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Physiological and psychosocial factors influencing exercise capacity and exercise training in cardiac patients

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It always seems impossible until it's done.

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Grants

A

ACE-I   Angiotensin Converting Enzyme Inhibitor

ACS   Acute Coronary Syndrome

AF   Atrial Fibrillation

ANS   Autonomic Nervous System

ARB   Angiotensin Receptor Blocker

AT   Anaerobic Threshold

A-V O_2 difference   Arterio – Venous Oxygen Difference

AVS   Aortic Valve Surgery

B

β blockers   Beta Blockers

BF   Breathing Frequency

BIO-HF   BIO – Heart Failure

BMI   Body Mass Index

BNP   Brain Natriuretic Peptide

BP   Blood Pressure

C

CABG   Coronary Artery Bypass Graft

CAD   Coronary Artery Disease

CHF   Chronic Heart Failure

CI   Confidence Interval

CNS   Central Nervous System

CO   Cardiac Output

COPD   Chronic Obstructive Pulmonary Disease

CPET   Cardiopulmonary Exercise Test

CR   Cardiac Rehabilitation

CRT   Cardiac Resynchronization Therapy

CVA   Cerebrovascular Accident

D

DBP   Diastolic Blood Pressure

E

ECG	Electrocardiography
(e)GFR	(estimated) Glomerular Filtration Rate
EQ-5D(-3L)	EuroQoL 5 Dimensions (3 level)
EQ-5D VAS	EuroQol 5 Dimensions Visual Analogue Scale
ESC	European Society of Cardiology
EuroSCORE	European System for Cardiac Operative Risk Evaluation
EOV	Exercise Oscillatory Ventilation

H

HADS	Hospital Anxiety and Depression Scale
HADS-A	Anxiety dimension of the Hospital Anxiety and Depression Scale
HADS-D	Depression dimension of the Hospital Anxiety and Depression Scale
HF	Heart Failure
HFREF	Heart Failure with Reduced Ejection Fraction
HFPEF	Heart Failure with Preserved Ejection Fraction
HR	Heart Rate

I

ICD	Implantable Cardioverter Defibrillator
IHD	Ischemic Heart Disease
IQR	Interquartile Range

L

LBBB	Left Bundle Branch Block
LVEF	Left Ventricular Ejection Fraction

M

MAGGIC	Meta-Analysis Global Group in Chronic Heart Failure
MRA	Mineralocorticoid Receptor Antagonist
MVS	Mitral Valve Surgery

N

NO	Nitric Oxide
nNOS	neuronal Nitric Oxide Synthase

NSTEMI	Non ST Elevation Myocardial Infarction
NTS	Nucleus Tractus Solitarius
NT-proBNP	N-Terminal Pro Brain Natriuretic Peptide
NYHA	New York Heart Association

O

OR	Odds Ratio

P

$PaCO_2$	Arterial CO_2 Tension
PA(O)D	Peripheral Arterial (Occlusive) Disease
PNS	Parasympathetic Nervous System
Peak VO_2	Peak Oxygen Consumption
$P_{ET}CO_2$	Partial Pressure of End-Tidal CO_2
PH-RCO	Post-Handgrip Regional Circulatory Occlusion

R

RAAS	Renin-Angiotensin-Aldosterone System

S

6MWD	Six-Minute Walking Distance
6MWT	Six-Minute Walking Test
SBP	Systolic Blood Pressure
SNS	Sympathetic Nervous System
STEMI	ST Elevation Myocardial Infarction

V

V_D/V_T	Dead Space/Tidal Volume Ratio
VE	Ventilation
VE/VCO_2 slope	Minute Ventilation in response to Carbon Dioxide Production, ventilatory slope
VHD	Valvular Heart Disease
VCO_2	Carbon Dioxide Production
VO_2	Oxygen Consumption
VO_2 max	Maximum Oxygen Uptake

Abbreviations

VT   Tidal Volume

[^{123}I]-MIBG   iodine-123 Metaiodobenzylguanidine

1 General introduction

Cardiovascular disease remains the leading cause of death, being responsible for almost one third of all deaths worldwide and close to half of all deaths in Europe. However, in some parts of Europe including Belgium, cancer is now for the first time the cause of more deaths than cardiovascular disease among men. This may be partly explained by a decrease in mortality in coronary artery disease (CAD) due to a better prevention and treatment policy.[1]

Together with the ageing of the population, this success in secondary prevention and prolonging survival in patients suffering from coronary events, may contribute to the increasing overall prevalence of heart failure (HF). HF affects about 1-2% of the population with a sharp rise to more than 10% above the age of 70 years.[2] CAD is by far the most common cause of HF, but also hypertension, tachyarrhythmia, cardiomyopathies and valvular heart disease (VHD) may eventually lead to HF.[3] VHD is usually less regarded as a major public-health problem, however a substantial burden of this disease exists and will probably further increase, due to increasing life expectancy and its link with degenerative valve disease.[4, 5]

Exercise intolerance is a hallmark feature of HF with symptoms of breathlessness and fatigue and indicates a poor prognosis. Likewise, an impaired exercise capacity is also seen in CAD and VHD patients[6-9] with a similar prognostic value.[6, 10] Cardiac rehabilitation (CR) has been recommended in both CAD and HF to reduce risk factors and to improve exercise tolerance, health-related quality of life and prognosis.[2, 11, 12] Nevertheless, more than half of eligible cardiac patients do not attend CR or drop out prematurely.[13, 14]

To date, the mechanisms underlying exercise intolerance in patients both with and without HF are not entirely clear, suggesting further investigation. In addition, the outcome in hospitalized HF patients has not been investigated in Belgium thus far and needs to be further explored as well as the value of exercise training as a treatment modality in a broader spectrum of cardiac patients. Finally, the implementation of CR in the 'real-life setting' encounters several barriers, which should be adequately addressed to further increase participation in CR.

1 Exercise intolerance in heart failure

HF can be defined as an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate corresponding with the requirements of the metabolizing tissues.[2] While traditionally associated with a pump failure or reduced ejection fraction (HFREF), it has become widely recognized that HF can occur even when left ventricular ejection fraction (LVEF) is preserved (HFPEF).[15] Unlike HFREF, which is diagnosed when signs and symptoms of HF are present together with a reduced LVEF, patients with HFPEF have similar signs and symptoms but evidence of a normal systolic LV function and diastolic LV dysfunction.[2, 16] HFPEF is currently observed in 50% of HF patients and outcomes are similar to those in HFREF.[17]

1.1 Pathophysiology

In HFREF, left ventricular remodeling is driven by a progressive loss of cardiomyocytes, because of oxidative stress usually resulting from ischemia, infection or toxicity. This results in a shift in the balance between collagen deposition and degradation, contributing to LV dilatation and eccentric LV remodeling. In advanced HFREF, endothelial dysfunction is also present and contributes to the raised plasma levels of inflammatory parameters such as tumor necrosis factor alpha and interleukin 6 which affects diastolic function. A novel paradigm has been proposed in HFPEF with comorbidities contributing to a systemic inflammatory state. This inflammatory state induces oxidative stress in the coronary microvascular endothelium, which reduces myocardial nitric oxide bioavailability and leads to a reduced protein kinase G activity in cardiomyocytes which therefore become stiff and hypertrophied, resulting in impaired left ventricular filling.[18]

1.2 From 'pump failure' to a systemic disease

HF is marked by an interplay between the underlying myocardial dysfunction and the compensatory neurohormonal mechanisms, including the sympathetic nervous system, the renin-angiotensin-aldosteron system (RAAS) and several cytokines. Although the activation of these systems can initially compensate for the depressed myocardial function, their long-term activation results in a further impairment of cardiac function and cardiac remodelling leading to progression of heart failure and cardiac decompensation. [19-21] One of the key stones of this neurohormonal activation, the autonomic nervous system (ANS), is described in Part 1 of this thesis, but is also summarized in the following section. The majority of research has focused on the impact of autonomic imbalance in HFREF, limited information exists in HFPEF.[22, 23]

The ANS enables the body to adjust its circulation and respiration to maintain an appropriate oxygen delivery to tissues. The balance between the sympathetic (SNS) and parasympathetic nerve system (PNS) is mediated by the interaction between the central command originating from the central motor areas and peripheral feedback afferents, including the baroreflex, chemoreflex and ergoreflex.[24, 25] The nucleus tractus solitarius (NTS) is the integrating centre located in the medulla oblongata.[25-27] SNS activation is mediated via the release of norepinephrine and epinephrine, whereas the PNS acts through the release of acetylcholine. [21, 28]

The SNS exerts a wide variety of cardiovascular effects, including heart rate acceleration, increase in cardiac contractility, accelerated cardiac relaxation and decrease in venous capacitance in order to increase cardiac performance as part of the so called fight – or flight response. Conversely, the PNS slows the heart rate but has no effect on cardiac contractility.[21] Baroreceptors are together with ergoreceptors and peripheral chemoreceptors responsible for these hemodynamic changes with baroreceptors having an inhibitory function whereas the other receptors rather stimulate the SNS.[24, 29] In HF, an increase in chemoreflex and ergoreflex responsiveness is seen with a reduction in baroreflex activity, resulting in an increase in adrenergic outflow.[20, 24, 29, 30] This results in an enhanced peripheral vasoconstriction during exercise in order to preserve an adequate blood pressure level, thereby unfortunately limiting blood flow in the exercising muscle which further exacerbates muscular abnormalities typically seen in HF.

Ergoreceptors and chemoreceptors also take part in the regulation of ventilation by influencing the respiratory neurons in the pons and medulla.[31] Very recently, a synaptic interaction between respiratory and sympathetic neurons has been proposed with the NTS as a coordinating centre.[27] Overactivity of these receptors is related to the inappropriate increase in the ventilatory drive in HF with a detrimental impact on prognosis.[32-35]
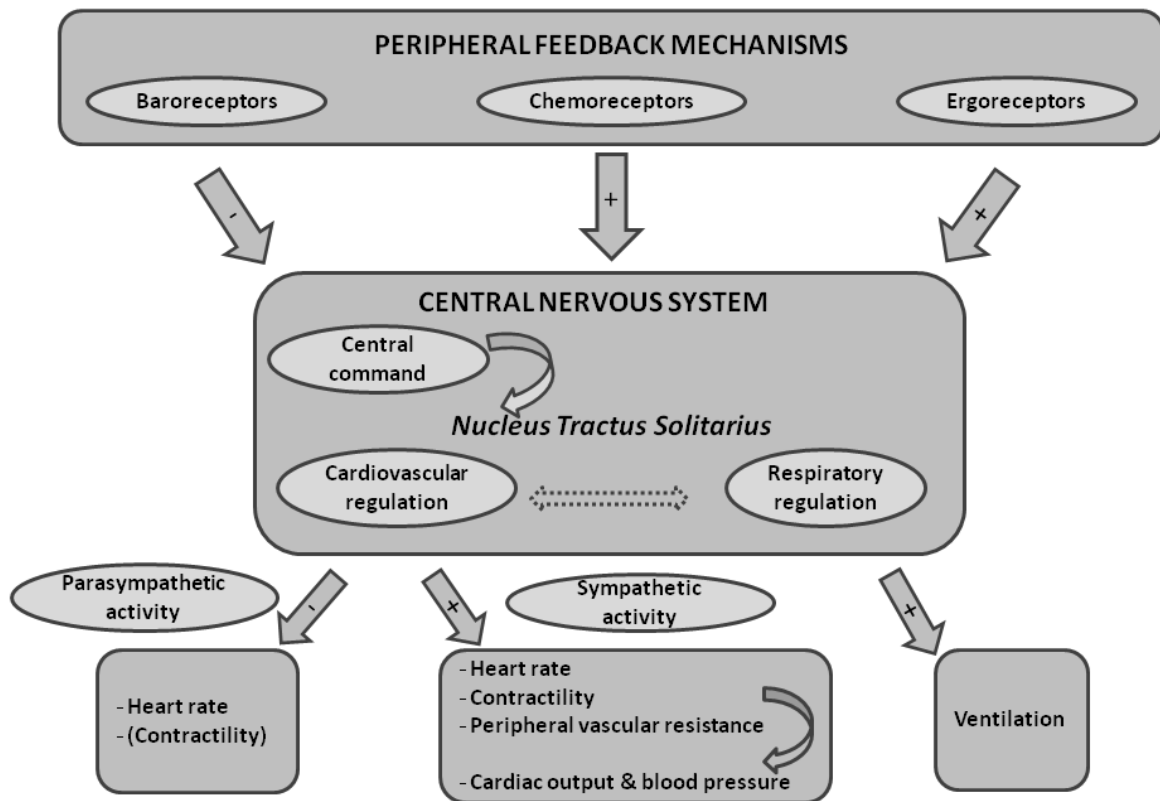
Figure 1. Mechanisms of autonomic control. Under normal conditions, the inhibitory input of the baroreceptors is the major controlling mechanism. As heart failure progresses, baroreceptor activity is blunted and the excitatory input of the chemoreceptors and ergoreceptors predominates with an increase in sympathetic activity and ventilation.

RAAS is a second neurohormonal mechanism that is activated in response to a decrease in blood pressure with the conversion of angiotensinogen to angiotensin I via the secretion of renin. Angiotensin I is cleaved further by angiotensin converting enzyme (ACE) to generate the active angiotensin II. This latter peptide helps to maintain the extracellular fluid volume and arterial blood pressure 1) by its stimulation of aldosterone secretion which promotes renal salt and water retention, 2) by a generalized vasoconstriction through direct action and also through boosting of sympathetic activity and finally 3) by stimulating the sensation of thirst and hence fluid intake. In HF, this cascade ultimately results in an excessive vasoconstriction and fluid retention.[19, 36]

Neurohormonal activation is also characterized by an increase in several biomarkers, including natriuretic peptides of which brain natriuretic peptides (BNP) are most commonly used for evaluation. The main stimulus is stretch of cardiac myocytes, but also certain hormones (such as catecholamines and angiotensin II) and hypoxia in the setting of acute coronary syndrome (ACS) may

activate these peptides. On secretion, the propeptide is split into the biologically active BNP and the remaining part of the prohormone N-terminal proBNP (NT-proBNP). Activation of natriuretic peptides causes diuresis, vasodilatation and a decrease in renin and aldosterone secretion in order to oppose the acute increase in ventricular volume.[37-39]

1.3 Markers of exercise intolerance

Exercise intolerance is a hallmark feature of HF and indicates a poor prognosis. In general, exercise capacity is slightly more impaired in HFREF as in HFPEF.[40] Since the landmark study of Mancini, peak oxygen consumption (peak VO_2) has become widely accepted as a prognosticator.[41] However, several drawbacks have led to a search for novel prognostic exercise parameters. The VE/VCO_2 slope, which describes the increase in ventilation in response to a rising CO_2 production,[42] has been proven to be prognostically superior, not only in predicting mortality but also in providing additional information regarding hospitalization,[43] both in HFREF as in HFPEF.[44] Instead of the traditional cut-off values of peak VO_2 <14 $ml.min^{-1}.kg^{-1}$ and a VE/VCO_2 slope >34 to indicate a poor prognosis, a 4-level classification has recently been introduced. Under current medical management strategies, a VE/VCO_2 slope ≥45 and a peak VO_2 <10 $ml.min^{-1}.kg^{-1}$ are indicative of a particularly poor prognosis.[45, 46] Likewise, an impaired peak VO_2 and a steep ventilatory slope are seen in a substantial part of CAD patients with a similar prognostic value.[6, 47-51]

Different pathophysiological mechanisms are thought to underlie these parameters. The peak VO_2 is dependent on the cardiac output (CO) and the arterio-venous O_2 difference, whereas the VE/VCO_2 slope is rather attributable to a combination of an elevated dead space and a reduced arterial CO_2 tension with the latter being partly driven by the ergoreflex. These mechanisms are further described in detail in Part 1 of this thesis.

