCUSSION

This review examined methods currently reported and utilised to handle missing change SDs in the statistical analysis of exercise capacity in heart failure patients after exercise therapy interventions. While all publications in the current review included details of the applied statistical methods for meta-analysis, reporting of the specific approach that would be employed to handle missing change SDs was absent in 45% of publications. The omission of an approach to deal with missing change SD is not to say that the approach or methods applied by the meta-analysts are in anyway contrary to what is recommended. However it does raise a number of issues when interpreting the results and drawing conclusions. Not only does the interpretation of MAs become difficult with absent or ambiguous information, but insufficient detail on methods and assumptions applied to handle missing change SDs impacts the transparency and reproducibility of the meta-analysis[32].

An increasing number of methods to dealing with missing variance data, including SDs are reported in the literature [7, 8, 33-35]. Of the MAs included in our review, use of algebraic or approximate algebraic recalculations using study summary statistics, was the most commonly reported approach. However, in the majority of cases, identification as to whether MAs utilised actual or approximate algebraic recalculations and which summary statistics, was only evident upon an individual examination of the studies included in the MAs.

Three imputation methods were reported in the reviewed publications; use of a correlation to calculate a change SD, direct substitution using an alternative SD (e.g., baseline or follow-up SD), and conversion of non-parametric data. Missing change SDs can be calculated if pre

and post SDs are available utilising an imputed value for the correlation coefficient[6]. The correlation value can be acquired from a number of sources, including using data from a similar study, from a similar meta-analysis, use of what is often considered a conservative value (0.5), or an assumption of no correlation (0.0), which is the most conservative[6, 7]. However, only one of the included MAs to adopt a correlation value provided a reason for the value. While non-parametric data is actual, and not borrowed data it is also considered a method of imputation[7], and hence was included as an approach in our review. However, the conversion and use of non-parametric data in MAs is usually in addition to parametric data. Interestingly, while four MAs made note of the conversion of non-parametric data in the methods, only two provided an approach to dealing with missing change SDs.

Only one[21] MA identified the studies with missing change SDs and how different approaches were applied. The finding that the majority of the MAs did not specifically identify which studies had imputed SDs or whether SD data was acquired from authors, is in accordance with findings of Page and Colleagues (2018)[32] in their review of reproducibility of research practices in systematic reviews.

In the case of approximate algebraic recalculation or imputation, no MA reported performing sensitivity analysis in regard to these assumptions. While previous studies have suggested that different methods of imputation for missing variances do not alter the conclusion of MAs[36, 37], the results of these reviews in specific populations or involving specific interventions, cannot be generalised and applied to all MAs. Importantly, as imputation involves making assumptions, it is recommended that sensitivity analysis be performed to assess the impact of changing assumptions [6-8].

Given the large percentage of publications without a clear statement of approach to dealing with missing change SDs, and in an attempt to create a more accurate picture of the range of methods currently utilised, we reviewed a sample of individual studies included within the identified MAs. Upon further investigation we were able to determine the methods utilised by the majority of authors; which were consistent with the reported approaches. We did not attempt to completely reproduce any meta-analysis, but identify what methods may have been utilised in the case of missing change SDs. Interestingly, two studies[38, 39] not meeting the inclusion criteria for the review, due to the use of follow-up scores for statistical analysis, specifically noted the use of follow-up scores due to the lack of reporting of change SDs.

One of the reasons for performing a meta-analysis is to increase statistical power and provide context[2], and the omission of studies from a systematic review and meta-analysis due to missing SDs may result in bias and reduce the overall power[7]. If meta-analysts consider it inappropriate, for whatever reason, to calculate or impute missing SDs, it may be appropriate to present studies not included in the statistical analysis in a non-pooled tabulated format or provide an additional narrative review [6-8] so as not to exclude possible valuable information.

While individual studies are essential for providing data, with the increasing volume of studies, clinicians, researchers and policy makers have less time to sift through and make sense of this primary research. Systematic reviews and MAs therefore play a key role; however, a review is only as robust as the data supporting it; therefore rigor in design and

reporting is crucial. A number of reporting guidelines exist to assist the meta-analyst, with the PRISMA Statement[3] one of the most frequently used. Designed to improve the transparency and reliability of systematic reviews and meta-analyses it states that authors should make note of how missing data was handled, any data transformations that are to be undertaken and which study results were not directly reported and required estimation[3]. In deciding on an approach to dealing with missing SDs, previously Wiebe and colleagues (2006)[7] provided a brief guideline, to which Weir et al. (2018)[8] suggest an additional step, and these guidelines represent a good starting point for the meta-analysts.

The identification of fifteen new methods for handling missing SDs[8], in addition to the methods previously identified[7], highlight the expansion of statistical methodology applied in meta-analyses. There is no consensus as to which approach for dealing with missing SDs is best[34] and meta-analysts need to consider not only why the SD may be missing, but also the best approach in order to provide a comprehensive and robust presentation of the available evidence. Therefore, to improve the value of MAs, authors are encouraged to accurately report what they did and what they found. Meta-analysts should not only report the approach and methodology for handling missing change SDs in the methods section, or supplementary material, but also detail the number of studies with missing change SDs and identify the studies to which a particular approach has been applied. This can be done annotated in tables or supplementary files. All of which increase the transparency and reliability of the MA.

Strengths and Limitations in the systematic review

To our knowledge this is the first review of reported methods for handling missing change SDs in MAs of exercise training in heart failure patients. A limitation of this review was that it only considered MAs that measured exercise capacity as a continuous outcome, however, this is the most common continuous outcome reported to date in this population in regard to exercise training. Meta-analyses of other continuous outcomes may have reported and utilised additional methods to deal with missing change SD. Furthermore, the results of this review are only applicable to the population and intervention investigated. In studies in which no approach for handling missing change SDs was noted, we conducted a review of a sample of studies included in the MA in order to identify possible methods that had been applied.

CONCLUSION

Systematic reviews and meta-analyses are a key component of evidenced-based healthcare and provide valuable information for researchers. Currently there is no one or standardised approach utilised in dealing with missing change SDs when assessing continuous outcomes and exercise interventions in heart failure. As a minimum Meta-analysts should clearly stipulate how they will handle missing change SDs in the methods, and conduct sensitivity analysis when SDs are imputed.