Besides peak VO_2 and VE/VCO_2 slope, also other cardiopulmonary exercise test (CPET) parameters have been proven to be prognostically important. An irregular breathing pattern that persists during exercise with cyclic fluctuations in minute ventilation and gas exchange kinetics, also known as exercise oscillatory ventilation (EOV) and the partial pressure of end-tidal CO_2 (P_{ET})CO_2 are further described in part 1 of this thesis. In addition, chronotropic incompetence which is an inadequate heart rate response to exercise, is also a marker of poor prognosis even in the setting of β blockade.[52-54]

A frequently used submaximal exercise test is the six-minute walking test (6MWT), which approximates the capacity to perform activities of daily living but does not allow for a thorough investigation into the pathogenetic mechanisms involved in fatigue and dyspnoea sensation.[55] Although the distance walked in six minutes (6MWD) is described as a prognostic marker of cardiac death and cardiovascular events,[56, 57] there is currently no supportive evidence for its use as an alternative to CPET derived variables.[55]

1.4 Treatment

The introduction of medication influencing neurohormonal activation, was a milestone in the treatment and outcome of HFREF. Beta (β) blockers, angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB) and aldosterone receptor antagonists are known to reduce neurohormonal activation with a positive influence on prognosis.[2] In addition, β blocker therapy has also been shown to reduce the VE/VCO_2 slope without significantly altering peak VO_2,[43, 58] whereas ACE-I may influence both peak VO_2 and VE/VCO_2 slope although this is not supported in all studies.[59-63]

Recently, Cha et al.[64] reported that cardiac resynchronization therapy (CRT) may also modulate the sympathetic function. Furthermore, CRT may increase peak VO_2 with a concomitant decrease in the VE/VCO_2 slope.[65] The role of exercise training in the treatment of HF is discussed in the next section.

1.5 Exercise training

Cardiac rehabilitation (CR) has been recommended in both CAD and HF to reduce risk factors and to improve exercise tolerance, health-related quality of life and prognosis.[2, 11, 12, 66, 67] A recent meta-analysis demonstrates that CR has no effect on short-term mortality in HF but a trend towards a decrease in long-term mortality is present. A small body of evidence suggests that CR may also benefit HFPEF patients, but further studies are needed.[68]

An improvement in exercise intolerance after exercise training has been widely recognized with an increase in peak VO_2 and a concomitant decrease in ventilatory abnormalities. Peripheral rather than central adaptations are thought to be responsible, with changes in skeletal muscle mass, muscle metabolism, endothelial function, inflammatory state and changes occurring at the lung level.[69-73] These changes in the periphery may result in a decrease in ergoreflex and chemoreflex activation with a concomitant decrease in hyperventilation and sympathetic outflow.[74-79] Likewise, a decrease

in natriuretic peptides after exercise training suggests neurohormonal improvement.[80, 81] Although far less described, also central adaptations are reported with an increase in CO due to changes in heart rate and stroke volume.[82]

Because of its proven efficacy and safety, aerobic training is widely recommended.[2] To affect the muscle alterations typically seen in HF patients, strength training should also be considered.[83] In order to further improve the effects of exercise training, novel training modalities are currently being tested such as high-intensity aerobic interval training[84, 85] and inspiratory muscle training.[86]

1.6 Research questions

According to the aforementioned literature, ergoreflex activity may play a major role in exercise intolerance in HF. Nevertheless, the presence of ergoreflex activity in the current situation is less clear because of changes in pharmacological treatment. In addition, an increased ventilatory drive has been demonstrated not only in HF, but also in CAD with a similar prognostic value.[50, 51] However, information on the ergoreflex is currently lacking in this population. Therefore, the first part of this thesis will focus on exercise intolerance and the relevance of the ergoreflex.

2   Outcome and the key role of exercise training in heart failure

2.1 Outcome of HF

Despite improvements in medical treatment, mortality and readmission rates remain high in HF, with an increase in patients with HFPEF.[87] In the latter group, the use of similar drugs as in HFREF did not result in an improvement in prognosis,[16] indicating the urgent need for novel treatment strategies.

Data from hospitalized HF patients may be useful to better understand the clinical characteristics, patient management and outcomes and may ultimately help to improve patient outcomes.[88, 89] Research has shown that important geographic variations exist, both in patient characteristics and treatment.[89-91] Therefore, country specific data are important but for Belgium, no such data have been published so far.

2.2 The role of natriuretic peptides in exercise capacity and exercise training

Natriuretic peptides have become increasingly important for the diagnosis and prognosis of HF patients, both with reduced and preserved ejection fraction.[38, 92] Despite significantly higher baseline levels of natriuretic peptides in HFREF, the prognosis in patients with HFPEF is as poor as in those with HFREF for a given BNP level. This may indicate that neurohormonal activation is the primary driver of outcome instead of LVEF. [92, 93] In addition, natriuretic peptides have also been demonstrated to be predictive for cardiac events and mortality in other clinical settings such as acute coronary syndrome, coronary artery bypass graft (CABG), VHD and even in patients without CAD at baseline. [38, 94-98]

The link between natriuretic peptides and an impaired exercise capacity or increased ventilatory drive has already been demonstrated in HF.[99-103] Furthermore, exercise training may improve both exercise intolerance and neurohormonal activation.[75, 80, 81, 104-108] However, it is not clear whether exercise capacity and the improvement after exercise training are primarily affected by left ventricular function or natriuretic peptides.

2.3 Research questions

Because of the lack of data on the clinical characteristics and outcome of HF patients in Belgium, the second part of this dissertation will provide data on this subject. In addition, since natriuretic peptides seem to have a major impact on outcome, its influence on exercise capacity and the training response will be further explored, both in cardiac patients with reduced and preserved LVEF.

3 Barriers in the implementation of cardiac rehabilitation

3.1 Participation and drop-out in cardiac rehabilitation

Despite the clear benefits of CR as described in the previous section, figures on participation in CR are disappointing with less than 50% attendance of the eligible patients.[13] In addition, a considerable number of those patients who actually attend CR, drop out prematurely varying from 22% to 65%.[14, 109] Patients after myocardial infarction and CABG are most commonly provided by CR. Despite evidence on the benefits of CR for the increasing population of HF patients, this is not reflected in the

sobering number of less than 20% participating in CR.[13, 110] Specific data on participation in CR are lacking for Belgium.

Adherence to application of exercise recommendations is dependent on both the adherence of health-care providers to clinical guidelines (guideline adherence) as well as to adherence of the patient to clinician's advice (patient adherence).

Barriers for guideline adherence are related to the physician's knowledge about the effects of exercise training as well as to organizational and political issues such as availability of exercise training sites and reimbursement for enrolment in CR.[83] Referral is a prerequisite to have access to CR, but remains suboptimal particularly among women.[111]

Patient adherence is a multidimensional phenomenon, determined by the interplay of a set of five dimensions: social and economic factors, factors related to the health-care system, factors related to the patient's condition, the therapy and the patients themselves. Literature has shown that adherence is particularly determined by age, female gender, a low socio-economic status, a lack of motivation, psychological characteristics, and financial and medical concerns. [83] Also the perception of self-control of the problem and illness cognition may play a key role.[112] Several of these barriers are potentially modifiable and should therefore be adequately addressed in order to increase participation in CR.

3.2 Valvular heart disease

Although VHD is less common in industrialized countries than CAD, HF, or hypertension, VHD is frequent and often requires intervention.[4, 5] In industrialized countries, the prevalence of VHD is estimated at 2.5%. Because of the predominance of degenerative aetiologies, the prevalence of VHD increases markedly after the age of 65 years, in particular with regard to aortic stenosis and mitral regurgitation which accounts for 3 in 4 cases of VHD.[4, 113]

Decision-making for intervention is complex, since VHD is often seen at an older age and, as a consequence, there is a higher frequency of comorbidity, contributing to increased risk of intervention.[4, 5] Several registries worldwide have consistently shown that, in current practice, therapeutic intervention for VHD is underused in high-risk patients with symptoms, for reasons which are often unjustified. This stresses the importance of the widespread use of careful risk stratification.[114] The two most widely used scores are the European System for Cardiac Operative

Risk Evaluation (EuroSCORE) and the Society of Thoracic Surgeons score, the latter having the advantage of being specific to VHD but less user-friendly than the EuroSCORE.[115]

In the past two decades, progress has been made regarding minimal invasive surgery to reduce the surgical trauma. Minimal invasive surgery, such as ministernotomy for aortic valve and port access procedures for mitral valve disease, has been considered to have several advantages besides the cosmetic aspect, including a reduced ventilation time, less bleeding and a reduced hospital stay. Few of these aspects however, have been objectively established.[116-120]

Although exercise capacity is an important parameter of prognosis and quality of life, there is limited information regarding the effect of valvular surgery on exercise capacity. Current literature suggests that despite improvements in symptomatic status, exercise capacity does not recover spontaneously after aortic (AVS) or mitral valve surgery (MVS).[7-9] This argues in favour of the need for cardiac rehabilitation, although this is currently not mentioned in the management guidelines on VHD.

3.3 Research questions

Attendance and adherence in CR seem to be disappointing but specific data on the Belgian situation are scarce. Therefore, the third part of this work will assess participation and drop-out and will try to gain insight in the current barriers in the implementation of CR. Another type of barrier is the lack of knowledge on exercise capacity and exercise training in an important subgroup of the cardiac patient population, i.e. VHD patients. This will therefore, be the focus of the final chapter.

4 References

1. Nichols M, Townsend N, Scarborough P and Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. *Eur Heart J*. 2014.

2. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2012; 14: 803-69.

3. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail*. 2008; 10: 933-89.

4. Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur Heart J*. 2003; 24: 1231-43.

5. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG and Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet*. 2006; 368: 1005-11.

6. Keteyian SJ, Brawner CA, Savage PD, et al. Peak aerobic capacity predicts prognosis in patients with coronary heart disease. *Am Heart J*. 2008; 156: 292-300.

7. Le Tourneau T, de Groote P, Millaire A, et al. Effect of mitral valve surgery on exercise capacity, ventricular ejection fraction and neurohormonal activation in patients with severe mitral regurgitation. *J Am Coll Cardiol*. 2000; 36: 2263-9.

8. Tamas E, Nielsen NE, Vanhanen I and Nylander E. Measurement of physical work capacity in patients with chronic aortic regurgitation: a potential improvement in patient management. *Clin Physiol Funct Imaging.* 2009; 29: 453-7.

9. Hedman K, Tamas E and Nylander E. Decreased aerobic capacity 4 years after aortic valve replacement in male patients operated upon for chronic aortic regurgitation. *Clin Physiol Funct Imaging.*. 2012; 32: 167-71.

10. Dhoble A, Enriquez-Sarano M, Kopecky SL, et al. Cardiopulmonary responses to exercise and its utility in patients with aortic stenosis. *Am J Cardiol*. 2014; 113: 1711-6.

11. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J*. 2012; 33: 1635-701.

12. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013; 34: 2949-3003.

13. Bjarnason-Wehrens B, McGee H, Zwisler AD, et al. Cardiac rehabilitation in Europe: results from the European Cardiac Rehabilitation Inventory Survey. *Eur J Cardiovasc Prev Rehabil*. 2010; 17: 410-8.

14. Worcester MU, Murphy BM, Mee VK, Roberts SB and Goble AJ. Cardiac rehabilitation programmes: predictors of non-attendance and drop-out. *Eur J Cardiovasc Prev Rehabil*. 2004; 11: 328-35.

15. Lam CS, Donal E, Kraigher-Krainer E and Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2011; 13: 18-28.

16. Paulus WJ and van Ballegoij JJ. Treatment of heart failure with normal ejection fraction: an inconvenient truth! *J Am Coll Cardiol*. 2010; 55: 526-37.

17. Borlaug BA and Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J*. 2011; 32: 670-9.

18. Paulus WJ and Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol*. 2013; 62: 263-71.

19. Mann DL and Bristow MR. Mechanisms and models in heart failure: the biomechanical model and beyond. *Circulation*. 2005; 111: 2837-49.

20. Triposkiadis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G and Butler J. The sympathetic nervous system in heart failure physiology, pathophysiology, and clinical implications. *J Am Coll Cardiol*. 2009; 54: 1747-62.

21. Lymperopoulos A, Rengo G and Koch WJ. Adrenergic nervous system in heart failure: pathophysiology and therapy. *Circ Res*. 2013; 113: 739-53.

22. Kishi T. Heart failure as an autonomic nervous system dysfunction. *Journal of cardiology*. 2012; 59: 117-22.

23. Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol*. 2014; 11: 507-15.

24. O'Leary DS. Altered reflex cardiovascular control during exercise in heart failure: animal studies. *Exp Physiol*. 2006; 91: 73-7.

25. Decherchi P, Dousset E and Jammes Y. Respiratory and cardiovascular responses evoked by tibialis anterior muscle afferent fibers in rats. *Exp Brain Res*. 2007; 183: 299-312.

26. Dampney RA, Coleman MJ, Fontes MA, et al. Central mechanisms underlying short- and long-term regulation of the cardiovascular system. *Clin Exp Pharmacol Physiol*. 2002; 29: 261-8.

27. Zoccal DB, Furuya WI, Bassi M, Colombari DS and Colombari E. The nucleus of the solitary tract and the coordination of respiratory and sympathetic activities. *Front Physiol*. 2014; 5: 238.

28. Florea VG and Cohn JN. The autonomic nervous system and heart failure. *Circ Res*. 2014; 114: 1815-26.

29. Piepoli MF, Dimopoulos K, Concu A and Crisafulli A. Cardiovascular and ventilatory control during exercise in chronic heart failure: role of muscle reflexes. *Int J Cardiol*. 2008; 130: 3-10.

30. Ponikowski P, Chua TP, Piepoli M, et al. Augmented peripheral chemosensitivity as a potential input to baroreflex impairment and autonomic imbalance in chronic heart failure. *Circulation*. 1997; 96: 2586-94.

31. Schmidt H, Francis DP, Rauchhaus M, Werdan K and Piepoli MF. Chemo- and ergoreflexes in health, disease and ageing. *Int J Cardiol*. 2005; 98: 369-78.

32. Chua TP, Clark AL, Amadi AA and Coats AJ. Relation between chemosensitivity and the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol*. 1996; 27: 650-7.

33. Piepoli M, Ponikowski P, Clark AL, Banasiak W, Capucci A and Coats AJ. A neural link to explain the "muscle hypothesis" of exercise intolerance in chronic heart failure. *Am Heart J*. 1999; 137: 1050-6.

34. Ponikowski P, Francis DP, Piepoli MF, et al. Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. *Circulation*. 2001; 103: 967-72.

35. Ponikowski PP, Chua TP, Francis DP, Capucci A, Coats AJ and Piepoli MF. Muscle ergoreceptor overactivity reflects deterioration in clinical status and cardiorespiratory reflex control in chronic heart failure. *Circulation*. 2001; 104: 2324-30.

36. Levick JR. Control of blood vessels: II. Extrinsic control by nerves and hormones in: J Koster, F Naish (eds) An introduction to cardiovascular physiology. Fifth edition. Great Britain: Hodder Arnold Publishers, 2010, p 258-278.

37. Hall C. NT-ProBNP: the mechanism behind the marker. *J Card Fail*. 2005; 11: S81-3.

38. Daniels LB and Maisel AS. Natriuretic peptides. *J Am Coll Cardiol*. 2007; 50: 2357-68.

39. Rocchiccioli JP, McMurray JJ and Dominiczak AF. Biomarkers in heart failure: a clinical review. *Heart Fail Rev*. 2010; 15: 251-73.

40. Moore B, Brubaker PH, Stewart KP and Kitzman DW. VE/VCO2 slope in older heart failure patients with normal versus reduced ejection fraction compared with age-matched healthy controls. *J Card Fail*. 2007; 13: 259-62.

41. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH, Jr. and Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation*. 1991; 83: 778-86.

42. Tabet JY, Beauvais F, Thabut G, Tartiere JM, Logeart D and Cohen-Solal A. A critical appraisal of the prognostic value of the VE/VCO2 slope in chronic heart failure. *Eur J Cardiovasc Prev Rehabil*. 2003; 10: 267-72.

43. Arena R, Myers J and Guazzi M. The clinical and research applications of aerobic capacity and ventilatory efficiency in heart failure: an evidence-based review. *Heart Fail Rev*. 2008; 13: 245-69.

44. Guazzi M, Myers J and Arena R. Cardiopulmonary exercise testing in the clinical and prognostic assessment of diastolic heart failure. *J Am Coll Cardiol*. 2005; 46: 1883-90.

45. Arena R, Myers J, Abella J, et al. Defining the optimal prognostic window for cardiopulmonary exercise testing in patients with heart failure. *Circ Heart Fail*. 2010; 3: 405-11.

46. Guazzi M, Adams V, Conraads V, et al. EACPR/AHA Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation*. 2012; 126: 2261-74.

47. Kavanagh T, Mertens DJ, Hamm LF, et al. Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation. *Circulation*. 2002; 106: 666-71.

48. Kavanagh T, Mertens DJ, Hamm LF, et al. Peak oxygen intake and cardiac mortality in women referred for cardiac rehabilitation. *J Am Coll Cardiol*. 2003; 42: 2139-43.

49. Myers J, Prakash M, Froelicher V, Do D, Partington S and Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*. 2002; 346: 793-801.

50. Tomita T, Takaki H, Hara Y, et al. Attenuation of hypercapnic carbon dioxide chemosensitivity after postinfarction exercise training: possible contribution to the improvement in exercise hyperventilation. *Heart (British Cardiac Society)*. 2003; 89: 404-10.

51. Tsurugaya H, Adachi H, Kurabayashi M, Ohshima S and Taniguchi K. Prognostic impact of ventilatory efficiency in heart disease patients with preserved exercise tolerance. *Circ J*. 2006; 70: 1332-6.

52. Dresing TJ, Blackstone EH, Pashkow FJ, Snader CE, Marwick TH and Lauer MS. Usefulness of impaired chronotropic response to exercise as a predictor of mortality, independent of the severity of coronary artery disease. *Am J Cardiol*. 2000; 86: 602-9.

53. Azarbal B, Hayes SW, Lewin HC, Hachamovitch R, Cohen I and Berman DS. The incremental prognostic value of percentage of heart rate reserve achieved over myocardial perfusion single-photon emission computed tomography in the prediction of cardiac death and all-cause mortality: superiority over 85% of maximal age-predicted heart rate. *J Am Coll Cardiol*. 2004; 44: 423-30.

54. Khan MN, Pothier CE and Lauer MS. Chronotropic incompetence as a predictor of death among patients with normal electrograms taking beta blockers (metoprolol or atenolol). *Am J Cardiol*. 2005; 96: 1328-33.

55. Guazzi M, Dickstein K, Vicenzi M and Arena R. Six-minute walk test and cardiopulmonary exercise testing in patients with chronic heart failure: a comparative analysis on clinical and prognostic insights. *Circ Heart Fail*. 2009; 2: 549-55.

56. Rostagno C, Olivo G, Comeglio M, et al. Prognostic value of 6-minute walk corridor test in patients with mild to moderate heart failure: comparison with other methods of functional evaluation. *Eur J Heart Fail*. 2003; 5: 247-52.

57. Beatty AL, Schiller NB and Whooley MA. Six-minute walk test as a prognostic tool in stable coronary heart disease: data from the heart and soul study. *Arch Int Med*. 2012; 172: 1096-102.

58. Sue DY. Excess ventilation during exercise and prognosis in chronic heart failure. *Am J Respir Crit Care Med*. 2011; 183: 1302-10.

59. Guazzi M, Marenzi G, Alimento M, Contini M and Agostoni P. Improvement of alveolar-capillary membrane diffusing capacity with enalapril in chronic heart failure and counteracting effect of aspirin. *Circulation*. 1997; 95: 1930-6.

60. Kitaoka H, Takata J, Hitomi N, et al. Effect of angiotensin-converting enzyme inhibitor (enalapril or imidapril) on ventilation during exercise in patients with chronic heart failure secondary to idiopathic dilated cardiomyopathy. *Am J Cardiol*. 2000; 85: 658-60, A10.

61. Gundersen T, Swedberg K, Amtorp O, Remes J and Nilsson B. Absence of effect on exercise capacity of 12-weeks treatment with ramipril in patients with moderate congestive heart failure. Ramipril Study Group. *Eur Heart J*. 1994; 15: 1659-65.

62. Hampton JR, Cowley AJ and Wnuk-Wojnar AM. Failure of an ACE inhibitor to improve exercise tolerance. A randomized study of trandolapril. Trandolapril study group. *Eur Heart J*. 1998; 19: 1823-8.

63. Cooke GA, Williams SG, Marshall P, et al. A mechanistic investigation of ACE inhibitor dose effects on aerobic exercise capacity in heart failure patients. *Eur Heart J*. 2002; 23: 1360-8.

64. Cha YM, Chareonthaitawee P, Dong YX, et al. Cardiac sympathetic reserve and response to cardiac resynchronization therapy. *Circ Heart Fail*. 2011; 4: 339-44.

65. Varma C, Sharma S, Firoozi S, McKenna WJ and Daubert JC. Atriobiventricular pacing improves exercise capacity in patients with heart failure and intraventricular conduction delay. *J Am Coll Cardiol*. 2003; 41: 582-8.

66. Piepoli MF, Davos C, Francis DP and Coats AJ. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ (Clinical research ed)*. 2004; 328: 189.

67. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. 2009; 301: 1439-50.

68. Taylor RS, Sagar VA, Davies EJ, et al. Exercise-based rehabilitation for heart failure. *Cochrane Database Syst Rev*. 2014; 4: Cd003331.

69. Adamopoulos S, Coats AJ, Brunotte F, et al. Physical training improves skeletal muscle metabolism in patients with chronic heart failure. *J Am Coll Cardiol*. 1993; 21: 1101-6.

70. Hambrecht R, Niebauer J, Fiehn E, et al. Physical training in patients with stable chronic heart failure: effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. *J Am Coll Cardiol*. 1995; 25: 1239-49.

71. Hambrecht R, Fiehn E, Yu J, et al. Effects of endurance training on mitochondrial ultrastructure and fiber type distribution in skeletal muscle of patients with stable chronic heart failure. *J Am Coll Cardiol*. 1997; 29: 1067-73.

72. Hambrecht R, Fiehn E, Weigl C, et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. *Circulation*. 1998; 98: 2709-15.

73. Gielen S, Adams V, Mobius-Winkler S, et al. Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. *J Am Coll Cardiol*. 2003; 42: 861-8.

74. Piepoli M, Clark AL, Volterrani M, Adamopoulos S, Sleight P and Coats AJ. Contribution of muscle afferents to the hemodynamic, autonomic, and ventilatory responses to exercise in patients with chronic heart failure: effects of physical training. *Circulation*. 1996; 93: 940-52.

75. Zurek M, Corra U, Piepoli MF, Binder RK, Saner H and Schmid JP. Exercise training reverses exertional oscillatory ventilation in heart failure patients. *Eur Respir J*. 2012.

76. Larsen AI, Gjesdal K, Hall C, Aukrust P, Aarsland T and Dickstein K. 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*. 2004; 11: 162-7.

77. Malfatto G, Branzi G, Riva B, Sala L, Leonetti G and Facchini M. Recovery of cardiac autonomic responsiveness with low-intensity physical training in patients with chronic heart failure. *Eur J Heart Fail*. 2002; 4: 159-66.

78. Murad K, Brubaker PH, Fitzgerald DM, et al. Exercise training improves heart rate variability in older patients with heart failure: a randomized, controlled, single-blinded trial. *Congest Heart Fail*. 2012; 18: 192-7.

79. Roveda F, Middlekauff HR, Rondon MU, et al. The effects of exercise training on sympathetic neural activation in advanced heart failure: a randomized controlled trial. *J Am Coll Cardiol*. 2003; 42: 854-60.

80. Passino C, Severino S, Poletti R, et al. Aerobic training decreases B-type natriuretic peptide expression and adrenergic activation in patients with heart failure. *J Am Coll Cardiol*. 2006; 47: 1835-9.

81. Guazzi M, Vitelli A and 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. *Int J Cardiol*. 2012; 158: 290-1.

82. Mezzani A, Corra U and Giannuzzi P. Central adaptations to exercise training in patients with chronic heart failure. *Heart Fail Rev*. 2008; 13: 13-20.

83. Piepoli MF, Conraads V, Corra U, 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. *Eur J Heart Fail*. 2011; 13: 347-57.

84. Rognmo O, Hetland E, Helgerud J, Hoff J and Slordahl SA. High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. *Eur J Cardiovasc Prev Rehabil*. 2004; 11: 216-22.

85. Wisloff U, Stoylen A, Loennechen JP, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. *Circulation*. 2007; 115: 3086-94.

86. Adamopoulos S, Schmid JP, Dendale P, et al. Combined aerobic/inspiratory muscle training vs. aerobic training in patients with chronic heart failure: The Vent-HeFT trial: a European prospective multicentre randomized trial. *Eur J Heart Fail*. 2014; 16: 574-82.

87. Mosterd A and Hoes AW. Clinical epidemiology of heart failure. *Heart*. 2007; 93: 1137-46.

88. Jonsson A, Edner M, Alehagen U and Dahlstrom U. Heart failure registry: a valuable tool for improving the management of patients with heart failure. *Eur J Heart Fail*. 2010; 12: 25-31.

89. Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol*. 2014; 63: 1123-33.

90. Ventura HO and Gaddam KK. Geographic variations of acute heart failure syndromes: the importance of clinical registries. *Am Heart J*. 2011; 162: 1-2.

91. Maggioni AP, Dahlstrom U, Filippatos G, et al. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail*. 2013; 15: 808-17.

92. 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. *J Am Coll Cardiol*. 2013; 61: 1498-506.

93. Levy WC and Anand IS. Heart Failure Risk Prediction Models: What Have We Learned? *JACC Heart failure*. 2014.

94. Schnabel RB, Schulz A, Messow CM, et al. Multiple marker approach to risk stratification in patients with stable coronary artery disease. *Eur Heart J*. 2010; 31: 3024-31.

95. Holm J, Vidlund M, Vanky F, Friberg O, Hakanson E and Svedjeholm R. Preoperative NT-proBNP independently predicts outcome in patients with acute coronary syndrome undergoing CABG. *Scand Cardiovasc J Suppl*. 2013; 47: 28-35.

96. Gibson PH, Croal BL, Cuthbertson BH, et al. Use of preoperative natriuretic peptides and echocardiographic parameters in predicting new-onset atrial fibrillation after coronary artery bypass grafting: a prospective comparative study. *Am Heart J*. 2009; 158: 244-51.

97. Omland T, Persson A, Ng L, et al. N-terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes. *Circulation*. 2002; 106: 2913-8.

98. Leistner DM, Klotsche J, Pieper L, et al. Prognostic value of NT-pro-BNP and hs-CRP for risk stratification in primary care: results from the population-based DETECT study. *Clin Res Cardiol*. 2013; 102: 259-68.

99. Kruger S, Graf J, Kunz D, Stickel T, Hanrath P and Janssens U. brain natriuretic peptide levels predict functional capacity in patients with chronic heart failure. *J Am Coll Cardiol*. 2002; 40: 718-22.

100. Passino C, Poletti R, Bramanti F, Prontera C, Clerico A and Emdin M. Neuro-hormonal activation predicts ventilatory response to exercise and functional capacity in patients with heart failure. *Eur J Heart Fail*. 2006; 8: 46-53.

101. Kallistratos MS, Dritsas A, Laoutaris ID and Cokkinos DV. N-terminal prohormone brain natriuretic peptide as a marker for detecting low functional class patients and candidates for cardiac transplantation: linear correlation with exercise tolerance. *J Heart Lung Transplant*. 2007; 26: 516-21.

102. 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. *Am Heart J*. 2009; 158: S37-44.

103. Guazzi M, Labate V, Cahalin LP and Arena R. Cardiopulmonary exercise testing reflects similar pathophysiology and disease severity in heart failure patients with reduced and preserved ejection fraction. *Eur J Prev Cardiol*. 2013.

104. Coats AJ, Adamopoulos S, Radaelli A, et al. Controlled trial of physical training in chronic heart failure. Exercise performance, hemodynamics, ventilation, and autonomic function. *Circulation*. 1992; 85: 2119-31.

105. Belardinelli R, Paolini I, Cianci G, Piva R, Georgiou D and Purcaro A. Exercise training intervention after coronary angioplasty: the ETICA trial. *J Am Coll Cardiol*. 2001; 37: 1891-900.

106. Lan C, Chen SY, Hsu CJ, Chiu SF and Lai JS. Improvement of cardiorespiratory function after percutaneous transluminal coronary angioplasty or coronary artery bypass grafting. *Am J Phys Med Rehabil*. 2002; 81: 336-41.

107. Currie KD, Dubberley JB, McKelvie RS and MacDonald MJ. Low-volume, high-intensity interval training in patients with CAD. *Med Sci Sports Exerc*. 2013; 45: 1436-42.

108. Lara Fernandes J, Serrano CV, Jr., Toledo F, et al. Acute and chronic effects of exercise on inflammatory markers and B-type natriuretic peptide in patients with coronary artery disease. *Clin Res Cardiol*. 2011; 100: 77-84.

109. Yohannes AM, Yalfani A, Doherty P and Bundy C. Predictors of drop-out from an outpatient cardiac rehabilitation programme. *Clin Rehabil*. 2007; 21: 222-9.

110. Conraads VM, Van Craenenbroeck EM, De Maeyer C, Van Berendoncks AM, Beckers PJ and Vrints CJ. Unraveling new mechanisms of exercise intolerance in chronic heart failure: role of exercise training. *Heart Fail Rev*. 2013; 18: 65-77.

111. Colella TJ, Gravely S, Marzolini S, et al. Sex bias in referral of women to outpatient cardiac rehabilitation? A meta-analysis. *Eur J Prev Cardiol*. 2014.

112. Neubeck L, Freedman SB, Clark AM, Briffa T, Bauman A and Redfern J. Participating in cardiac rehabilitation: a systematic review and meta-synthesis of qualitative data. *Eur J Prev Cardiol*. 2012; 19: 494-503.

113. Iung B and Vahanian A. Epidemiology of Acquired Valvular Heart Disease. *Can J Cardiol*. 2014; 30: 962-70.

114. Rosenhek R, Iung B, Tornos P, et al. ESC Working Group on Valvular Heart Disease Position Paper: assessing the risk of interventions in patients with valvular heart disease. *Eur Heart J*. 2012; 33: 822-8, 8a, 8b.

115. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardiothorac Surg*. 2012; 42: S1-44.

116. Chaney MA, Durazo-Arvizu RA, Fluder EM, et al. Port-access minimally invasive cardiac surgery increases surgical complexity, increases operating room time, and facilitates early postoperative hospital discharge. *Anesthesiology*. 2000; 92: 1637-45.

117. Farhat F, Lu Z, Lefevre M, Montagna P, Mikaeloff P and Jegaden O. Prospective comparison between total sternotomy and ministernotomy for aortic valve replacement. *J Card Surg*. 2003; 18: 396-401; discussion 2-3.

118. Bakir I, Casselman FP, Wellens F, et al. Minimally invasive versus standard approach aortic valve replacement: a study in 506 patients. *Ann Thorac Surg*. 2006; 81: 1599-604.

119. Ryan WH, Brinkman WT, Dewey TM, Mack MJ, Prince SL and Herbert MA. Mitral valve surgery: comparison of outcomes in matched sternotomy and port access groups. J Heart Valve Dis. 2010; 19: 51-8; discussion 9.

120. Brown ML, McKellar SH, Sundt TM and Schaff HV. Ministernotomy versus conventional sternotomy for aortic valve replacement: a systematic review and meta-analysis. *J Thorac Cardiovasc Surg*. 2009; 137: 670-9 e5.