References

1. Gough D, Oliver S, Thomas J. An introduction to systematic reviews: Sage; 2017.
2. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Introduction to meta-analysis: John Wiley & Sons; 2011.
3. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS medicine. 2009;6(7):e1000100.
4. Djulbegovic B, Guyatt GH. Progress in evidence-based medicine: a quarter century on. The Lancet. 2017;390(10092):415-23.
5. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. Bmj. 2015;349:g7647.
6. Higgins JP. Green S. Cochrane handbook for systematic reviews of interventions version 5.1. 0. The cochrane collaboration. 2011;5(0).
7. Wiebe N, Vandermeer B, Platt RW, Klassen TP, Moher D, Barrowman NJ. A systematic review identifies a lack of standardization in methods for handling missing variance data. Journal of clinical epidemiology. 2006;59(4):342-53.
8. Weir CJ, Butcher I, Assi V, Lewis SC, Murray GD, Langhorne P, et al. Dealing with missing standard deviation and mean values in meta-analysis of continuous outcomes: a systematic review. BMC medical research methodology. 2018;18(1):25.
9. Keteyian SJ, Patel M, Kraus WE, Brawner CA, McConnell TR, Piña IL, et al. Variables measured during cardiopulmonary exercise testing as predictors of mortality in chronic systolic heart failure. Journal of the American College of Cardiology. 2016;67(7):780-9.
10. Sato T, Yoshihisa A, Kanno Y, Suzuki S, Yamaki T, Sugimoto K, et al. Cardiopulmonary exercise testing as prognostic indicators: Comparisons among heart failure patients with reduced, mid-range and preserved ejection fraction. European journal of preventive cardiology. 2017;24(18):1979-87.
11. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European heart journal. 2016;37(27):2129-200.
12. Adsett JA, Mudge AM, Morris N, Kuys S, Paratz JD. Aquatic exercise training and stable heart failure: A systematic review and meta-analysis. International journal of cardiology. 2015;186:22-8.
13. Chan E, Giallauria F, Vigorito C, Smart NA. Exercise training in heart failure patients with preserved ejection fraction: a systematic review and meta-analysis. Monaldi Archives for Chest Disease. 2016;86(1-2).
14. Dieberg G, Ismail H, Giallauria F, Smart NA. Clinical outcomes and cardiovascular responses to exercise training in heart failure patients with preserved ejection fraction: a systematic review and meta-analysis. Journal of applied physiology. 2015;119(6):726-33.
15. Fukuta H, Goto T, Wakami K, Ohte N. Effects of drug and exercise intervention on functional capacity and quality of life in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. European journal of preventive cardiology. 2016;23(1):78-85.
16. Giuliano C, Karahalios A, Neil C, Allen J, Levinger I. The effects of resistance training on muscle strength, quality of life and aerobic capacity in patients with chronic heart failure—A meta-analysis. International journal of cardiology. 2017;227:413-23.
17. Gu Q, Wu S-J, Zheng Y, Zhang Y, Liu C, Hou J-C, et al. Tai Chi Exercise for Patients with Chronic Heart Failure: A Meta-analysis of Randomized Controlled Trials. American journal of physical medicine & rehabilitation. 2017;96(10):706-16.
18. Ismail H, McFarlane JR, Dieberg G, Smart NA. Exercise training program characteristics and magnitude of change in functional capacity of heart failure patients. International journal of cardiology. 2014;171(1):62-5.

19. Jewiss D, Ostman C, Smart N. The effect of resistance training on clinical outcomes in heart failure: a systematic review and meta-analysis. International journal of cardiology. 2016;221:674-81.
20. Montemezzo D, Fregonezi GA, Pereira DA, Britto RR, Reid WD. Influence of inspiratory muscle weakness on inspiratory muscle training responses in chronic heart failure patients: a systematic review and meta-analysis. Archives of physical medicine and rehabilitation. 2014;95(7):1398-407.
21. Neves LMT, Cahalin LP, Silva VZM, Silva ML, Arena R, Spielholz NI, et al. Effect of chronic neuromuscular electrical stimulation on primary cardiopulmonary exercise test variables in heart failure patients: a systematic review and meta-analysis. IJC Metabolic & Endocrine. 2014;5:28-35.
22. Neto MG, Oliveira FA, Dos Reis HFC, de Sousa Rodrigues E, Bittencourt HS, Carvalho VO. Effects of neuromuscular electrical stimulation on physiologic and functional measurements in patients with heart failure: a systematic review with meta-analysis. Journal of cardiopulmonary rehabilitation and prevention. 2016;36(3):157-66.
23. Gomes-Neto M, Rodrigues-Jr ES, Silva-Jr WM, Carvalho VO. Effects of yoga in patients with chronic heart failure: a meta-analysis. Arquivos brasileiros de cardiologia. 2014;103(5):433-9.
24. Neto MG, Durães AR, Conceição LSR, Saquetto MB, Ellingsen Ø, Carvalho VO. High intensity interval training versus moderate intensity continuous training on exercise capacity and quality of life in patients with heart failure with reduced ejection fraction: A systematic review and meta-analysis. International journal of cardiology. 2018.
25. Neto MG, Conceição CS, de Jesus FLA, Carvalho VO. Hydrotherapy on exercise capacity, muscle strength and quality of life in patients with heart failure: A meta-analysis. International journal of cardiology. 2015;198:216-9.
26. Neto MG, Martinez BP, Conceição CS, Silva PE, Carvalho VO. Combined exercise and inspiratory muscle training in patients with heart failure: a systematic review and meta-analysis. Journal of cardiopulmonary rehabilitation and prevention. 2016;36(6):395-401.
27. Pandey A, Parashar A, Kumbhani D, Agarwal S, Garg J, Kitzman D, et al. Exercise training in patients with heart failure and preserved ejection fraction: a meta-analysis of randomized control trials. Circulation: Heart Failure. 2014:CIRCHEARTFAILURE. 114.001615.
28. Ren X, Li Y, Yang X, Li J, Li H, Yuan Z, et al. The Effects of Tai Chi Training in Patients with Heart Failure: A Systematic Review and Meta-Analysis. Front Physiol 8: 989 doi: 103389/fphys. 2017.
29. Santos FV, Chiappa GR, Ramalho SHR, de Lima ACGB, de Souza FSJ, Cahalin LP, et al. Resistance exercise enhances oxygen uptake without worsening cardiac function in patients with systolic heart failure: a systematic review and meta-analysis. Heart failure reviews. 2018;23(1):73-89.
30. Vromen T, Kraal J, Kuiper J, Spee R, Peek N, Kemps H. The influence of training characteristics on the effect of aerobic exercise training in patients with chronic heart failure: a meta-regression analysis. International journal of cardiology. 2016;208:120-7.
31. Zhang Y, Xu L, Yao Y, Guo X, Sun Y, Zhang J, et al. Effect of short-term exercise intervention on cardiovascular functions and quality of life of chronic heart failure patients: A meta-analysis. Journal of Exercise Science & Fitness. 2016;14(2):67-75.
32. Page MJ, Altman DG, Shamseer L, McKenzie JE, Ahmadzai N, Wolfe D, et al. Reproducible research practices are underused in systematic reviews of biomedical interventions. Journal of clinical epidemiology. 2018;94:8-18.
33. Ma J, Liu W, Hunter A, Zhang W. Performing meta-analysis with incomplete statistical information in clinical trials. BMC medical research methodology. 2008;8(1):56.
34. Fu R, Vandermeer BW, Shamliyan TA, O'Neil ME, Yazdi F, Fox SH, et al. Handling continuous outcomes in quantitative synthesis. 2013.
35. Stevens JW. A note on dealing with missing standard errors in meta-analyses of continuous outcome measures in WinBUGS. Pharmaceutical statistics. 2011;10(4):374-8.
36. Philbrook HT, Barrowman N, Garg A. Imputing variance estimates do not alter the conclusions of a meta-analysis with continuous outcomes: a case study of changes in renal function after living kidney donation. Journal of clinical epidemiology. 2007;60(3):228-40.

37. Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. Journal of clinical epidemiology. 2006;59(1):7-10.
38. Uddin J, Zwisler A-D, Lewinter C, Moniruzzaman M, Lund K, Tang LH, et al. Predictors of exercise capacity following exercise-based rehabilitation in patients with coronary heart disease and heart failure: a meta-regression analysis. European journal of preventive cardiology. 2016;23(7):683-93.
39. Zwisler A-D, Norton RJ, Dean SG, Dalal H, Tang LH, Wingham J, et al. Home-based cardiac rehabilitation for people with heart failure: A systematic review and meta-analysis. International journal of cardiology. 2016;221:963-9.