2 Aims and scope

The general aim of this thesis is to obtain knowledge on the mechanisms of exercise intolerance in cardiac patients both with and without heart failure, to evaluate outcome in heart failure and the effects of exercise training in a broader cardiac patient population. In addition, the implementation of cardiac rehabilitation in 'the real life setting' encounters several barriers regarding participation and drop-out, which are further explored in this work.

Part 1

It is remarkable that a reflex arising from the exercising muscle, i.e. the ergoreflex, may influence both fatigue and dyspnoea, being the major characteristics of exercise intolerance in HF. Ergoreflex activity has been related to exercise intolerance and in particular to the increased ventilatory drive typically seen in HF. Moreover, overactivity of the ergoreflex has been proven to be an ominous sign for a poor prognosis.[1-4] However, numerous issues regarding this mechanism remain unanswered. Since pharmacological treatment has changed over the past decades with the introduction of neurohormonal agents with an impact on survival and exercise intolerance, ergoreflex activity in HF patients at present is unknown. In addition, an increased ventilatory drive is not exclusively seen in HF patients but also in cardiac patients without signs of HF,[5, 6] a population whose ergoreflex activity has not been investigated thus far. Even in healthy subjects, the contribution of the ergoreflex to ventilation remains unclear.[1, 3, 4, 7] Therefore, the **first part** of this thesis handles about exercise intolerance and its mechanisms. Because of the extensive amount of literature on this topic and its complexity, available literature has been reviewed and the current knowledge about this topic has been described in the first two chapters of this work. **Chapter 1** provides an overview on the role of the autonomic nervous system of the heart in the development of HF, with a special focus on its role during exercise. In **chapter 2**, an update is given on prognostically important cardiopulmonary exercise variables and their determinants in HF. **Chapter 3** reports on the activity of the ergoreflex and its current relationship to exercise intolerance and subsequent prognosis in a broad spectrum of subjects, ranging from healthy subjects and patients with coronary artery disease to HF patients.

Part 2

Despite improvements in the treatment of HF, mortality and readmission rates remain high with an increase in HF patients with preserved ejection fraction.[8] In the latter group, the use of similar drugs does not result in an improvement in prognosis,[9] indicating the urgent need for novel treatment strategies. Data from hospitalized HF patients are useful to better understand the clinical characteristics, patient management and outcomes and may help to improve patient outcomes,[10, 11]

however, such data are currently lacking for Belgium. In addition, the similarities in outcome between HF patients with reduced and preserved LVEF for a given BNP level,[12] led us to investigate whether exercise capacity is predominantly affected by neurohormonal activation or LVEF and how exercise training may provide an answer for exercise intolerance, (in)dependent of the aforementioned factors. Hence, the **second part** of this dissertation focuses on outcome in HF in the Belgian situation but also on the role of neurohormonal activation in exercise capacity and the possibilities of exercise training as an effective treatment modality. In **chapter 4**, the first results of the Belgian BIO-HF registry are presented regarding patient characteristics and short-term outcome of patients hospitalized for HF. **Chapter 5** evaluates the impact of NT-proBNP on exercise capacity in CAD patients with a wide range of left ventricular function and neurohormonal activation as well as whether the improvement after exercise training depends on one of these factors.

Part 3

Despite the clear benefits of CR, figures on participation in CR are disappointing with more than half of eligible patients who do not attend CR.[13] In addition a considerable number of those patients who actually attend CR, drop out prematurely.[14] In Belgium, specific data on participation among the different patient groups and in HF in particular, are lacking. A variety of reasons for drop-out have been described in literature but may be different among countries because of different legislation and environmental conditions. Therefore, the **third part** of this work assesses the current barriers in the implementation of CR. **Chapter 6** reports on participation in CR among different patient groups with a focus on HF. In addition, potential predisposing clinical characteristics for (non-) participation are evaluated in HF as well as the benefit of exercise training in comparison with other patient groups. In **chapter 7**, drop-out is evaluated in a broad spectrum of cardiac patients with a focus on potential predisposing clinical characteristics, exercise parameters and psychosocial factors which could lead to drop-out. Despite the recommendation for CR in several cardiac patient groups, the effects of CR are not fully acknowledged in VHD thus far. Moreover, the influence of the preoperative state and the type of valvular surgery on exercise capacity are not known. Therefore, **chapter 8** focuses on exercise capacity and the effects of exercise training after valvular surgery according to the preoperative state, as assessed by the EuroSCORE, and to the type of surgery.

References

1. Piepoli M, Ponikowski P, Clark AL, Banasiak W, Capucci A and Coats AJ. A neural link to explain the "muscle hypothesis" of exercise intolerance in chronic heart failure. *Am Heart J*. 1999; 137: 1050-6.

2. Ponikowski P, Francis DP, Piepoli MF, et al. Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. *Circulation*. 2001; 103: 967-72.

3. Ponikowski PP, Chua TP, Francis DP, Capucci A, Coats AJ and Piepoli MF. Muscle ergoreceptor overactivity reflects deterioration in clinical status and cardiorespiratory reflex control in chronic heart failure. *Circulation*. 2001; 104: 2324-30.

4. Scott AC, Francis DP, Davies LC, Ponikowski P, Coats AJ and Piepoli MF. Contribution of skeletal muscle 'ergoreceptors' in the human leg to respiratory control in chronic heart failure. *The Journal of physiology*. 2000; 529 Pt 3: 863-70.

5. Tomita T, Takaki H, Hara Y, et al. Attenuation of hypercapnic carbon dioxide chemosensitivity after postinfarction exercise training: possible contribution to the improvement in exercise hyperventilation. *Heart (British Cardiac Society)*. 2003; 89: 404-10.

6. Tsurugaya H, Adachi H, Kurabayashi M, Ohshima S and Taniguchi K. Prognostic impact of ventilatory efficiency in heart disease patients with preserved exercise tolerance. *Circ J*. 2006; 70: 1332-6.

7. Piepoli M, Clark AL and Coats AJ. Muscle metaboreceptors in hemodynamic, autonomic, and ventilatory responses to exercise in men. *The American journal of physiology*. 1995; 269: H1428-36.

8. Mosterd A and Hoes AW. Clinical epidemiology of heart failure. *Heart*. 2007; 93: 1137-46.

9. Paulus WJ and van Ballegoij JJ. Treatment of heart failure with normal ejection fraction: an inconvenient truth! *J Am Coll Cardiol*. 2010; 55: 526-37.

10. Jonsson A, Edner M, Alehagen U and Dahlstrom U. Heart failure registry: a valuable tool for improving the management of patients with heart failure. *Eur J Heart Fail*. 2010; 12: 25-31.

11. Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol*. 2014; 63: 1123-33.

12. 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. *J Am Coll Cardiol*. 2013; 61: 1498-506.

13. Bjarnason-Wehrens B, McGee H, Zwisler AD, et al. Cardiac rehabilitation in Europe: results from the European Cardiac Rehabilitation Inventory Survey. *Eur J Cardiovasc Prev Rehabil*. 2010; 17: 410-8.

14. Worcester MU, Murphy BM, Mee VK, Roberts SB and Goble AJ. Cardiac rehabilitation programmes: predictors of non-attendance and drop-out. *Eur J Cardiovasc Prev Rehabil*. 2004; 11: 328-35.

3 Methodology

The analyses of this work are based on different datasets which are further explained in this section.

To gain insight in the working mechanism of the ergoreflex (chapter 3), a broad spectrum of patients was tested ranging from healthy subjects to CAD patients and HF patients in different stages of disease severity. These patients were recruited between April 2011 and March 2013 in two participating hospitals: AZ Maria Middelares Ghent and Onze-Lieve-Vrouw Hospital Aalst.

The BIO - Heart Failure (BIO-HF) registry was used to evaluate clinical characteristics and short-term outcome in hospitalized HF patients (chapter 4) as well as to analyze the participation rate in cardiac rehabilitation among HF patients (chapter 6). This Belgian ongoing prospective HF registry is the result of a cooperation since 2008 between the departments of cardiology of two hospitals (AZ Maria Middelares Ghent and University Hospital Brussels). The objective of this registry is to prospectively collect data regarding baseline characteristics, in-hospital treatments, medication at discharge and outcome for consecutive patients admitted with acute HF (NYHA III or IV). For the analysis concerning outcome, data from both hospitals were used. Data from AZ Maria Middelares Ghent were also used to evaluate the participation rate in CR among HF patients, by using both the BIO-HF registry and the Cardiac Rehabilitation database.

The Cardiac Rehabilitation database is a multidisciplinary registry, which was started in October 2007 in AZ Maria Middelares Ghent and since April 2011 simultaneously recorded in AZ Maria Middelares Ghent en Onze-Lieve-Vrouw Hospital Aalst. These data are prospectively collected at start and end of the rehabilitation program by the different disciplines (cardiologist, physiotherapist, social nurse, dietician and psychologist) and include medical background, medication use, laboratory results, exercise parameters, anthropometric measures, social and psychological characteristics of all patients entering CR, irrespective of the diagnosis. The aim of this project is to gain insight in the characteristics and pathologies of the diverse population that participates in CR, to study the effects of CR on different aspects of the patient's condition and to evaluate outcome regarding hospitalization and mortality. Data from AZ Maria Middelares Ghent were used for the analysis of the impact of neurohormonal activation on exercise capacity and training effects (chapter 5) . Data from both hospitals were analyzed to evaluate drop-out (chapter 7) and to study the effects of exercise training in VHD patients (chapter 8) .
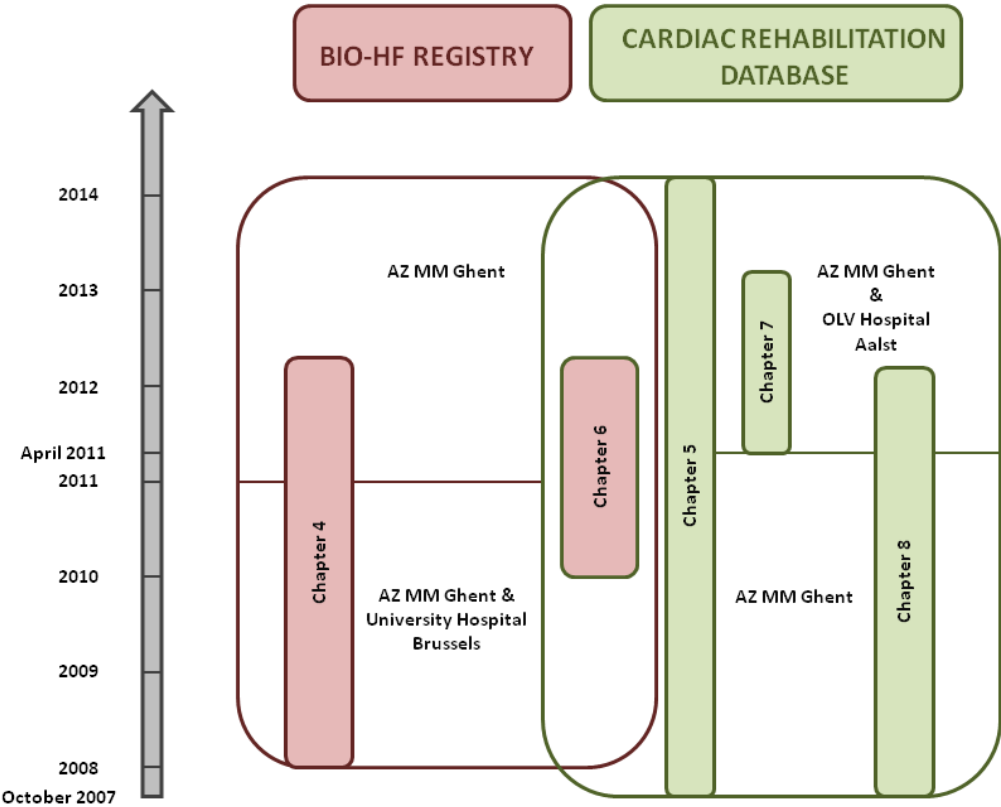
Figure 2. Overview of the two datasets used in this thesis. The timeline at the left side shows the period of data collection. The horizontal lines represent the time at which the cooperation with a participating hospital was started or ended. Studies based on the BIO-HF registry are indicated in red and studies based on the Cardiac Rehabilitation Database are indicated in green. The study in the middle of the figure is based on both datasets.

4 Research

Part 1.

Exercise intolerance in heart failure:

mechanisms and relevance of the ergoreflex

Chapter 1.

Development of heart failure and the role of the autonomic nervous system of the heart

Pardaens Sofie, De Sutter Johan

1   Introduction

Heart failure is a clinical syndrome that develops in response of a cardiac insult, resulting in a decline of cardiac performance. Several neurohormonal mechanisms are activated in response to the underlying myocardial dysfunction, including the sympathetic nervous system (SNS) and the renin-angiotensin-aldosteron axis (RAAS axis). Although the activation of these systems can initially compensate for the depressed myocardial function, their long-term activation results in a further impairment of cardiac function leading to progression of heart failure and cardiac decompensation.[1, 2]

As pointed out by Parati and Esler,[3] sympathetic activation occurs subsequently to the development of heart failure and then impacts adversely on clinical outcome. This is in contrast to essential hypertension where SNS activation is already important in the initiation and the maintenance of hypertension. Also, there is now clear evidence that besides sympathetic activation, also reduced vagal function plays a role in the development of heart failure.[4] In this chapter we will briefly review the normal cardiovascular actions of the autonomic nervous system (ANS) and then discuss the pathophysiology and potential therapeutic implications of sympathetic hyperactivity and reduced vagal function in heart failure.

2   The ANS and normal cardiac function

In the normal heart, the SNS has different cardiovascular actions, including acceleration of the heart rate, increase in cardiac contractility, reduction of venous capacitance and constriction of resistance vessels. The cardiac sympathetic nerve fibers are located subepicardially and travel along the major coronary arteries.[2, 5] The sympathetic outflow to the heart and peripheral circulation is regulated by cardiovascular reflexes. Afferent fibers are carried toward the central nervous system (CNS) by autonomic nerves, whereas efferent impulses travel from the CNS toward different organs. The main reflex responses originate from the aortic arch and carotid baroreceptors (SNS inhibition), cardiopulmonary baroreceptors (including the Bezold-Jarish reflex, SNS inhibition), cardiovascular low-threshold polymodal receptors (SNS activation) and peripheral chemoreceptors (SNS activation).[6] As already summarized by Van Stee,[7] the effect of SNS activation on the periphery is mediated by 4 pathways: (1) norepinephrine releasing neurons through the right stellate ganglion reaching the sinus and atrioventricular nodes (resulting in an increase in heart rate and shortening of atrioventricular conduction) and through the left stellate ganglion reaching the left ventricle (resulting in an increase in contractile strength), (2) epinephrine released in circulation by the adrenal

cortex affecting both the myocardium and peripheral vessels, (3) direct effect on peripheral vessels through local release of epinephrine and norepinephrine, (4) circulating norepinephrine which can act on multiple locations (e.g. increase in heart rate during exercise in heart transplant recipients). Norepinephrine and epinephrine bind to specific adrenergic receptors, of which there are at least 9 subtypes (3 alpha1-receptor subtypes, 3 alpha2-receptor subtypes and 3 beta-receptor subtypes). In the human heart, activation of beta1 and beta2 adrenergic receptors is the most powerful physiologic mechanism to acutely increase cardiac performance and the beta adrenergic receptor density is greatest at the apical myocardium.[8] Approximately 80% of norepinephrine released by the sympathetic nerve terminals is recycled by the norepinephrine transporter 1, whereas the remainder clears into the circulation.[9]

The parasympathetic nervous system affects the cardiovascular system by slowing heart rate through vagal impulses. The parasympathetic fibers run with the vagus nerve subendocardially, and are mainly present in the atrial myocardium and less abundantly in the ventricular myocardium.[2, 5] Acetylcholine released from post-ganglionic cardiac parasympathetic nerves reduces heart rate by binding to muscarinic cholinergic receptors (primarily M2 subtype) on sinoatrial nodal cells.[10, 11] Parasympathetic-mediated changes in heart rate are initiated primarily in the CNS or originate from activation or inhibition of sensory nerves. Stimulation of arterial baroreceptors, trigeminal receptors and subsets of cardiopulmonary receptors with vagal afferents, reflexively increase cardiovagal activity and decrease heart rate. In contrast, stimulation of pulmonary stretch receptors with vagal afferents and subsets of visceral and somatic receptors with spinal afferents reflexively decrease cardiovagal activity and increase heart rate.[12] Importantly, the parasympathetic nervous system and the SNS are often working interactively with opposing resulting effects.

3 Heart failure and sympathetic hyperactivity

3.1 Pathophysiology

Patients with heart failure are characterized by an abnormally activated sympathetic and altered parasympathetic tone, with also attenuated cardiovascular reflexes and a maladaptive downregulation of adrenergic nerve terminals.[13, 14] In the early changes of heart failure there is a selective cardiac change in the autonomic regulation with a decrease in heart rate variability and a selective increase in cardiac norepinephrine spillover in order to preserve cardiac output (CO). Chronic persistent myocardial dysfunction is associated with a more generalized sympathetic

hyperactivity. Evidence for this increased sympathetic activity in patients with heart failure includes increased central sympathetic outflow and increased norepinephrine spillover to plasma from activated sympathetic nerve fibers, and consequently increased plasma norepinephrine levels. Besides the increased muscle sympathetic nerve activity and norepinephrine spillover, patients with heart failure and reduced ejection fraction may also have a decreased neuronal density and a decreased neuronal function resulting in decreased norepinephrine concentration within the cardiomyocytes. Compared with myocardium of healthy individuals, the myocardium of patients with chronic left ventricular dysfunction is also characterized by a significant reduction of presynaptic norepinephrine uptake and postsynaptic beta1 adrenergic receptor density.[15, 16] This latter phenomenon has been documented in patients after acute myocardial infarction where it contributes to adverse left ventricular remodeling, in patients with heart failure due to dilated cardiomyopathy as well as in patients with hypertrophic cardiomyopathy who develop left ventricular dilatation and heart failure.[17-19] The increase in norepinephrine levels apparently results in a decrease in beta1 adrenergic receptor density and a beta1 adrenergic receptor desensitization which appears to be a predominantly protective adaptation. The role of cardiac beta2 and beta3 adrenergic receptors as well as cardiac alpha1 adrenergic receptors in heart failure has not been fully elucidated yet.[2]

3.2 Effects during exercise

Hemodynamic effects

During exercise, cardiovascular and respiratory responses are regulated by the ANS in order to provide a sufficient oxygen supply to the working muscles.[20] The balance between parasympathetic and sympathetic nerve activity is mediated by the interaction between the central command, originating from the central motor areas, and peripheral feedback afferents, including the baroreflex, chemoreflex, and ergoreflex.[20, 21] Sensory input from these cardiovascular afferents is projected to the nucleus tractus solitarius in the medulla oblongata, which plays a pivotal role in integrating and referring this information to other regions of the CNS with an impact on the sympathetic-parasympathetic outflow.[22]

Activation of the SNS during exercise normally induces a rise in heart rate and contractility resulting in an increased CO.[2] Together with local metabolic vasodilatation, increased CO amplifies the blood flow to the working muscles. Local vasodilatation is, however, partially restrained by a SNS mediated vasoconstriction in order to maintain an adequate level of blood pressure.[23]

Baroreceptors, located in the aortic arch and carotid sinuses,[24] are together with ergoreceptors, group III and IV skeletal muscle afferents,[25] responsible for these hemodynamic changes. Once activated, the main function of these baroreceptors is to maintain the arterial blood pressure at an adequate level (set point) by increasing or decreasing peripheral vasoconstriction.[24] During exercise, a rapid resetting of this set point occurs (towards a higher level) in order to allow a higher arterial pressure and increased blood flow to adjust to the increased metabolic demands.[22] Importantly, in a significant number of conditions, including coexisting sleep apnoea, myocardial ischemia, obesity and inflammation, additional nonbaroreflex mediated excitatory stimuli may elevate the set point for central sympathetic outflow or neurotransmitter release at rest and during exercise.

As metabolites accumulate during exercise and signal insufficient oxygen supply to the exercising muscles, ergoreceptors become activated and provide a rise in arterial pressure and blood flow primarily via an increased ventricular contractility and stroke volume with a resultant increase in CO.[21, 26, 27] The effect of the ergoreflex on heart rate has been a matter of debate. Some authors suggested that the ergoreflex has only a minor influence on HR.[28] However, when the mean arterial pressure is elevated, arterial baroreflex should decrease heart rate to lower mean arterial pressure.[29] As heart rate remains unchanged, the influence of the ergoreflex on heart rate regulation is thought to be masked by counterregulation of the arterial baroreflex.[30] During severe exercise the ability of the ergoreflex to elicit further increases in CO becomes limited. Pressor responses are then mediated via peripheral vasoconstriction, but are smaller in comparison with the contribution of CO.[31] In normal healthy subjects, ergoreflex activity is buffered by the arterial baroreflex. If this reflex is left unbuffered, than instead of a rise in CO, peripheral vasoconstriction in the active skeletal muscle is induced as a response to ergoreflex activation.[32]

Due to a chronic left ventricular dysfunction, a catabolic state is seen in heart failure with metabolic changes and chronic underperfusion of the skeletal muscle. A shift from type I to type IIb muscular fibers has been reported with a decrease in oxidative enzyme capacity and a concomitant rise in lactate and lactate dehydrogenase activity.[33, 34] Skeletal muscle apoptosis has also been described in heart failure and is thought to be triggered by pro inflammatory cytokines.[35, 36]

This altered muscle metabolism may elicit an accumulation of metabolic byproducts which results in a chronic activation of the ergoreceptors and subsequently sympathetic hyperactivity. Whereas in normal conditions the ergoreflex increases CO, a shift towards peripheral vasoconstriction is seen in heart failure, further limiting blood flow and exacerbating skeletal muscle abnormalities and fatigue complaints.[37, 38] The loss of the CO response likely reflects the impaired ability to increase ventricular

function[21, 31, 38] and the shift towards a peripheral vasoconstriction indicates a reduced baroreflex buffering in pathologic situations.[39]

Ventilatory effects

Apart from hemodynamic changes, ergoreceptors are also thought to take part in ventilatory responses during exercise. However, the role of these receptors in modulating ventilation in healthy subjects has been questioned due to conflicting results in the literature.[28, 40, 41] On the other hand, in patients with heart failure, an overactive ergoreflex mechanism has been demonstrated resulting in an excessive increase in ventilation and symptoms of breathlessness. A disruption of this reflex has been shown to correlate with several prognostic exercise parameters, including the peak VO_2 and the ventilatory slope.[40, 42, 43]

Chemoreceptors may also play a critical role in the increased ventilatory response in heart failure.[44, 45] According to their location, they are subdivided into central medullary and peripheral carotid afferents with the former being particularly sensitive to changes in CO_2 while the latter are activated in hypoxic conditions.[22] In patients with heart failure, enhanced hypoxic and central hypercapnic chemosensitivity has been described.[44-46] This hypersensitivity is associated with a higher incidence of arrhythmias, Cheyne-Stokes respiration and indicates a poor prognosis.[45] When the chemoreflex and ergoreflex are combined, the response to ventilation is greater than the sum of the two responses separately, suggesting that their interaction has an additional stimulatory effect on ventilation.[47]

In conclusion, in a generalized sympathetic state which is seen in patients with heart failure, an enhanced peripheral vasoconstriction occurs during exercise in order to preserve an adequate blood pressure level. Consequently, this limits blood flow in the exercising muscle and thereby further exacerbates muscular abnormalities. Concerning the ventilatory aspect, an inappropriate rise in ventilation is seen which is related to the complaints of breathlessness and indicates a poor prognosis. As such, sympathetic hyperactivity contributes to the downward vicious cycle characteristic for heart failure, with fatigue and dyspnoea being the major barriers for exercise tolerance.

3.3 Therapeutic implications

Medication

Several classes of medication can interact with the SNS and inhibit its activity in patients with heart failure. Chronic β blocker therapy has been extensively evaluated in patients with heart failure. Several large scale clinical trials have shown that bisoprolol, carvedilol, metoprolol succinate and nebivolol reverse left ventricular remodeling, reduce the risk of hospitalization and improve survival in patients with chronic heart failure.[48] This protective effect of β blockers is multifactorial and related to several factors, including the inhibition of catecholamine cardiotoxic effects, beta1 adrenergic receptor up regulation, attenuation of the RAAS-axis, subendocardial coronary flow enhancement and restoration of the reflex control on the heart and circulation.[2, 49] A meta-analysis in almost 20.000 patients demonstrated that the risk reduction with β blockers in patients with systolic heart failure was predominantly due to heart rate reduction achieved by β blockade rather than the type of β blockade, the dose of the β blockade, the underlying course of heart failure and many other potential confounders.[50]

The RAAS-axis is up regulated in heart failure and the resulting angiotensin-II and aldosterone production enhances the release and inhibits the uptake of norepinephrine at nerve endings. Because of this interaction with the SNS, a part of the beneficial effect of angiotensin-converting enzyme inhibitors and aldosterone antagonists in heart failure can probably be attributed to their effect on norepinephrine.[49] However not all medications that interact with the SNS have shown beneficial effects in patients with heart failure. Prazosin for example inhibits the alpha1 receptor but causes an increase in cathecholamine levels which probably explains a worse outcome in clinical trials.[51] Also, moxonidine that acts through both alpha2 and imidazolidine receptors and causes a marked dose-related reduction in plasma norepinephrine, was associated with an increased mortality in clinical trials.[52]

Device therapy

Cardiac resynchronization therapy (CRT) is an effective therapy in patients with advanced heart failure and electrical/mechanical dyssynchrony. Several large outcome studies have shown that this device therapy is associated with an improvement of symptoms, quality of life and survival.[48] Cha et al.[53] recently reported that CRT modulates sympathetic function by up regulating presynaptic receptor function as evidenced by increased iodine-123 metaiodobenzylguanidine ([123I]-MIBG)

imaging. Importantly, the reversal of neuronal remodeling in response to CRT appeared to be beyond that achieved by medical therapy. Also, patients with a less impaired presynaptic adrenergic preservation (or a better sympathetic reserve) showed a better response to CRT.

Exercise training

Exercise training has been demonstrated to improve exercise tolerance and quality of life, and reduce hospitalisations in heart failure.[54, 55] There is also limited evidence that exercise training reduces mortality. One of the responsible mechanisms for these beneficial effects is the counteraction of the sympathetic hyperactivity. Heart rate variability, beat to beat variations in time of consecutive heartbeats expressed in a normal sinus rhythm, is frequently used to evaluate the ANS.[56] Training has been shown to improve heart rate variability, indicating that the ANS and the sinoatrial node respond dynamically to environmental changes.[56-60]

Regular exercise reverses sympathetic hyperactivity in favor of exercise tolerance, through its influence on the different receptors which mediate the sympathico-vagal balance. Training effects have traditionally been attributed to peripheral rather than central adaptations. A (partial) reversal of structural abnormalities in skeletal muscle such as a decreased oxidative capacity, an impaired leg muscle blood flow with endothelial dysfunction and a glycolytic fiber type distribution, has been demonstrated after exercise training.[61-64] This reshift towards an aerobic metabolism may result in a decreased ergoreflex activity with a concomitant reduced activation of the sympathetic outflow.[42, 65, 66] Another effect of exercise training is the restoration of the blunted baroreflex sensitivity.[67, 68] The baroreflex is known to buffer the ergoreflex mediated vasoconstriction.[32] This buffering mechanism together with a reduced triggering of the ergoreceptors, results in an improved skeletal muscle blood flow which has a positive effect on fatigue complaints.

As ergoreflex activity is also known to influence ventilation, a decrease in its activation through exercise training, has a positive impact on the prognostic important ventilatory inefficiency, typically seen in patients with heart failure.[42] Exercise training also reduces chemoreceptor activity, another mediator of the ventilatory drive.[69]

Through its impact on the periphery, exercise training is able to influence the ANS thereby dealing with the two main reasons for exercise intolerance, dyspnoea and fatigue.

4   Heart failure and reduced vagal function

4.1   Pathophysiology

Dysfunction of the parasympathetic nervous system has been documented extensively in heart failure in both animal studies and humans. Already in 1971, Eckberg et al.[70] showed that arterial baroreflex control of heart rate was reduced in patients with left ventricular dysfunction. Moreover, altered vagal control of heart rate appears to be present early in the development of left ventricular dysfunction[71] and is associated with a poor prognosis in patients post myocardial infarction and heart failure.[72, 73] Despite the recognition of a reduced vagal control in heart failure and its association with worse outcomes, the precise anatomical sites and mechanisms of abnormal vagal control are not very clear.[4] The overall (limited) evidence suggests that the anatomical level of dysfunction seems to lie at the level of the ganglion since postganglionic mechanisms are up regulated and functional.[4] Different non-invasive techniques can be used to measure vagal nerve activity including resting heart rate, heart rate variability, baroreflex sensitivity and heart rate turbulence (for an extensive review, see[12]).

4.2   Effects during exercise

In normal subjects, vagal control results in a reduction in resting heart rate through its inhibitory effect on the SNS and hyperpolarization of the sinus nodal cells. Via a NO pathway, parasympathetic activation can cause vasorelaxation, but vasoconstriction through its action on vascular smooth muscle has also been described.[74] Apart from the bradycardic effect, a negative inotropic effect resulting in a decreased myocardial contractility has been demonstrated after vagal nerve stimulation.[75] As such, parasympathetic activity decreases the cardiac work and myocardial oxygen demand.[76]

Vagal function is blunted in heart failure[71, 77, 78] and is thought to originate from a withdrawal of baroreflex activity. As blood pressure falls in heart failure, baroreflex activity is reduced resulting in a decrease in the inhibitory input to adrenergic control.[79] Whereas in normal conditions, baroreceptor activity modulates chemoreceptor[80, 81] and ergoreflex activation,[32] this inhibition is impaired in heart failure, with a resultant increase in ergoreflex-mediated vasoconstriction[39] and a hyperventilatory response during exercise.[42-44]

4.3   Therapeutic implications

While β blockade has found its place as a corner stone therapy for heart failure that impacts the SNS, far less is known about medication and interventions that augment parasympathetic function.

Medication

Since there is a close interaction between the sympathetic and vagal nervous system, medical therapy that influences the SNS may also have an effect on the vagal nervous system. This has been shown both experimentally and clinically for β blockers in heart failure. They can augment the vagal nerve control of heart rate by blocking the cardiac sympathetic pre-junctional beta2 adrenoreceptor that facilitates norepinephrine release.[82] Also, they can increase the density of M2 receptors especially in the endocardial tissues of the left ventricle free wall, and change heart rate variability measurements, suggesting increased parasympathetic function.[83, 84] Accordingly, studies with ACE-inhibitors and angiotensin receptor blockers suggest an additional protective role by their reduction of angiotensine II, which potentiates sympathetic activity and blunts vagal inhibitory action. Also, spironolactone might have sympatholytic effects. In contrast, loop diuretics inducing transient disturbances in fluid balances, may cause a greater suppression of parasympathetic tone (for an in depth review of this issue see[85]).