Supporting Information

S1 Table. Meta-analyses reviewed but excluded

S2 Table. Details of Meta-analyses included in review

S3 Table. Additional details of Meta-analyses included in review

S4 Table. Sample Literature Search

Online supplementary material

S1 Supplementary Table Meta-analyses reviewed but excluded

Author	Reason for Exclusion
Anderson 2017	SR included other cardiovascular populations, as well as HF
Cipriano 2017	No pooling of measure of exercise capacity in MA
Cornelis 2016	Meta-analysis conducted using post-intervention mean±SD (i.e., follow-up scores)
Ganga 2017	HF patients with LVAD – an exclusion criteria for this review
Grossman-Rimon 2018	HF patients with LVAD – an exclusion criteria for this review
Lee 2017	No pooling of measure of exercise capacity in MA
Lewinter 2015	Meta-analysis conducted using post-intervention mean±SD (i.e., follow-up scores)
Ostman 2017	No pooling of measure of exercise capacity in MA
Neto 2014	Meta-analysis conducted using post-intervention mean±SD (i.e., follow-up scores)
Pandey 2017	HF patients with ICDs – an exclusion criteria for this review
Sties 2018	SR only, no MA
Taylor 2014	No pooling of measure of exercise capacity in SR
Taylor 2015	SR included other cardiovascular populations, as well as HF
Tu 2018	No pooling of measure of exercise capacity in MA
Uddin 2015	Meta-analysis conducted using post-intervention mean±SD (i.e., follow-up scores)
Wu 2018	No data pooling of 6MWT
Zwisler 2016	Meta-analysis conducted using post-intervention mean±SD (i.e., follow-up scores)

Supplementary Table S2 Meta-analyses included in review and details of methods for handling missing change SD as reported in publications

Study	Exercise Intervention Modality	Exercise Capacity Measure	Method for handling missing SD
Adsett (2015)	Aquatic training	VO_{2peak}, 6MWT, Peak Power	No clear detail of methods for handling missing SDs. It was noted that a number of studies included in the SR were not included in MA due to insufficient raw data, but this appears to be when both mean and SD not available.
Chan (2016)	Exercise training (included: aerobic, combined, IMT, FES)	VO_{2peak}, 6MWT	Actual p values if available, otherwise default p values for NS or S, i.e., p value for S if p< 0.05, becomes p=0.049. No mention of the number of studies for which SD was calculated or performance of any sensitivity analysis.
Dieberg (2015)	Exercise training (included: aerobic, combined, IMT, FES)	VO_{2peak}, 6MWT	Actual p values if available, otherwise default p values Significant, i.e., p value for S if p< 0.05, p becomes p=0.049. No mention of the number of studies for which SD was calculated or performance of any sensitivity analysis. Use of default p-values is noted as a limitation and that this could introduce errors.
Fukuta (2016)[(1)]	Exercise Training (included: aerobic, combined)	VO_{2peak}, 6MWT	For studies in which did not report SD or change in SD correlation conservatively estimated at 0.5. No details of which studies or the number of studies to which this was applied. No mention of any associated sensitivity analysis.
Giuliano (2017)	Resistance training	VO_{2peak}, 6MWT	SD of the change score was calculated from the baseline and follow-up SD by using a correlation between baseline and follow-up scores estimated as 0.8. No mention of the number of studies for which SD was calculated or performance of any sensitivity analysis
Gu (2017)	Tai Chi	6MWT	If data was Median and IQR, SD was calculated as IQR/1.35. No details provided of any other methods to be utilised to handle missing SD and no mention of missing SD. Review notes one failure to acquire raw data, but does no details what data this was in relation to.
Ismail (2014)	Aerobic Training	VO_{2peak}	Actual p values if available, otherwise default p values Significant, i.e., p value for S if p< 0.05, p becomes p=0.049. No mention of the number of studies for which SD was calculated or performance of any sensitivity analysis. Use of default p-values is noted as a limitation and that this could introduce errors.
Jewiss (2016)	Resistance training	VO_{2peak}, 6MWT	Actual p values if available, otherwise default p values Significant, i.e., p value for S if p< 0.05, p becomes p=0.049. No mention of the number of studies for which SD was calculated or performance of any sensitivity analysis. Use of default p-values is noted as a limitation and that this could introduce errors.

Montemezzo (2014)	Inspiratory Muscle Training (IMT)	VO_{2peak}, 6MWT	When SD not available, SD of baseline used for meta-analysis. No details of which studies the baseline SD was utilised for.
Neves (2014)	Neuromuscular Electrical Stimulation (NMES)	VO_{2peak}, Peak Workload	SD of each study calculated using change score method. Doesn't state correlation utilised or any associated sensitivity analysis. Review notes that if no SD available to calculate change score, study excluded. Review notes SD not given in 2 studies; one was extracted from visual analyses and one was excluded and these studies are referenced and identifiable.
Neto (2018)	Aerobic Training	VO_{2peak}	When SD not available, but CI was SD was converted using guidance of Higgins and Green. Non-parametric data was converted to mean and SD using established methods of Wan et al. (2014).
Neto (2016)a	Neuromuscular Electrical Stimulation (NMES)	VO_{2peak}, 6MWT	No details provided of any methods to handle missing SD and no mention of missing SD.
Neto (2016)b	Combined (endurance) training and Inspiratory Muscle Training (IMT)	$VO_{2peak,}$ Exercise Time	No details provided of any methods to handle missing SD and no mention of missing SD.
Neto (2015)	Hydrotherapy	VO_{2peak}, 6MWT	No details provided of any methods to handle missing SD and no mention of missing SD.
Neto (2014)a	Yoga	VO_{2peak}	No details provided of any methods to handle missing SD and no mention of missing SD.
Pandey (2015)	Exercise training (included: aerobic, combined)	VO_{2peak}	No details provided of any methods to handle missing SD and no mention of missing SD. Baseline and post mean and SD data provided in supplementary material.
Ren (2017)	Tai Chi	VO_{2peak}, 6MWT	Review notes that one study did not report the SDs of the mean change, t-values used to calculate the SD (study not identified). Non-parametric data converted for one study using formula, but doesn't state formula.
Santos (2018)	Aerobic, Resistance, Combined training	VO_{2peak}	No specific details provided of any methods to handle missing SD and no mention of missing SD. Papers were to be excluded if absence of data in means and SD. Non-parametric data converted (method provided in paper), one study identified to which this applied .
Vromen (2016)	Aerobic training	VO_{2peak}	No details provided in methods section, however, in limitations section it is noted that SD of change was missing for several studies and that a correlation of 0.7 was used. No details of which studies this was applied to. No details of any associated sensitivity analysis.

Zhang (2016)	Exercise training (included: aerobic, resistance, combined, tai Chi, yoga)	VO_{2peak}	No details provided of any methods to handle missing SD and no mention of missing SD. The analysis method appears to be a comparison of pre-post change in the experimental groups and not difference between control and exercise group, and no mention of any possible missing follow-up SDs or any approach to deal with.

(1) Analysis also included effect of drug trials, but exercise intervention analysis presented separately. MA: meta-analysis, SD: standard deviation, SE: standard error, SR: systematic review

Supplementary Table S3 Additional details of included meta-analyses

Study	Population	Study Designs Included	End Search Date	Summary Statistical Methods for exercise capacity	Number of studies included in MA of Exercise Capacity
Adsett (2015)	HFrEF	RCTs, Controlled, Single Group Studies	March 2014	CMA Hedges g for mean difference between change in groups Random Effects	VO_{2peak} = 3 (4 included SR, but insufficient raw data of one study for MA) 6MWT = 2 (4 included SR, but insufficient raw data of one study for MA) Peak Power = 3
Chan (2016)	HFpEF	RCT	September 2015	Revman MD change pre-post between groups Fixed Effects	VO_{2peak} = 5 6MWT = 5
Dieberg (2015)	HFpEF	RCT	October 2014	Revman MD change pre-post between groups Fixed Effects	VO_{2peak} = 5 6MWT = 5
Fukuta (2014)	HFpEF	RCT	June 2014	CMA MD change pre-post between groups Fixed Effects	VO_{2peak} = 4 6MWT = 4
Giuliano (2017)	HFrEF	RCT & Controlled	10 July 2016	Stata MD change pre-post between groups Fixed Effects	VO_{2peak} = 9 6MWT = 4
Gu (2017)	HF	RCT	2 June 2016	Revman & Stata MD change pre-post between groups Random Effects	6MWT = 10
Ismail (2014)	HFrEF	RCT	2012	Revman MD change pre-post between groups Random Effects	VO_{2peak} = 3 (High intensity) VO_{2peak} = 29 (Vigorous intensity) VO_{2peak} = 20 (Moderate intensity) VO_{2peak} = 2 (Low intensity)
Jewiss (2016)	HFrEF	RCT	May 2016	Revman MD change pre-post between groups	VO_{2peak} = 10 (combined) VO_{2peak} = 4 (resistance)