Device therapy

The association between impaired vagal reflexes and increased cardiac mortality raised the possibility that increasing vagal activity could have a protective effect. This has been shown in different animal models by direct electrical stimulation of the right cervical vagus.[86-88] The first human experience of chronic vagal stimulation in patients with heart failure suggests that this treatment is feasible, safe and tolerable and leads to a subjective clinical improvement.[89] Potential mechanisms of a favorable effect include a heart rate mediated effect, anti-adrenergic effects (that may occur at the central level and at the peripheral level), anti-apoptotic effects, increase in NO and anti-inflammatory effects.[74, 90] Larger clinical trials are currently ongoing to further evaluate the safety and efficacy of vagus nerve stimulation in patients with heart failure.[91]

Exercise training

Numerous studies have demonstrated that exercise training increases heart rate variability and baroreflex sensitivity, indicating a restoration of the baroreflex function and the concomitant vagal activity.[59, 68, 92-95]

These training effects are thought to be related to the mediation of different neuromodulators of the parasympathetic nerve activity. A decrease in neuronal nitric oxide synthase (nNOS) has been shown in heart failure and may be involved in the parasympathetic withdrawal.[96] Another modulator is angiotensin II, which is known to inhibit vagal function through its action on the baroreflex function and to facilitate sympathetic activity.[97, 98] Exercise training increases NO bioavailability and endothelial function, and suppresses angiotensin II, thereby improving vagal function.[97, 99, 100] By restoring baroreflex function, exercise training limits the detrimental effects of ergoreflex and chemoreflex activity which results in improvements of exercise tolerance in patients suffering from heart failure.

5   References

1. Mann DL and Bristow MR. Mechanisms and models in heart failure: the biomechanical model and beyond. *Circulation*. 2005; 111: 2837-49.

2. Triposkiadis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G and Butler J. The sympathetic nervous system in heart failure physiology, pathophysiology, and clinical implications. *J Am Coll Cardiol*. 2009; 54: 1747-62.

3. Parati G and Esler M. The human sympathetic nervous system: its relevance in hypertension and heart failure. *Eur Heart J*. 2012; 33: 1058-66.

4. Bibevski S and Dunlap ME. Evidence for impaired vagus nerve activity in heart failure. *Heart Fail Rev*. 2011; 16: 129-35.

5. Zipes DP. Heart-brain interactions in cardiac arrhythmias: role of the autonomic nervous system. *Cleve Clin J Med*. 2008; 75 Suppl 2: S94-6.

6. Malliani A, Pagani M, Pizzinelli P, Furlan R and Guzzetti S. Cardiovascular reflexes mediated by sympathetic afferent fibers. *J Auton Nerv Syst*. 1983; 7: 295-301.

7. Van Stee EW. Autonomic innervation of the heart. *Environ Health Perspect*. 1978; 26: 151-8.

8. Leineweber K, Wangemann T, Giessler C, et al. Age-dependent changes of cardiac neuronal noradrenaline reuptake transporter (uptake1) in the human heart. *J Am Coll Cardiol*. 2002; 40: 1459.

9. Feldman DS, Carnes CA, Abraham WT and Bristow MR. Mechanisms of disease: beta-adrenergic receptors--alterations in signal transduction and pharmacogenomics in heart failure. *Nat Clin Pract Cardiovasc Med*. 2005; 2: 475-83.

10. Brodde OE, Bruck H, Leineweber K and Seyfarth T. Presence, distribution and physiological function of adrenergic and muscarinic receptor subtypes in the human heart. *Basic Res Cardiol*. 2001; 96: 528-38.

11. Katona PG, Lipson D and Dauchot PJ. Opposing central and peripheral effects of atropine on parasympathetic cardiac control. *Am J Physiol*. 1977; 232: H146-51.

12. Chapleau MW and Sabharwal R. Methods of assessing vagus nerve activity and reflexes. *Heart Fail Rev*. 2011; 16: 109-27.

13. Himura Y, Felten SY, Kashiki M, Lewandowski TJ, Delehanty JM and Liang CS. Cardiac noradrenergic nerve terminal abnormalities in dogs with experimental congestive heart failure. *Circulation*. 1993; 88: 1299-309.

14. Liang CS, Fan TH, Sullebarger JT and Sakamoto S. Decreased adrenergic neuronal uptake activity in experimental right heart failure. A chamber-specific contributor to beta-adrenoceptor downregulation. *J Clin Invest* 1989; 84: 1267-75.

15. Caldwell JH, Link JM, Levy WC, Poole JE and Stratton JR. Evidence for pre- to postsynaptic mismatch of the cardiac sympathetic nervous system in ischemic congestive heart failure. *J Nucl Med*. 2008; 49: 234-41.

16. Ungerer M, Bohm M, Elce JS, Erdmann E and Lohse MJ. Altered expression of beta-adrenergic receptor kinase and beta 1-adrenergic receptors in the failing human heart. *Circulation*. 1993; 87: 454-63.

17. Choudhury L, Rosen SD, Lefroy DC, Nihoyannopoulos P, Oakley CM and Camici PG. Myocardial beta adrenoceptor density in primary and secondary left ventricular hypertrophy. *Eur Heart J*. 1996; 17: 1703-9.

18. Merlet P, Delforge J, Syrota A, et al. Positron emission tomography with 11C CGP-12177 to assess beta-adrenergic receptor concentration in idiopathic dilated cardiomyopathy. *Circulation*. 1993; 87: 1169-78.

19. Spyrou N, Rosen SD, Fath-Ordoubadi F, et al. Myocardial beta-adrenoceptor density one month after acute myocardial infarction predicts left ventricular volumes at six months. *J Am Coll Cardiol*. 2002; 40: 1216-24.

20. Decherchi P, Dousset E and Jammes Y. Respiratory and cardiovascular responses evoked by tibialis anterior muscle afferent fibers in rats. *Exp Brain Res*. 2007; 183: 299-312.

21. O'Leary DS. Altered reflex cardiovascular control during exercise in heart failure: animal studies. *Exp Physiol*. 2006; 91: 73-7.

22. Dampney RA, Coleman MJ, Fontes MA, et al. Central mechanisms underlying short- and long-term regulation of the cardiovascular system. *Clin Exp Pharmacol Physiol*. 2002; 29: 261-8.

23. Khan MH and Sinoway LI. Muscle reflex control of sympathetic nerve activity in heart failure: the role of exercise conditioning. *Heart Fail Rev*. 2000; 5: 87-100.

24. Kougias P, Weakley SM, Yao Q, Lin PH and Chen C. Arterial baroreceptors in the management of systemic hypertension. *Med Sci Monit*. 2010; 16: RA1-8.

25. Kaufman MP, Longhurst JC, Rybicki KJ, Wallach JH and Mitchell JH. Effects of static muscular contraction on impulse activity of groups III and IV afferents in cats. *J Appl Physiol Respir Environ Exerc Physiol* 1983; 55: 105-12.

26. Crisafulli A, Scott AC, Wensel R, et al. Muscle metaboreflex-induced increases in stroke volume. *Med Sci Sports Exerc*. 2003; 35: 221-8; discussion 9.

27. Crisafulli A, Salis E, Pittau G, et al. Modulation of cardiac contractility by muscle metaboreflex following efforts of different intensities in humans. *Am J Physiol Heart Circ Physiol*. 2006; 291: H3035-42.

28. Piepoli M, Clark AL and Coats AJ. Muscle metaboreceptors in hemodynamic, autonomic, and ventilatory responses to exercise in men. *Am J Physiol*. 1995; 269: H1428-36.

29. Nishiyasu T, Tan N, Morimoto K, Nishiyasu M, Yamaguchi Y and Murakami N. Enhancement of parasympathetic cardiac activity during activation of muscle metaboreflex in humans. *J Appl Physiol*. 1994; 77: 2778-83.

30. Iellamo F, Pizzinelli P, Massaro M, Raimondi G, Peruzzi G and Legramante JM. Muscle metaboreflex contribution to sinus node regulation during static exercise: insights from spectral analysis of heart rate variability. *Circulation*. 1999; 100: 27-32.

31. Augustyniak RA, Collins HL, Ansorge EJ, Rossi NF and O'Leary DS. Severe exercise alters the strength and mechanisms of the muscle metaboreflex. *Am J Physiol Heart Circ Physiol*. 2001; 280: H1645-52.

32. Kim JK, Sala-Mercado JA, Rodriguez J, Scislo TJ and O'Leary DS. Arterial baroreflex alters strength and mechanisms of muscle metaboreflex during dynamic exercise. *Am J Physiol Heart Circ Physiol*. 2005; 288: H1374-80.

33. Mancini DM, Coyle E, Coggan A, et al. Contribution of intrinsic skeletal muscle changes to 31P NMR skeletal muscle metabolic abnormalities in patients with chronic heart failure. *Circulation*. 1989; 80: 1338-46.

34. Schaufelberger M, Eriksson BO, Grimby G, Held P and Swedberg K. Skeletal muscle alterations in patients with chronic heart failure. *Eur Heart J*. 1997; 18: 971-80.

35. Vescovo G and Dalla Libera L. Skeletal muscle apoptosis in experimental heart failure: the only link between inflammation and skeletal muscle wastage? *Curr Opin Clin Nutr Metab Care*. 2006; 9: 416-22.

36. Vescovo G, Volterrani M, Zennaro R, et al. Apoptosis in the skeletal muscle of patients with heart failure: investigation of clinical and biochemical changes. *Heart (British Cardiac Society)*. 2000; 84: 431-7.

37. Clark AL, Poole-Wilson PA and Coats AJ. Exercise limitation in chronic heart failure: central role of the periphery. *J Am Coll Cardiol*. 1996; 28: 1092-102.

38. Hammond RL, Augustyniak RA, Rossi NF, Churchill PC, Lapanowski K and O'Leary DS. Heart failure alters the strength and mechanisms of the muscle metaboreflex. *Am J Physiol Heart Circ Physiol*. 2000; 278: H818-28.

39. Kim JK, Sala-Mercado JA, Hammond RL, Rodriguez J, Scislo TJ and O'Leary DS. Attenuated arterial baroreflex buffering of muscle metaboreflex in heart failure. *Am J Physiol Heart Circ Physiol*. 2005; 289: H2416-23.

40. Piepoli M, Ponikowski P, Clark AL, Banasiak W, Capucci A and Coats AJ. A neural link to explain the "muscle hypothesis" of exercise intolerance in chronic heart failure. *Am Heart J*. 1999; 137: 1050-6.

41. Scott AC, Francis DP, Davies LC, Ponikowski P, Coats AJ and Piepoli MF. Contribution of skeletal muscle 'ergoreceptors' in the human leg to respiratory control in chronic heart failure. *J Physiol*. 2000; 529 Pt 3: 863-70.

42. Piepoli M, Clark AL, Volterrani M, Adamopoulos S, Sleight P and Coats AJ. Contribution of muscle afferents to the hemodynamic, autonomic, and ventilatory responses to exercise in patients with chronic heart failure: effects of physical training. *Circulation*. 1996; 93: 940-52.

43. Ponikowski P, Francis DP, Piepoli MF, et al. Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. *Circulation*. 2001; 103: 967-72.

44. Chua TP, Clark AL, Amadi AA and Coats AJ. Relation between chemosensitivity and the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol*. 1996; 27: 650-7.

45. Ponikowski P, Chua TP, Anker SD, et al. Peripheral chemoreceptor hypersensitivity: an ominous sign in patients with chronic heart failure. *Circulation*. 2001; 104: 544-9.

46. Ponikowski P, Chua TP, Piepoli M, et al. Augmented peripheral chemosensitivity as a potential input to baroreflex impairment and autonomic imbalance in chronic heart failure. *Circulation*. 1997; 96: 2586-94.

47. Lykidis CK, Kumar P and Balanos GM. The respiratory responses to the combined activation of the muscle metaboreflex and the ventilatory chemoreflex. *Adv Exp Med Biol*. 2009; 648: 281-7.

48. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2012; 14: 803-69.

49. Adamson PB and Gilbert EM. Reducing the risk of sudden death in heart failure with beta-blockers. *J Card Fail*. 2006; 12: 734-46.

50. McAlister FA, Wiebe N, Ezekowitz JA, Leung AA and Armstrong PW. Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. *Ann Intern Med*. 2009; 150: 784-94.

51. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med*. 1986; 314: 1547-52.

52. Cohn JN, Pfeffer MA, Rouleau J, et al. Adverse mortality effect of central sympathetic inhibition with sustained-release moxonidine in patients with heart failure (MOXCON). *Eur J Heart Fail*. 2003; 5: 659-67.

53. Cha YM, Chareonthaitawee P, Dong YX, et al. Cardiac sympathetic reserve and response to cardiac resynchronization therapy. *Circ Heart Fail*. 2011; 4: 339-44.

54. Flynn KE, Pina IL, Whellan DJ, et al. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. 2009; 301: 1451-9.

55. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. 2009; 301: 1439-50.

56. McMillan DE. Interpreting heart rate variability sleep/wake patterns in cardiac patients. *J Cardiovasc Nurs*. 2002; 17: 69-81.

57. Larsen AI, Gjesdal K, Hall C, Aukrust P, Aarsland T and Dickstein K. 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*. 2004; 11: 162-7.

58. Malfatto G, Branzi G, Riva B, Sala L, Leonetti G and Facchini M. Recovery of cardiac autonomic responsiveness with low-intensity physical training in patients with chronic heart failure. *Eur J Heart Fail*. 2002; 4: 159-66.

59. Murad K, Brubaker PH, Fitzgerald DM, et al. Exercise training improves heart rate variability in older patients with heart failure: a randomized, controlled, single-blinded trial. *Congestive heart failure (Greenwich, Conn)*. 2012; 18: 192-7.

60. Roveda F, Middlekauff HR, Rondon MU, et al. The effects of exercise training on sympathetic neural activation in advanced heart failure: a randomized controlled trial. *J Am Coll Cardiol*. 2003; 42: 854-60.

61. Hambrecht R, Niebauer J, Fiehn E, et al. Physical training in patients with stable chronic heart failure: effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. *J Am Coll Cardiol*. 1995; 25: 1239-49.

62. Hambrecht R, Fiehn E, Yu J, et al. Effects of endurance training on mitochondrial ultrastructure and fiber type distribution in skeletal muscle of patients with stable chronic heart failure. *J Am Coll Cardiol*. 1997; 29: 1067-73.

63. Hambrecht R, Fiehn E, Weigl C, et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. *Circulation*. 1998; 98: 2709-15.

64. Sullivan MJ, Higginbotham MB and Cobb FR. Exercise training in patients with severe left ventricular dysfunction. Hemodynamic and metabolic effects. *Circulation*. 1988; 78: 506-15.

65. Wang HJ, Pan YX, Wang WZ, et al. Exercise training prevents the exaggerated exercise pressor reflex in rats with chronic heart failure. *J Appl Physiol*. 2010; 108: 1365-75.

66. Wang HJ, Zucker IH and Wang W. Muscle reflex in heart failure: the role of exercise training. *Front Physiol.* 2012; 3: 398.

67. Gademan MG, Swenne CA, Verwey HF, et al. Effect of exercise training on autonomic derangement and neurohumoral activation in chronic heart failure. *J Card Fail*. 2007; 13: 294-303.

68. Iellamo F, Manzi V, Caminiti G, et al. Dose-response relationship of baroreflex sensitivity and heart rate variability to individually-tailored exercise training in patients with heart failure. *Int J Cardiol*. 2011.

69. Li YL, Ding Y, Agnew C and Schultz HD. Exercise training improves peripheral chemoreflex function in heart failure rabbits. *J Appl Physiol*. 2008; 105: 782-90.

70. Eckberg DL, Drabinsky M and Braunwald E. Defective cardiac parasympathetic control in patients with heart disease. *N Engl J Med*. 1971; 285: 877-83.

71. Kinugawa T and Dibner-Dunlap ME. Altered vagal and sympathetic control of heart rate in left ventricular dysfunction and heart failure. *Am J Physiol*. 1995; 268: R310-16.

72. Kleiger RE, Miller JP, Bigger JT, Jr. and Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol*. 1987; 59: 256-62.

73. La Rovere MT, Bigger JT, Jr., Marcus FI, Mortara A and Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet*. 1998; 351: 478-84.

74. Olshansky B, Sabbah HN, Hauptman PJ and Colucci WS. Parasympathetic nervous system and heart failure: pathophysiology and potential implications for therapy. *Circulation*. 2008; 118: 863-71.

75. Lewis ME, Al-Khalidi AH, Bonser RS, et al. Vagus nerve stimulation decreases left ventricular contractility in vivo in the human and pig heart. *J Physiol*. 2001; 534: 547-52.