				Random Effects	6MWT = 7 (combined) 6MWT = 2 (resistance)
Montemezzo (2014)	HF	RCT	August 2013	Revman & CMA MD change pre-post between groups Random Effects	VO_{2peak} =4 6MWT = 4
Neves (2014)	HFrEF	RCT	March 2014	Revman & CMA MD change pre-post between groups Random Effects	VO_{2peak} = 7 (NMES v. Exercise) Peak Workload = 2 (NMES vs. exercise) VO_{2peak} = 9 (NMES v. Control) Peak Workload = 3 (NMES vs. Control)
Neto (2018)	HFrEF	RCT	October 2017	Revman MD change pre-post between groups Random & Fixed Effects	VO_{2peak} = 13
Neto (2016)a	HF	RCT	May 2014	Revman MD change pre-post between groups Random Effects	VO_{2peak} = 6 (NMES vs. Aerobic) VO_{2peak} = 3 (NMES vs. Control) 6MWT = 5 (NMES vs. Aerobic) 6MWT = 6 (NMES vs. Control)
Neto (2016)b	HF	RCT	April 2015	Revman MD change pre-post between groups Fixed Effects	VO_{2peak} = 3 Exercise Time = 2
Neto (2015)	HF	RCT	May 2014	Revman MD change pre-post between groups Random & Fixed Effects	VO_{2peak} = 2 (Hydro vs. Control) VO_{2peak} = 2 (Hydro vs. Aerobic) 6MWT = 2 (Hydro vs. Control)
Neto (2014)a	HF	RCT	December 2013	Revman MD change pre-post between groups Fixed Effects	VO_{2peak} = 2
Pandey (2015)	HFpEF	RCT	NR	Stata (Metan & Metareg) & Revman WMD change from baseline between groups Random Effects	VO_{2peak} = 4

Ren (2017)	HF	RCT	16 Sep 2017	Revman & Stata MD change pre-post between groups Random Effects	VO_{2peak} = 3 6MWT = 7
Santos (2018)	HFrEF	RCT	March 2016	Revman MD change pre-post between groups Random Effects	VO_{2peak} = 46 (Exercise vs. Control) VO_{2peak} = 8 (Combined vs. Aerobic) VO_{2peak} = 3 (Resistance vs. Aerobic)
Vromen (2016)	HFrEF	RCT	1st April 2015	WMD for change pre-post between groups Random Effects	VO_{2peak} = 17
Zhang (2016)	HF	RCT	2014	Revman & Stata MD of pre-post values for HF exercise group only Random Effects	VO_{2peak} = 20

Supplementary Table S4. Sample EMBASE Search Strategy No. 1

Date Range 1.1.2014 – 31.3.2018

Query No.	Query	Results
16	#15 AND (2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py)	276
15	#12 AND #13 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta-analysis]/lim) AND [humans]/lim AND [english]/lim	603
14	#12 AND #13	22,427
13	'heart failure':ab,kw,ti	245,835
12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	907,500
11	'kinesiotherapy'/exp OR 'kinesiotherapy'	70,653
10	'physiotherapy'/exp OR 'physiotherapy'	119,184
9	'physical activity'/exp OR 'physical activity'	407,335
8	'hydrotherapy'/exp OR 'hydrotherapy'	4,763
7	'inspiratory muscle training'/exp OR 'inspiratory muscle training’	779
6	'functional electrical stimulation'/exp OR 'functional electrical stimulation'	3,582
5	'tai chi'/exp OR 'tai chi'	2,690
4	'yoga'/exp OR 'yoga'	7,901
3	'resistance training'/exp OR 'resistance training’	15,787
2	'aerobic exercise'/exp OR 'aerobic exercise'	16,770
1	'exercise'/exp OR 'exercise'	498,080

10 Chapter 10 – Conclusion

Throughout history the benefits of physical activity and exercise have been touted. Over the last four decades heart failure patients have gone from bed rest to as far as high-intensity interval training. Exercise training in stable heart failure patients is safe and a now a widely recommended adjunct treatment due to a number of benefits it confers. This change in opinion from a sedentary lifestyle to exercise has come from well-designed RCTs and research synthesis via systematic reviews and meta-analyses. As the number of trials investigating various aspects of exercise therapy in heart failure patients continues to grow, systematic reviews and meta-analyses continue to have an important role. They are an important research method that allows for information and data synthesis; informing clinical practice, policy development and future research.

This thesis had two main aims:

1. Firstly to identify the current level of systematic review and meta-analysis research activity dealing with the benefits and/or effects of exercise training; informing research synthesis gaps; and
2. To undertake research synthesis using systematic review as the research methodology and where appropriate apply meta-analysis to determine an effect size

An evidence map of current systematic reviews, which applied meta-analysis techniques was undertaken to identify research synthesis gaps and areas in which an update of research synthesis was deemed to be valuable. The results of the mapping exercise revealed gaps in relation to endothelial function, autonomic function, inflammatory markers, circulating biomarkers (both traditional and emerging), and diastolic function. Systematic reviews and meta-analyses were then conducted.

Endothelial dysfunction is involved in the development and progression of heart failure and predicts mortality risk. Data from the systematic review and meta-analysis (Chapter 3) on the effects of exercise training for improved endothelial function revealed that flow-mediated dilation (FMD), a measure of endothelial-dependent dilation was improved with exercise training in HFrEF patients. Furthermore, results revealed that Endothelial

Progenitor Cells (EPCs), which are involved in endothelial repair, are also improved with exercise training, however, the number of studies to assess EPCs in heart failure patients was small; hence more work in this area is required to confirm the improvement and effect size in relation to EPCs. As the study was only conducted using HFrEF patients, the findings cannot be generalised to HFpEF patients. While endothelial dysfunction is implicated in the pathogenesis and progression of HF irrespective of ejection fraction, at the time of conducting the analysis only two controlled exercise training studies had measured FMD, hence more work is required in HFpEF patients in regard to endothelial function.

Now that exercise training is considered safe in stable heart failure patients, a number of trials have attempted to identify optimal characteristics, with aerobic training intensity one area of focus. Based on the favourable results demonstrated in Chapter 3, the aim of Chapter 4 was to investigate whether aerobic training intensity reflected the magnitude of change in FMD. Data synthesis indicated that both moderate and vigorous aerobic intensity resulted in significant improvements. However, conclusive evidence as to whether one is better than the other is still unclear as the difficulty in assessing any training intervention based on intensity is that while many studies detail the prescribed training intensity, actual training intensity achieved is not always reported.

Autonomic dysfunction; reflected as increased SNS activity and reduced PNS activity is a characteristic of heart failure, and is associated with adverse outcomes. A number of pharmacological treatments in HFrEF target the inhibition of the SNS and RAAS. Research and data synthesis in Chapter 5 revealed that exercise training, an adjunct therapy in heart failure, results in statistically significant improvements in direct (MSNA) and indirect (HRR and HRV) measures of SNS activity and therefore reflects improved overall autonomic function.

Elevated levels of inflammatory markers are associated with heart failure severity and adverse outcome. Furthermore, the important role of inflammation in heart failure has become more widely recognised, evidenced by trials investigating pharmacological approaches to modify inflammatory status. Exercise is considered to have an anti-inflammatory effect; therefore data synthesis presented in Chapter 6 reveals how aerobic

and resistance training interventions affect inflammation in heart failure patients. While meta-analyses indicated small but significant improvements in circulating levels of TNF-α and IL-6, a descriptive synthesis of a number of non-pooled studies provides limited evidence for any significant improvement. No significant improvement in acute-phase reactants or vascular adhesion molecules was evident from pooled or non-pooled analyses, however, there are limited studies dealing with Fibrinogen and vascular adhesion molecules at this point in time. While the review and analysis does not provide strong support for improvements in inflammatory markers from exercise training in the heart failure population, it does not rule out benefits in regard to inflammation. A number of pathways are involved in the immune and inflammatory process, and as our understanding of the role of inflammation in heart failure is improving, more research is required considering comorbidities, many of which are associated with inflammation, in addition to more trials, which investigate local skeletal muscle inflammatory markers which may more accurately portray the anti-inflammatory effect of exercise in this population.

Biomarkers have greatly improved our understanding of the pathophysiology of heart failure and are currently utilised in the diagnosis, risk stratification and management of heart failure. Chapter 7 provides an up to date synthesis and data analysis of evidence in regard to the effect exercise therapy on BNP and NT-proBNP; biomarkers of myocardial stretch. Meta-analysis indicated the both BNP and NT-proBNP are improved with exercise therapy, but only when using traditional modes of therapy, however, a descriptive analysis of a number of other studies indicated contrasting findings. As heart failure biomarkers tend to be categorised according to the pathophysiological processes they inform, there has been an increase in research in this area with the possibility that biomarker profiles may help guide treatment strategies, including exercise. Only a minimal number of studies to date have investigated the effect of exercise therapy on emerging biomarkers, such as Gal-3, sST2, MR-proANP, MR-proADM and CT-proAVP, hence this is an avenue of future research that may identify certain patients who will benefit more.

Chapter 8 provides research and data synthesis on the effects of exercise training on diastolic function in heart failure patients. Diastolic dysfunction is evident in both HFrEF and HFpEF patients and is associated with reduced exercise capacity. Statistically significant

improvements in E/E' were evident in HFrEF and HFpEF patients. Data synthesis did not provide any conclusive evidence as to the positive effects of exercise training on indices of diastolic dysfunction measured using conventional echocardiography (E/A, DT). As not one non-invasive measure of diastolic function is a perfect marker of diastolic function, future trials utilising the grade of diastolic dysfunction pre and post training may provide an additional measure of diastolic function that can be used to assess the effect of the exercise intervention.

As a result of the six systematic reviews and meta-analyses undertaken a number of methodological issues presented themselves, the most frequent of which was the absence of change standard deviations, required in the analysis of continuous outcomes when the change score method is utilised. In light of this issue a systematic review of current methods reported and utilised by meta-analysts was conducted, using meta-analyses of exercise capacity changes in heart failure patients as a model and presented in Chapter 9. Understanding how meta-analysts deal with missing data is important for many reasons, one of which is the interpretation of findings. While meta-analysts included studies with missing change SDs; of the publications examined, 45% did not report the exact method utilised. Only after individual examination of samples of studies included in the meta-analysis could the method utilised be determined; a time-consuming and skill-based task that defeats one of the reasons a reader seeks out a meta-analysis in the first place. No one method for dealing with missing variance data is currently recommended and a range of methods were utilised in the analyses examined. Meta-analysts need to accurately report methods utilised to increase transparency and reproducibility of analyses.

Generalisability

Currently women and non-Caucasians are underrepresented in heart failure trials (Colvin et al., 2015; Nguyen et al., 2018) and this is also true of heart failure exercise therapy trials. In the systematic reviews and meta-analyses included in this thesis, males and Caucasians comprised the majority of patients in the included studies and it was not possible to conduct subgroup analyses based on sex or race; therefore all results should be interpreted within this context, as inadequate representation of specific populations impairs generalisability (Nguyen et al., 2018).

To date no meta-analysis has been conducted on women only or a comparison of women to men. Women are generally older, more likely to have multiple comorbidities, a higher LVEF (Corra et al., 2017), and a greater percentage of women present with HFpEF, then men. Only a small number of trials have specifically considered women and these are also generally small in sample size. From trials to date to specifically consider sex, aerobic training has demonstrated improvement in $VO_{2peak,}$ HRQoL and muscle strength in women (Haykowsky, Vonder Muhll, Ezekowitz & Armstrong, 2005). No gender differences for improvements were observed between men and women from progressive resistance and aerobic training (Swank et al., 2010), and no gender differences have been noted for HRV (Murad et al., 2012) and MSNA changes (Antunes-Correa et al., 2010) after exercise training. However, a recent prespecified subgroup analysis of the HF-ACTION trial that reviewed outcomes by sex in HFrEF patients (Piña et al., 2014) found that while the change in VO_{2peak} in women was similar to men, endurance training was associated with a 26% reduction in all-cause death or all-cause hospital stay in women assigned to exercise (n=290) with no reduction in men (n=682). Women achieved the greater reduction in the combined hard clinical end-points despite lower baseline VO_{2peak} and exercise adherence (37% vs. 45%) than men, suggesting women with HFrEF might particularly benefit most from exercise training (Piña et al., 2014). However, at this point in time the mechanism for this difference in the benefit is unclear (Fleg et al., 2015).

In contrast to HFrEF, women make up the majority of HFpEF patients, and therefore the number of female patients in these trials included in the thesis was generally greater than men. Only one of the included studies for HFpEF patients included less than 50% of women (Alves et al., 2012), while one study (Gary et al., 2004) included 100% women. However, only a small number of trials to date have investigated the effect of exercise therapy in HFpEF and no researcher has yet provided any statistical data of observed differences between sexes as a result of exercise therapy, which is an important area that requires addressing in designing future exercise therapy trials.

The reported reasons for underrepresentation of women and non-Caucasians are considered multifactorial. Referrals to cardiac rehabilitation are lower in women (Colella et al., 2015), they are less likely to enrol if referred and adherence rates are low if they enrol

(Supervia et al., 2017). Specific barriers to participation in cardiac rehabilitation in women include lack of social support, transportation, family responsibilities, multiple comorbid conditions and lower level education (Supervia et al., 2017). Additionally, cardiac rehabilitation characteristics and self-reported health beliefs have been identified as specific barriers in women (Resurreccion et al., 2018). The majority of exercise trials to date have utilised conventional modalities of exercise training (i.e., aerobic and/or resistance training), however, women may be more likely to attend interventions such as Yoga and Tai Chi for cardiac rehabilitation purposes (Liu et al., 2018; Salmoirago-Blotcher et al., 2017) and future trial designs need to carefully consider the inclusion of newer and non-conventional modalities. In non-Caucasians, barriers to participation in heart failure trials in general include economic factors, communication, mistrust and lack of awareness (Colvin et al, 2015), which need to be factored into future trial design.

While exercise trials have included women and non-Caucasians, no meta-analyses have been conducted in these specific populations to date. In order to be able to investigate the effect of exercise therapy in specific heart failure populations and make robust conclusions and evidenced-based recommendations, exercise trials and cardiac rehabilitation programs need to be specifically tailored to each of these populations, taking into account the identified barriers. While female representation in overall cardiology trials has started to improve, it is considered that if the current trends continue in the underrepresentation of women in general heart failure trials, it will take decades to resolve the gaps (Nguyen et al., 2018). In terms of exercise training studies, until more trials with adequate representation of women occur, a collaborative effort amongst researchers of past studies via an individual patient data (IPD) meta-analysis could assist in providing some level of evidence as to any possible differences between men and women and/or additional benefits.

Limitations

To assess study quality in each of the included meta-analyses, the validated TESTEX score was utilised. A median score of 7.5/15 or greater was recorded for all reviews and analyses. However, most studies included in the reviews, as reported in the publications, scored poorly in relation to the provision of specific randomisation details (for RCTs), allocation concealment (for RCTs), activity monitoring of the control group and review of relative

exercise intensity and provision of enough data to accurately calculate energy expenditure during trials. This does not imply that these areas were not addressed and dealt with by the researchers; however, the details of these areas were not reported within the published trial. Accordingly the findings of the thesis need to be interpreted with this in mind.

All meta-analyses included in the thesis were analyses of continuous outcomes, however in some instances standard deviation data were missing. Where individual trial authors did not supply missing standard deviations on request, these were calculated and inevitably introduced errors of various magnitudes. However, all imputations or algebraic recalculations utilised published and established measures, and where appropriate sensitivity analyses were conducted.