76. Buch AN, Coote JH and Townend JN. Mortality, cardiac vagal control and physical training--what's the link? *Exp Physiol*. 2002; 87: 423-35.

77. Binkley PF, Nunziata E, Haas GJ, Nelson SD and Cody RJ. Parasympathetic withdrawal is an integral component of autonomic imbalance in congestive heart failure: demonstration in human subjects and verification in a paced canine model of ventricular failure. *J Am Coll Cardiol*. 1991; 18: 464-72.

78. Nolan J, Flapan AD, Capewell S, MacDonald TM, Neilson JM and Ewing DJ. Decreased cardiac parasympathetic activity in chronic heart failure and its relation to left ventricular function. *Br Heart J*. 1992; 67: 482-5.

79. Clark AL and Cleland JG. The control of adrenergic function in heart failure: therapeutic intervention. *Heart Fail Rev*. 2000; 5: 101-14.

80. Heistad D, Abboud FM, Mark AL and Schmid PG. Effect of baroreceptor activity on ventilatory response to chemoreceptor stimulation. *J Appl Physiol*. 1975; 39: 411-6.

81. Somers VK, Mark AL and Abboud FM. Interaction of baroreceptor and chemoreceptor reflex control of sympathetic nerve activity in normal humans. *J Clin Invest*. 1991; 87: 1953-7.

82. Kubo T, Parker JD, Azevedo ER, et al. Vagal heart rate responses to chronic beta-blockade in human heart failure relate to cardiac norepinephrine spillover. *Eur J Heart Fail*. 2005; 7: 878-81.

83. Goldsmith RL, Bigger JT, Bloomfield DM, et al. Long-term carvedilol therapy increases parasympathetic nervous system activity in chronic congestive heart failure. *Am J Cardiol*. 1997; 80: 1101-4.

84. Xu XL, Zang WJ, Lu J, Kang XQ, Li M and Yu XJ. Effects of carvedilol on M2 receptors and cholinesterase-positive nerves in adriamycin-induced rat failing heart. *Auton Neurosci*. 2006; 130: 6-16.

85. Desai MY, Watanabe MA, Laddu AA and Hauptman PJ. Pharmacologic modulation of parasympathetic activity in heart failure. *Heart Fail Rev*. 2011; 16: 179-93.

86. Li M, Zheng C, Sato T, Kawada T, Sugimachi M and Sunagawa K. Vagal nerve stimulation markedly improves long-term survival after chronic heart failure in rats. *Circulation*. 2004; 109: 120-4.

87. Sabbah HN, Wang M, Jiang A, Ruble SB and Hamann J. Right vagus nerve stimulation improves left ventricular systolic function in dogs with heart failure. *J Am Coll Cardiol*. 2010; 55: A16.E151.

88. Zhang Y, Popovic ZB, Bibevski S, et al. Chronic vagus nerve stimulation improves autonomic control and attenuates systemic inflammation and heart failure progression in a canine high-rate pacing model. *Circ Heart Fail*. 2009; 2: 692-9.

89. Schwartz PJ, De Ferrari GM, Sanzo A, et al. Long term vagal stimulation in patients with advanced heart failure: first experience in man. *Eur J Heart Fail*. 2008; 10: 884-91.

90. De Ferrari GM and Schwartz PJ. Vagus nerve stimulation: from pre-clinical to clinical application: challenges and future directions. *Heart Fail Rev*. 2011; 16: 195-203.

91. Hauptman PJ, Schwartz PJ, Gold MR, et al. Rationale and study design of the increase of vagal tone in heart failure study: INOVATE-HF. *Am Heart J*. 2012; 163: 954-62 e1.

92. Adamopoulos S, Ponikowski P, Cerquetani E, et al. Circadian pattern of heart rate variability in chronic heart failure patients. Effects of physical training. *Eur Heart J*. 1995; 16: 1380-6.

93. Coats AJ, Adamopoulos S, Radaelli A, et al. Controlled trial of physical training in chronic heart failure. Exercise performance, hemodynamics, ventilation, and autonomic function. *Circulation*. 1992; 85: 2119-31.

94. Kiilavuori K, Toivonen L, Naveri H and Leinonen H. Reversal of autonomic derangements by physical training in chronic heart failure assessed by heart rate variability. *Eur Heart J*. 1995; 16: 490-5.

95. Radaelli A, Coats AJ, Leuzzi S, et al. Physical training enhances sympathetic and parasympathetic control of heart rate and peripheral vessels in chronic heart failure. *Clin Sci (Lond)*. 1996; 91 Suppl: 92-4.

96. Nihei M, Lee JK, Honjo H, et al. Decreased vagal control over heart rate in rats with right-sided congestive heart failure: downregulation of neuronal nitric oxide synthase. *Circ J*. 2005; 69: 493-9.

97. Mousa TM, Liu D, Cornish KG and Zucker IH. Exercise training enhances baroreflex sensitivity by an angiotensin II-dependent mechanism in chronic heart failure. *J Appl Physiol*. 2008; 104: 616-24.

98. Townend JN, al-Ani M, West JN, Littler WA and Coote JH. Modulation of cardiac autonomic control in humans by angiotensin II. *Hypertension*. 1995; 25: 1270-5.

99. Hambrecht R, Wolf A, Gielen S, et al. Effect of exercise on coronary endothelial function in patients with coronary artery disease. *N Engl J Med*. 2000; 342: 454-60.

100. Kingwell BA. Nitric oxide as a metabolic regulator during exercise: effects of training in health and disease. *Clin Exp Pharmacol Physiol*. 2000; 27: 239-50.

Chapter 2.

Exercise intolerance in heart failure: update on exercise parameters for diagnosis, prognosis and therapeutic interventions

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Abstract

Exercise intolerance is a hallmark feature of chronic heart failure and is associated with poor prognosis. This review provides an update on cardiopulmonary exercise variables, proven to be prognostically important in heart failure. Besides the widely accepted peak oxygen consumption (peak VO_2) and VE/VCO_2 slope, other exercise variables – exercise oscillatory ventilation (EOV) and partial pressure of end-tidal CO_2 ($P_{ET}CO_2$) – should gain attention in the interpretation of cardiopulmonary exercise testing. In addition to prognosis, the pathophysiological origin is also discussed. Different mechanisms underlie these exercise variables with an important contribution of hemodynamic, pulmonary and peripheral abnormalities. Given the different pathophysiological origin, a multivariate assessment with the inclusion of all the aforementioned parameters should be encouraged, not only for diagnostic and prognostic purposes but also for evaluating the effect of interventions.

Keywords: heart failure, cardiopulmonary exercise testing, exercise intolerance, prognosis, diagnosis, intervention

1   Introduction

Heart failure is a syndrome, initiated by a reduction in cardiac function and mainly characterized by symptoms and signs which are the result of compensatory hemodynamic, autonomic and neurohormonal mechanisms.[1] Exercise intolerance is a hallmark feature of chronic heart failure and indicates a poor prognosis. This review provides an update on cardiopulmonary exercise variables which have proven to be prognostically important in heart failure.

2   Cardiopulmonary exercise parameters

2.1   Aerobic capacity: peak oxygen consumption

Originally, the heart was thought to be the major determinant of exercise intolerance. This presumption is partially true as exercise capacity, expressed by the peak oxygen consumption, is determined by cardiac output and the arterio-venous O_2 difference according to the Fick's principle. Since Stringer and his colleagues[2] demonstrated that the (A-V) O_2 difference was similar between normal subjects and heart failure patients, exercise intolerance in heart failure was assumed to be the result of an impaired cardiac function. This has, however, been questioned by others as there is only a weak correlation between resting measures of left ventricular function and exercise capacity.[3]

Since Mancini et al.[4] demonstrated its prognostic value in heart transplant candidates, peak oxygen consumption has become a widely accepted prognosticator. In contrast to healthy subjects who have a plateau in oxygen uptake in line with increasing workload (maximum oxygen uptake or VO_2 max), heart failure patients often do not achieve a plateau phase due to early occurrence of intolerable symptoms limiting exercise. Therefore, the term peak oxygen consumption (peak VO_2) has been used, calculated as the average oxygen consumption of the last 30 seconds of peak exercise (Figure 1A).[5]

During the last decade, this parameter appeared to have its drawbacks. Its predictive information is affected by the subject's effort and is limited in heart failure patients with an intermediate exercise tolerance, i.e. a peak VO_2 between 10 and 18ml.min^{-1}.kg^{-1}.[6] Moreover, the traditional cut point of 14ml.min^{-1}.kg^{-1} to indicate a heightened risk for mortality, did not seem to provide the same predictive information in female patients.[7] As β blockade has become a standard pharmacological intervention in recent years, the prognostic power of peak VO_2 in patients receiving β blockers, has

been questioned. Recent research in large study populations demonstrated that peak oxygen consumption is a determinant of survival, even in the setting of β blockade.[8, 9] Whether the threshold needs to be adjusted to the use of β blockers, is still a matter of debate. While some authors advise a downward adjustment of the traditional cut-off for an appropriate estimation of the risk,[8] others have found that the optimal prognostic threshold value (14 ml.min^{-1}.kg^{-1}) is similar between patients treated with or without β blockers.[9] Current guidelines recommend the use of the 4-level Weber classification of peak VO_2 for risk stratification in heart failure , with a peak VO_2 less than 10 ml.min^{-1}.kg^{-1} reflecting the worst prognosis (Table 1).[10]
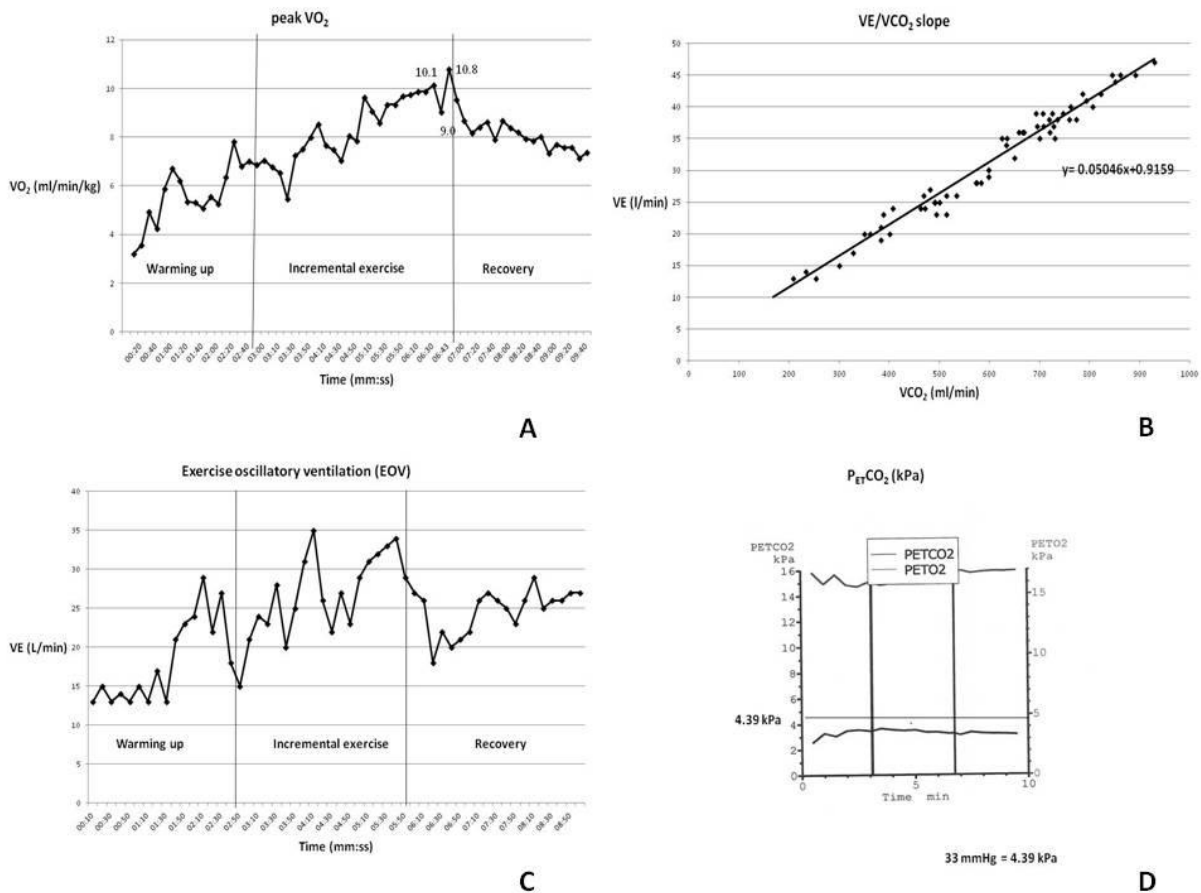
Figure 1. (A) Example of the peak oxygen consumption during exercise. Peak oxygen consumption is calculated as the average of the last 30 seconds of peak exercise. VO_2, oxygen consumption, peak VO_2, peak oxygen consumption. (B) Schematic representation of the linear increase in ventilation in response to a rising CO_2 production. The ventilatory slope is represented in the equation y=0.05046x+0.9159 as the slope = 50.46. VE/VCO_2 slope, ventilatory slope; VE, ventilation; VCO_2, carbon dioxide production. (C) Illustration of an oscillatory ventilation pattern during exercise. VE, ventilation. (D) Example of the partial pressure of end-tidal CO_2. The line at the bottom of the graph represents the $P_{ET}CO_2$. In this case, $P_{ET}CO_2$ is below the cut-off value of 33mmHg. $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide.

Table 1. Risk stratification and prognosis in chronic heart failure patients

Risk stratification and prognosis

	excellent prognosis low risk	→		progressively worse prognosis high risk
peak VO$_2$ Weber 1987	**Class A** >20.0 ml O2.kg-1.min-1 little or no evidence of heart failure	**Class B** 16.0-20.0 ml O2.kg-1.min-1 mild to moderate heart failure	**Class C** 10.0-15.9 ml O2.kg-1.min-1 moderate to severe heart failure	**Class D** <10.0 ml O2.kg-1.min-1 severe heart failure
VE/VCO$_2$ slope Arena 2007	**VCI** <30.0 neglible 2-year risk for adverse events <5%	**VC II** 30.0-35.9 low 2-year risk for adverse events ~15%	**VC III** 36.0-44.9 moderate 2-year risk for adverse events ~30%	**VC IV** ≥45.0 high 2-year risk for adverse events ~50%
peak VO$_2$ & VE/VCO$_2$ slope Arena 2010	↓ low risk for major cardiac events	↓ intermediate risk for major cardiac events		↓ high risk for major cardiac events
EOV	not present		present	
P$_n$CO$_2$	Resting PETCO2 ≥ 33.0 mmHg 3-8 mmHg increase during exercise		Resting PETCO2 <33.0 mmHg <3 nnHg increase during exercise	

EOV, exercise oscillatory ventilation; peak VO$_2$, peak oxygen consumption; P$_{ET}$CO$_2$, partial pressure end-tidal carbon dioxide; VE/VCO$_2$ slope, ventilatory slope; VC I, ventilatory class I; VC II, ventilatory class II; VC III, ventilatory class III; VC IV, ventilatory class IV.

2.2 Ventilatory inefficiency: the ventilatory slope

The limitations in the prognostic value of peak VO$_2$ have led to a search for novel prognostic parameters. As exercise ventilation inefficiency is a key characteristic in the complaints of heart failure patients, this phenomenon has gained attention.