In interpreting the results of this thesis it is important to recognise that adherence to exercise regimes in heart failure patients is an issue that requires consideration. As seen within the large HF-ACTION trial, adherence and control group participant crossover to exercise were reported as major limitations and may have impacted the results (O'Connor et al., 2009). Not all studies included within the reviews and meta-analyses within this thesis provided information on intervention adherence. Adherence or non-adherence and control group crossover to exercise may account for conflicting or non-significant results that may be observed in studies and limit the ability to determine the true exercise dose utilised and exercise dose from which any benefits were derived. Researchers need to accurately collect and report adherence data so that more accurate data on the dose of exercise tested is clear.

Implications for clinical practice, future research and policy

Aerobic exercise training is currently recommended as an adjunct therapeutic modality for patients with stable heart failure based on its ability to improve functional capacity, quality of life and reduce hospitalisation, with evidence derived from systematic reviews, meta-analyses and RCTs (Ponikowski et al., 2016). Furthermore, a number of guidelines, position statements and policy documents exist around the world for cardiac rehabilitation, some specifically devoted to heart failure (Price et al., 2016). The most recent guidelines of the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand:

Guidelines for the prevention, detection and management of heart failure in Australia 2018, provide a strong recommendation for moderate intensity exercise based on meta-analyses demonstrating reduced hospitalisation, improved quality of life and functional capacity. Evidence derived from the studies included in this thesis provide support for the use of exercise therapy in heart failure patients based on its ability to exert statistically significant beneficial effects on various pathophysiological pathways and processes, including endothelial function, autonomic function, diastolic function and conventional biomarkers (BNP/NT-proBNP). Based on these findings clinicians can provide patients with evidence for the additional benefits that may be obtained from exercise therapy and future policy makers can consider the evidence obtained when assessing the level and strength of evidence for exercise therapy in future policy documents.

Furthermore, the results of the studies included in this thesis have highlighted a number of areas, as presented in each of the publications that should be considered by researchers in the future. These identified areas of future research should not be considered in isolation but together with the noted underrepresentation of women and non-Caucasians in trials, as trials, particularly RCTs, and meta-analyses represent key evidence that drives clinical practice and future research (Nguyen et al., 2018). In particular, perhaps it is time to tailor trials more specifically to a heart failure phenotype and specific populations in order to provide more substantial and robust evidence that can only strengthen current policy in the area of heart failure management utilising exercise therapy.

Summary

Overall this thesis provides a comprehensive collection of studies investigating exercise training as a therapeutic modality for patients with chronic heart failure. The thesis utilised systematic reviews and meta-analyses as the research methodology as they are an integral component of evidenced-based medicine. This original body of work was designed to identify and address gaps in research synthesis with regard to the benefits and/or effects of exercise therapy in heart failure patients. While some of these effects are well established (e.g. functional capacity, quality of life and clinical outcomes of morbidity and mortality), several novel concepts have emerged. The series of systematic reviews and meta-analyses, presented within this thesis provide a contemporary summary of this knowledge field, but

also, as new evidence became available, fresh lines of pathophysiological enquiry. This work therefore contributes a contemporary update to the established evidence base, but also introduces the relatively new concepts of how exercise therapy can alter endothelial, autonomic, inflammatory and emerging biomarker function in chronic heart failure. Inevitably, attempts to answer a series of research questions, just leads to the identification of new forms of enquiry. So the conclusion of this thesis leads to the ejection (pardon the pun) of additional questions upon which we can conduct the next generation of research inquests.

APPENDIX

Addendum to Tables 1 & 3 in Chapter 2- An up-to-date Overview of Systematic Reviews and Meta-analyses published 1st January 2017 to 30th April 2018

Table 5– Addendum to Table 1 Chapter 2 -Systematic Reviews with Meta-analysis - 1st January 2017 to 30th April 2018

Author (year)	Last search date	Study designs in review	Total n =	HF phenotype	Intervention(s)/ Comparator	Outcome analysed by Meta-Analysis (n= no. studies in analysis of outcome)
Ganga (2017)	Dec 2015	RCTs =3 Observational = 5	205	HF - LVAD	Exercise vs. Usual Care/Daily Activity/Recommendations Exercise only	VO_{2peak} (n=4), QoL (n=4)
Giuliano (2017)	10 Jul 2016	RCTs/quasi = 8	240	HFrEF	Resistance Training vs. Usual Care	1RM (n=4), Isokinetic Torque 60 ^{o} /s (n=4), 180^{o}/s (n=2), VO_{2peak} (n=9), 6MWD (n=4), QoL (n=3)
Grosman-Rimon (2018)	Nov 2015	RCTs = 5 Observational =10 Quasi-Experimental = 1	280	HF – VAD	Exercise vs. Non-exercise	VO_{2peak} (n=4), 6MWD (n=3), V_E/VCO_2 (n=2), VAT (n=2)
Gu (2017)	2 Jun 2016	RCTs = 13	901	HF	Tai Chi vs. Usual Care/Aerobic Exercise	6MWD (n=10), QoL (n=8), LVEF (n= 7), BNP (n=6)
Haddad (2017)	May 2016	RCTs =3 Controlled =1 Cohort =2	183	HF - LVAD	Exercise vs. Standard Therapy	VO_{2peak} (n=3), 6MWD (n=3)
Lee (2017)	Apr 2017	RCTs = 6	268	HFrEF	Exercise vs. Usual Care/Normal Lifestyle	Serum TNF-α (n=3), serum IL-6 (n=2), serum GH (n=2), serum IGF-1 (n=2) *Descriptive review of skeletal muscle outcomes*
Neto (2018)	Oct 2017	RCTs = 13	411	HFrEF	HIIT vs. MCT	VO_{2peak} (n=13), V_E/VCO_2 (n=6), MLHFQ (n=4)
Ostman (2017)	Feb 2016	RCTs = 25	2385	HFrEF	Exercise vs. Usual Care	MLHFQ – total (n=22), MLHFQ – physical (n=8), MLHFQ – emotional (n=8), MLHFQ - total (high intensity n=2), MLHFQ – total (vigorous n=13), MLHFQ (aerobic n=11), MLHFQ (resistance n=3), MLHFQ (combined n=9)
Palmer (2018)	Jul 2017	RCTs = 27 Cohort =13	5411	HF	Exercise vs. Usual care	Physical Function (n=18), 6MWD (n=16) QoL (n=31), MLHFQ (n=17)

Pearson (2017)a[1]	Jun 2016	RCTs = 13 Non-RCTs = 3	529	HFrEF	Exercise vs. Usual Care	FMD (n=16), EPCs (n=3), NMD (n=9)
Pearson (2017)b[1]	Jun 2016	RCTs = 10 Non-RCTs = 3	458	HFrEF	Exercise vs. Usual Care	FMD (moderate intensity n= 6 & 7), FMD (vigorous intensity n=7 & 8), FMD (HIIT n= 3), FMD (interval vs. intermittent n=3), NMD (n=6)
Pearson (2017)c[1]	Jul 2016	RCTs = Non-RCTS =	1056	HFrEF & HFpEF	Exercise vs. Usual Care	E/E' (HFrEF n=6), E/E' (HFpEF n=5) *Descriptive analysis of E/A and DT*
Pearson (2018)a[1]	Jun 2017	RCT= 15 Non-RCTs =3	1665	HFrEF & HFpEF	Exercise vs. Usual Care	TNF-α (n=6), IL-6 (n=4), CRP (n=3), Fibrinogen (n=2), sVCAM (n=2), sICAM (n=2) *Descriptive analysis of markers in non-pooled studies*
Pearson (2018)b[1]	Mar 2017	RCTs =17 Non-RCTs =3	729	HFrEF & HFpEF	Exercise vs. Usual Care	HRR_1 (n=4), HRR_2 (n=2), Short-term HRV [HFnu (n=3), $HF_{ms/Hz}$ (n=2), LF_{nu} (n=3), LF/HF (n=5), RMSSD (n=3), SDNN (n=3)], $MSNA_{bursts/min}$ (n=5), $MSNA_{bursts/100hb}$ (n=5) *Descriptive analysis of long-term HRV*
Ren (2017)	16 Sep 2017	RCTs = 11	656	HF	Tai Chi vs. Usual Care/ or Other Exercise	6MWD (n=7), QoL (n=7), BNP and/or NT-proBNP (n=5), LVEF (n=5), HR (n=2), VO_{2peak} (n=3), TUG (n=2), SBP (n=3), DBP (n=3)
Saavedra (2018)	Feb 2017	RCTs =5	132	HFrEF	Exercise vs. Usual Care	$MSNA_{burst/min}$ (n=5), $MSNA_{burst/100hb}$ (n=5)
Santos (2018)	Mar 2018	RCTs =59	5046	HFrEF	Resistance vs. Usual Care Aerobic vs. Usual Care Combined vs. Usual Care Combined vs. Aerobic Resistance vs. Aerobic	<u>Resistance vs. Usual Care:</u> VO_{2peak} (n=5), LVEF (n=4), LVEDV (n=2) <u>Aerobic vs. Usual Care</u>: VO_{2peak} (n=28), LVEF (n=16), LVEDV (n=8) <u>Combined vs. Usual Care:</u> VO_{2peak} (n=13), LVEF (n=11, LVEDV (n=4)) <u>Combined vs. Aerobic:</u> VO_{2peak} (n=8), LVEF (n=3) <u>Resistance vs. Aerobic:</u> VO_{2peak} (n=3)

Wu (2018)	Nov 2016	RCTs = 7 Non-RCT =1	302	HF	Inspiratory Muscle Training vs. Usual Care/Sham Inspiratory Training or Traditional Training	PI_{max} (n=6), V_E/VCO_2 (n=5), Dyspnea (n=4)

BNP: brain-type natriuretic peptide, DBP: diastolic blood pressure, EPCs: endothelial progenitor cells, FMD: flow-mediated dilation, GH: growth hormone, HF: heart failure, HFpEF: heart failure preserved ejection fraction, HFrEF: heart failure reduced ejection fraction, HFnu: high frequency normalised units, HR: heart rate, HRR_1: heart rate recovery at 1 minutes, HRR_2: heart rate recovery at 2 minutes, HRV: heart rate variability, IGF-1: insulin like growth factor-1, IL-6: interleukin 6, LVAD: left ventricular assistive device, LVEDV: left ventricular end diastolic volume, LVEF: left ventricular ejection fraction, MLHFQ: Minnesota living with heart failure questionnaire, MSNA: muscle sympathetic nerve activity, NMD: non-endothelial mediated dilation, PI_{max}: maximal inspiratory pressure, QoL: quality of life, RCT: randomised controlled trials, RMSSD: root square mean difference successive intervals, SBP: systolic blood pressure, SDNN: standard deviation of normal to normal R-R intervals, TNF-α: tumor necrosis factor alpha, TUG: timed up and go, VAD: ventricular assistive device, VAT: ventilatory anaerobic threshold, V_E/VCO_2: ventilatory equivalent for carbon dioxide, VO_{2peak}: peak oxygen uptake, 1RM: one repetition maximum, 6MWD: six-minute walk distance, * HF Phenotype – if inclusion criteria of studies were specifically identified as HFpEF or HFrEF, if not then HF noted. (1) Reviews published from this thesis.

Table 6 - Addendum to Table 3 Chapter 2 - Systematic Reviews without Meta-analysis - 1st January 2017 to 30th April 2018

Author (year)	Last search date	Study Designs	Total n =	HF phenotype	Intervention(s)/ Comparator	Outcomes Reviewed
Shah (2017)	?	RCTs = 6[(1)]	136	HF	Swimming vs. Usual care/ or Other Exercise	HR, CO, SV, SVR, VO_{2peak}, LVEF, 6MWT
Sties (2018)	29 Jan 2017	RCTs = 12	353	HF	Exercise vs. Usual Care	Oxidative stress

CO: cardiac output, HF: heart failure, HR: heart rate, LVEF: left ventricular ejection fraction, RCTS: randomised controlled trials, SV: stroke volume, SVR: systemic vascular resistance, VO_{2peak}: peak oxygen uptake, 6MWT: six-minute walk test. (1) Excludes the acute studies

References

Alves, A. J., Ribeiro, F., Goldhammer, E., Rivlin, Y., Rosenschein, U., Viana, J. L., ... & Oliveira, J. (2012). Exercise training improves diastolic function in heart failure patients. *Medicine and Science in Sports and Exercise, 44(5),* 776-785.

Antunes-Correa, L. M., Melo, R. C., Nobre, T. S., Ueno, L. M., Franco, F. G., Braga, A. M., ... & Negrao, C. E. (2010). Impact of gender on benefits of exercise training on sympathetic nerve activity and muscle blood flow in heart failure. *European Journal of Heart Failure, 12(1),* 58-65.

Colella, T. J., Gravely, S., Marzolini, S., Grace, S. L., Francis, J. A., Oh, P., & Scott, L. B. (2015). Sex bias in referral of women to outpatient cardiac rehabilitation? A meta-analysis. *European Journal of Preventive Cardiology, 22(4),* 423-441.

Colvin, M., Sweitzer, N. K., Albert, N. M., Krishnamani, R., Rich, M. W., Stough, W. G., ... & Carson, P. E. (2015). Heart failure in non-Caucasians, women, and older adults: a white paper on special populations from the Heart Failure Society of America Guideline Committee. *Journal of Cardiac Failure, 21(8),* 674-693.

Corra, U., Agostoni, P. G., Anker, S. D., Coats, A. J., Crespo Leiro, M. G., de Boer, R. A., ... & Metra, M. (2018). Role of cardiopulmonary exercise testing in clinical stratification in heart failure. A position paper from the Committee on Exercise Physiology and Training of the Heart Failure Association of the European Society of Cardiology. *European Journal of Heart Failure, 20(1*), 3-15.

Fleg, J. L., Cooper, L. S., Borlaug, B. A., Haykowsky, M. J., Kraus, W. E., Levine, B. D., ... & Whellan, D. J. (2015). Exercise training as therapy for heart failure: current status and future directions. *Circulation: Heart Failure, 8(1),* 209-220.

Ganga, H. V., Leung, A., Jantz, J., Choudhary, G., Stabile, L., Levine, D. J., ... & Wu, W. C. (2017). Supervised exercise training versus usual care in ambulatory patients with left ventricular assist devices: A systematic review. *PloS ONE*, *12*(3), e0174323.

Gary, R. A., Sueta, C. A., Dougherty, M., Rosenberg, B., Cheek, D., Preisser, J., ... & McMurray, R. (2004). Home-based exercise improves functional performance and quality of life in women with diastolic heart failure. Heart & Lung: T*he Journal of Acute and Critical Care, 33(4),* 210-218.

Giuliano, C., Karahalios, A., Neil, C., Allen, J., & Levinger, I. (2017). The effects of resistance training on muscle strength, quality of life and aerobic capacity in patients with chronic heart failure—A meta-analysis. *International Journal of Cardiology, 227,* 413-423.

Grosman-Rimon, L., Lalonde, S. D., Sieh, N., Pakosh, M., Rao, V., Oh, P., & Grace, S. L. (2018). Exercise rehabilitation in ventricular assist device recipients: a meta-analysis of effects on physiological and clinical outcomes. *Heart Failure Reviews*, 1-13.

Gu, Q., Wu, S. J., Zheng, Y., Zhang, Y., Liu, C., Hou, J. C., ... & Fang, X. M. (2017). Tai Chi Exercise for Patients with Chronic Heart Failure: A Meta-analysis of Randomized Controlled Trials. *American Journal of Physical Medicine & Rehabilitation*, *96*(10), 706-716.

Haddad, T. M., Saurav, A., Smer, A., Azzouz, M. S., Akinapelli, A., Williams, M. A., & Alla, V. M. (2017). Cardiac Rehabilitation in Patients With Left Ventricular Assist Device: A systematic review and meta-analysis. *Journal of Cardiopulmonary Rehabilitation and Prevention*, *37*(6), 390-396.

Haykowsky, M., Vonder, I. M., Ezekowitz, J., & Armstrong, P. (2005). Supervised exercise training improves aerobic capacity and muscle strength in older women with heart failure. *The Canadian Journal of Cardiology, 21(14),* 1277-1280.

Lee, C. T., Chen, L. W., & Chien, M. Y. (2017). Effects of exercise training on anabolic and catabolic markers in patients with chronic heart failure: a systematic review. *Heart Failure Reviews*, *22*(6), 723-730.

Liu, T., Chan, A. W., Liu, Y. H., & Taylor-Piliae, R. E. (2018). Effects of Tai Chi-based cardiac rehabilitation on aerobic endurance, psychosocial well-being, and cardiovascular risk reduction among patients with coronary heart disease: A systematic review and meta-analysis. *European Journal of Cardiovascular Nursing, 17(4*), 368-383.

Murad, K., Brubaker, P. H., Fitzgerald, D. M., Morgan, T. M., Goff Jr, D. C., Soliman, E. Z., ... & Kitzman, D. W. (2012). Exercise Training Improves Heart Rate Variability in Older Patients With Heart Failure: A Randomized, Controlled, Single-Blinded Trial. *Congestive Heart Failure, 18(4),* 192-197.

Neto, M. G., Durães, A. R., Conceição, L. S. R., Saquetto, M. B., Ellingsen, Ø., & Carvalho, V.O. (2018). High intensity interval training versus moderate intensity continuous training on exercise capacity and quality of life in patients with heart failure with reduced ejection fraction: A systematic review and meta-analysis. *International Journal of Cardiology*, *261*, 134-141.

Nguyen, Q. D., Peters, E., Wassef, A., Desmarais, P., Rémillard-Labrosse, D., & Tremblay-Gravel, M. (2018). Evolution of age and female representation in the most-cited randomized controlled trials of cardiology of the last 20 years. *Circulation: Cardiovascular Quality and Outcomes*, *11(6),* e004713.

O'Connor, C. M., Whellan, D. J., Lee, K. L., Keteyian, S. J., Cooper, L. S., Ellis, S. J., ... & Rendall, D. S. (2009). Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA: Journal of the American Medical Association*, *301*(14), 1439-1450.

Ostman, C., Jewiss, D., & Smart, N. A. (2017). The effect of exercise training intensity on quality of life in heart failure patients: a systematic review and meta-analysis. *Cardiology*, *136*(2), 79-89.

Palmer, K., Bowles, K. A., Paton, M., Jepsen, M., & Lane, R. (2018). Chronic Heart Failure and Exercise Rehabilitation: A systematic review and meta-analysis. *Archives of Physical Medicine and Rehabilitation*.

Pearson, M. J., & Smart, N. A. (2017)a. Effect of exercise training on endothelial function in heart failure patients: a systematic review meta-analysis. *International Journal of Cardiology*, *231*, 234-243.

Pearson, M. J., & Smart, N. A. (2017)b. Aerobic Training Intensity for Improved Endothelial Function in Heart Failure Patients: A Systematic Review and Meta-Analysis. *Cardiology Research and Practice*.

Pearson, M. J., Mungovan, S. F., & Smart, N. A. (2017)c. Effect of exercise on diastolic function in heart failure patients: a systematic review and meta-analysis. *Heart Failure Reviews*, *22*(2), 229-242.

Pearson, M. J., Mungovan, S. F., & Smart, N. A. (2018)a. Effect of aerobic and resistance training on inflammatory markers in heart failure patients: systematic review and meta-analysis. *Heart Failure Reviews*, *23*(2), 209-223.

Pearson, M. J., & Smart, N. A. (2018)b. Exercise therapy and autonomic function in heart failure patients: a systematic review and meta-analysis. *Heart Failure Reviews*, *23*(1), 91-108.

Piña, I. L., Bittner, V., Clare, R. M., Swank, A., Kao, A., Safford, R., ... & Keteyian, S. J. (2014). Effects of exercise training on outcomes in women with heart failure: analysis of HF-ACTION (Heart Failure–A Controlled Trial Investigating Outcomes of Exercise Training) by sex. *JACC: Heart Failure, 2(2*), 180-186.

Ponikowski, P., Voors, A. A., Anker, S. D., Bueno, H., Cleland, J. G., Coats, A. J., ... & Jessup, M. (2016). 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *European Heart Journal*, *37*(27), 2129-2200.

Price, K. J., Gordon, B. A., Bird, S. R., & Benson, A. C. (2016). A review of guidelines for cardiac rehabilitation exercise programmes: Is there an international consensus?. *European Journal of Preventive Cardiology*, *23*(16), 1715-1733.

Ren, X., Li, Y., Yang, X., Li, J., Li, H., Yuan, Z., ... & Gao, Y. (2017). The Effects of Tai Chi Training in Patients with Heart Failure: A Systematic Review and Meta-Analysis. *Frontiers in Physiology. 8. doi: 10.3389/fphys*

Resurrección, D. M., Motrico, E., Rubio-Valera, M., Mora-Pardo, J. A., & Moreno-Peral, P. (2018). Reasons for dropout from cardiac rehabilitation programs in women: A qualitative study. *PloS One, 13(7),* e0200636.

Saavedra, M. J., Romero, F., Roa, J., & Rodríguez-Núñez, I. (2017). Exercise training to reduce sympathetic nerve activity in heart failure patients. A systematic review and meta-analysis. *Brazilian Journal of Physical Therapy*, *22(2),* 97-104.

Salmoirago-Blotcher, E., Wayne, P. M., Dunsiger, S., Krol, J., Breault, C., Bock, B. C., ... & Yeh, G. Y. (2017). Tai chi is a promising exercise option for patients with coronary heart disease declining cardiac rehabilitation. *Journal of the American Heart Association, 6(10),* e006603.

Santos, F. V., Chiappa, G. R., Ramalho, S. H. R., de Lima, A. C. G. B., de Souza, F. S. J., Cahalin, L. P., ... & Cipriano, G. (2018). Resistance exercise enhances oxygen uptake without worsening cardiac function in patients with systolic heart failure: a systematic review and meta-analysis. *Heart Failure Reviews*, *23*(1), 73-89.

Shah, P., Pellicori, P., Macnamara, A., Urbinati, A., & Clark, A. L. (2017). Is Swimming Safe in Heart Failure? A Systematic Review. *Cardiology in Review*, *25*(6), 321-325.

Sties, S. W., Andreato, L. V., de Carvalho, T., Gonzáles, A. I., Angarten, V. G., Ulbrich, A. Z., ... & Andrade, A. (2018). Influence of exercise on oxidative stress in patients with heart failure. *Heart Failure Reviews*, *23*(2), 225-235.

Supervía, M., Medina-Inojosa, J. R., Yeung, C., Lopez-Jimenez, F., Squires, R. W., Pérez-Terzic, C. M., ... & Thomas, R. J. (2017, April). Cardiac rehabilitation for women: a systematic review of barriers and solutions. *In Mayo Clinic Proceedings 92(4),* 565-577.

Swank, A. M., Funk, D. C., Manire, J. T., Allard, A. L., & Denny, D. M. (2010). Effect of resistance training and aerobic conditioning on muscular strength and submaximal fitness for individuals with chronic heart failure: influence of age and gender. *The Journal of Strength & Conditioning Research, 24(5),* 1298-1305.

Wu, J., Kuang, L., & Fu, L. (2018). Effects of inspiratory muscle training in chronic heart failure patients: A systematic review and meta-analysis. *Congenital Heart Disease*, *13*(2), 194-202.