The VE/VCO$_2$ slope describes the linear increase in ventilation in response to a rising CO$_2$ production (Figure 1B). Nevertheless, this relation is not linear during the whole exercise test. Beyond the respiratory compensation point, VE increases disproportionately to VCO$_2$ because it is driven both by CO$_2$ output and by a decrease in plasma pH when the buffering action of bicarbonates is exceeded.[11] Whether the calculation of the VE/VCO$_2$ slope from data of the early part of exercise provides equally prognostic power as data from the whole exercise test to peak exercise, has been an interesting point of discussion. Currently, there is important evidence in favour of the inclusion of the last part to peak exercise in the calculation of the VE/VCO$_2$ slope to optimize its prognostic sensitivity. The submaximal slope computed from the first 50% of the data points or below the respiratory compensation point, could provide a prognostic surrogate in those patients who are unable to perform a maximal test.[12]

Even though the peak oxygen consumption and the VE/VCO$_2$ slope seem to be related, there is no clear linear relation between these parameters (Figure 2). Different pathophysiological mechanisms have been proposed for elucidating the increased ventilatory demand. Using the modified alveolar equation VE/VCO$_2$ = 863/[PaCO$_2$ * (1-V$_D$/V$_T$)], the VE/VCO$_2$ slope can be explained by two main factors: the physiological dead space/tidal volume ratio (V$_D$/V$_T$) and the arterial CO$_2$ tension (PaCO$_2$). Early lactic acidosis has been proposed as an additional factor explaining the rise in ventilation.[13] However, this should rather be seen as being part of the change in arterial CO$_2$ tension, which will be discussed later in this review.

Increased dead space ventilation is a common finding in heart failure patients and is the result of injury to the lungs due to the backward hemodynamic effects of heart failure with a pressure and volume overload.[14] One of the disturbances occurring at the lung level is the development of a restrictive lung pattern with reductions in vital capacity and forced expiratory volume.[15] Also, disturbances in lung diffusion capacity are seen with a reduced alveolar-capillary membrane conductance.[16] A third plausible cause of an increased V$_D$/V$_T$ is a ventilation-perfusion mismatch with the blood flow distributed more to the upper part of the lungs in patients with a steep slope.[17]

Recent research has demonstrated an increased ventilatory drive with subsequent reductions in PaCO$_2$.[18] This hyperventilation is the second mechanism to explain ventilatory inefficiency in heart failure and is thought to originate from disturbances in the chemoreflex and the ergoreflex.
According to their location, chemoreceptors are subdivided into central medullary and peripheral carotid afferents with the former being particularly sensitive to changes in CO$_2$ while the latter are activated in hypoxic conditions.[19] In heart failure patients, enhanced hypoxic and central hypercapnic chemosensitivity has been described.[20] This hypersensitivity may play a critical role in the increased ventilatory response[20] and reflects a worse clinical status with a higher incidence of arrhythmias and Cheyne-Stokes respiration.[21] Moreover, it was found to be an independent predictor of death.[21]
Similar to the chemoreflex, overactivation of the ergoreflex has been proposed in chronic heart failure. Ergoreceptors are myelinated group-III and unmyelinated group-IV skeletal muscle afferents which are sensitive to mechanical deformations and metabolic products of the exercising muscles, respectively.[22] Several metabolites have been postulated as potential triggers, prostaglandins, bradykinins and a decrease in pH being the most important determinants.[23, 24] Endothelium impairment with a concomitant decreased muscle perfusion has also been linked to ergoreflex activation.[25] A disruption of this reflex has been shown to correlate with the ventilatory slope and is inversely related to the peak VO$_2$.[26] A link between the ergoreflex and the chemoreflex has been demonstrated, indicating a common mechanism of activation.[26] When these two reflexes are

combined, the response to ventilation is greater than the sum of the two responses separately, suggesting that their interaction has an additional stimulatory effect on ventilation.[27]

Besides the dead space ventilation and the arterial CO_2 tension, some authors have suggested that muscle deconditioning with concomitant early lactate acidosis is a third possible mechanism to explain the increased ventilatory demand.[13] However, it should rather be seen as a part of the so-called 'muscle hypothesis' with the ergoreflex playing a pivoting role. Due to a chronic left ventricular dysfunction, a catabolic state is seen in heart failure with metabolic changes and chronic underperfusion of the skeletal muscle. A shift from type-I to type-IIb muscular fibres has been reported with a decrease in oxidative enzyme capacity and a concomitant rise in lactate and lactate dehydrogenase activity.[28] This altered muscle metabolism may elicit an accumulation of metabolic byproducts which results in a chronic activation of the ergoreceptors. This enhanced activity causes an increase in the VE/VCO$_2$ slope with symptoms of breathlessness and sympathetic activation with an increased vascular resistance further exacerbating the skeletal muscle abnormalities and the fatigue complaints.[29]

Whether the hyperventilation or the increase in dead space ventilation is the most important determinant of ventilatory efficiency, has been discussed by several authors. While some of them argue there is an equal contribution of the two mechanisms,[30] Guazzi and his colleagues[18] demonstrated that a decrease in $PaCO_2$ at peak exercise retained a greater prognostic significance. Wensel et al.[30] described that the VE/VCO$_2$ ratio is predominantly related to the V_D/V_T ratio at rest and during aerobic exercise but as anaerobic metabolism ensues, the hyperventilatory response affects the VE/VCO$_2$ ratio. As such, hyperventilation leads to an increase in overall VE/VCO$_2$ slope. Since research has shown that the overall VE/VCO$_2$ slope is prognostically superior,[11] regulatory mechanisms involved in the tight control of ventilatory command and blood gas tension, rather than lung function abnormalities may play a critical pathophysiological role in the exercise ventilation inefficiency of CHF patients.[18] As literature shows that the overactive ergoreflex is more closely related to exercise tolerance than other autonomic indexes or reflexes, this mechanism arising from the periphery can be seen as the keystone in symptom generation and disease progression.[26]

Numerous studies have compared the VE/VCO$_2$ slope with the peak VO$_2$ to assess their value for predicting the risk for mortality and cardiovascular events. Arena et al.[31] recently analysed this extensive literature and resumed that the majority of these investigations indicated that the ventilatory response to exercise was superior to peak VO$_2$, not only in predicting mortality but also in providing additional information regarding hospitalisation. One study revealed that the VE/VCO$_2$

slope retained its prognostic significance up to 36 months whereas the peak VO_2 was related to adverse events for only 18 months.[32] Another strength of the slope is its potential to stratify the mortality risk in patients with intermediate exercise tolerance.[33] It should be noticed that the greater part of the current investigations concerned heart failure patients with a reduced ejection fraction. However, those who have focused on patients with preserved ejection fraction obtained similar findings.[34]

An abnormal slope is commonly identified as a value of more than 34. This threshold was originally introduced by Chua et al.[35] whose follow-up survey of 18 months demonstrated a survival rate of 95% in patients with a normal VE/VCO_2 slope compared with 69% in those with a high slope. Whether the use of β blockers affects the prognostic power of the ventilatory slope, has scarcely been studied. According to a study with 417 heart failure patients, it can be assumed that this parameter retains its prognostic significance, independently from the prescribed medication.[9]

Recently, the EACPR and AHA working group used the 4-level ventilatory classification to provide an appropriate risk stratification in heart failure, whereby a VE/VCO_2 slope higher than 45 is indicative of a particularly poor prognosis (Table 1).[10, 32]
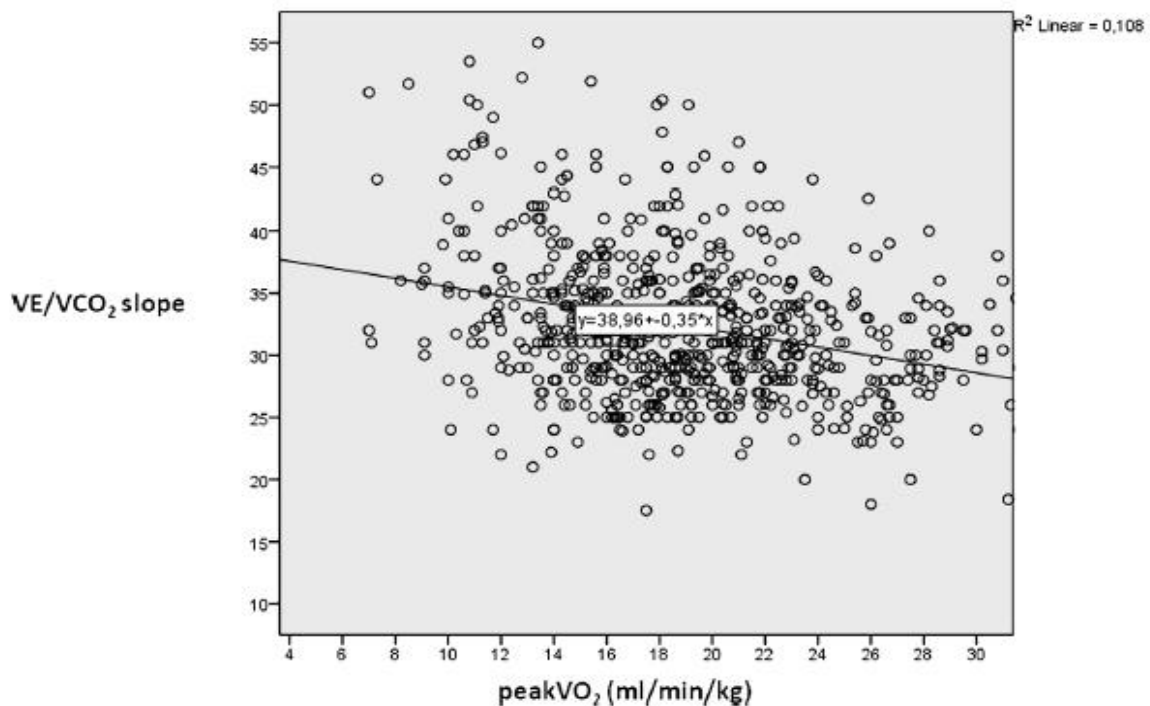

Figure 2. Illustration of the relationship between the peak oxygen consumption and the ventilatory slope. R^2 linear=0.108 represents a weak correlation between the two parameters. Peak VO_2, peak oxygen consumption; VE/VCO_2 slope, ventilatory slope.

2.3   A new marker of ventilatory inefficiency: exercise oscillatory ventilation (EOV)

A third parameter that recently gained more attention, is an irregular breathing pattern at rest that persists during exercise with cyclic fluctuations in minute ventilation and gas exchange kinetics, known as exercise oscillatory ventilation (Figure 1C).[10] This phenomenon is seen in 12 to 35% of heart failure patients.[36] The wide variation in prevalence may be due to the lack of unambiguous diagnostic criteria. The most commonly used definitions are those proposed by Corra[37] and Leite[38]. Both authors use the range and the amplitude of the ventilatory oscillations to describe this phenomenon but apply different practical cut-off values. Ingle et al.[36] evaluated the impact of the use of different criteria on the prevalence and prognostic significance of EOV and established that the prevalence varied between 25 and 31%, according to the Corra or the Leite criteria respectively. In addition, EOV using the Corra criteria, was a more powerful predictor of adverse outcome indicating the importance of the use of uniform criteria in future studies. The EACPR and AHA working group currently uses the definition of Corra to describe EOV as an oscillatory pattern at rest that persists for ≥60% of the exercise test at an amplitude of ≥15% of the average resting value (Table 1).[10, 37]

In contrast to the ventilatory slope, the origin of the oscillatory breathing pattern during exercise has been less explored. A recent study of Murphy et al.[39] demonstrated that the presence of EOV signals hemodynamic impairment during exercise as indicated by an impaired cardiac index and elevated filling pressures. While some authors suggest that a prolonged circulatory time between lung and chemoreceptors resulting in an imprecise control of respiration, is an important determinant of periodic breathing,[40] others have refuted this hypothesis.[41] A third potential mechanism is an increased chemoreceptor sensitivity,[42] although there is currently no consensus in literature.[39, 41] As the ergoreflex is linked to chemoreceptor sensitivity and periodic breathing is common in patients with disturbances in the muscle reflex, this peripheral feedback mechanism could also be a possible link to instability in exercise ventilation.[26] In conclusion, the presence of exercise oscillatory ventilation suggests a combination of an impaired hemodynamic function with disturbed autonomic reflex mechanisms.

The presence of EOV is always an abnormal ventilatory response to exercise and is associated with poor outcome. Although the majority of the studies focused on heart failure patients with a reduced ejection fraction, one study demonstrated a similar prevalence and prognostic value of oscillatory breathing in heart failure patients with a preserved ejection fraction.[43]
Both short-term follow-up of 6 months[44] as well as long-term investigations of 2 to 3 years[45-47] established that EOV is a strong predictor of poor prognosis and mortality. The presence of this

oscillatory breathing pattern might even have more predictive value than other prognosticators such as the peak VO_2 or the ventilatory slope.[45, 47] A recently published study by Guazzi et al.[45] assessed whether any additional prognostic indication may be obtained by combining an established cardiac biomarker such as N-terminal pro brain natriuretic peptide (NT-proBNP) and exercise ventilatory abnormalities assessed by cardiopulmonary exercise testing (CPET). Their conclusion was that NT-proBNP combined with EOV provided the highest level of risk prediction for cardiac outcome. The survival rate among patients with mild levels of neurohormonal activation but EOV was even worse than that observed in patients with the most unfavorable NT-proBNP but no EOV.

Although the pathogenetic bases for an increased ventilatory slope are in part similar to those proposed for the oscillatory gas kinetics, the presence of EOV does not necessarily imply an elevated ventilatory slope but when both are present, the burden of risk for cardiac death is considerably elevated.[47] Both ventilatory markers might also be different in predicting the mode of death. Whereas VE/VCO_2 slope was the strongest independent marker of cardiac pump failure events, exercise oscillatory breathing was the only exercise parameter providing predictive information on sudden cardiac death.[46]

2.4   Partial pressure of end-tidal CO_2 ($P_{ET}CO_2$)

Assessment of the partial pressure of end-tidal CO_2 ($P_{ET}CO_2$) as a prognostic exercise parameter has been strongly recommended by the current guidelines (Table 1).[10]

$P_{ET}CO_2$ is the CO_2 pressure which is non-invasively measured at the end of the expiration (Figure 1D). It reflects the elimination of carbon dioxide at rest and during exercise and represents, therefore, cardiac function and the matching of ventilation and perfusion within the pulmonary system.[10] If cardiac output (CO) is impaired, blood flow to the lungs is reduced resulting in a diminished carbon dioxide elimination, as expressed by a decreased $P_{ET}CO_2$. This presumption has been confirmed by several studies with a significant correlation between $P_{ET}CO_2$ and indicators of cardiac function.[48] A significant negative correlation with V_D/V_T ,a non-invasive indicator of ventilation-perfusion matching, was also found.[49] In the case of a ventilation-perfusion mismatch, which is not uncommon in heart failure, a steep line rather than a plateau phase is seen in $P_{ET}CO_2$, making the estimation of the absolute CO_2 pressure difficult. However, relative changes, e.g. after an intervention, are still interpretable. Besides cardiac function and ventilation-perfusion matching, a link with a decrease in the arterial CO_2 pressure has also been suggested.[50] Therefore, a reduced $P_{ET}CO_2$ is likely to be multifactorial with cardiac output, the enlarged physiologic dead space and the arterial CO_2 pressure being important mechanisms.

Under normal circumstances, resting values of 36-42 mmHg have been observed, with an increase between 3 and 8 mmHg at the ventilatory threshold.[10] A low resting $P_{ET}CO_2$, i.e. less than 33 mmHg, as well as a limited increase of $P_{ET}CO_2$ during exercise, particularly at the ventilatory threshold, is a marker of poor prognosis and predicts cardiac-related events and mortality independently from other exercise variables. Significant correlations with other prognostic parameters such as the peak VO_2 and the VE/VCO$_2$ slope have been demonstrated.[49]

3   Therapeutic possibilities: targets for the future

3.1   Pharmacological therapy

In the last two decades, pharmacological treatment has changed as β blocker therapy has become a standard of care in heart failure. The most remarkable effect of β blockade is seen in the decrease of the ventilatory slope,[51] which is in part the result of a reduction in peripheral chemosensitivity and ergoreflex activity. [52 51] On the other hand, the positive effect on diffusion capacity may also result in an improvement in ventilatory efficiency.[53]

Angiotensin converting enzyme (ACE) inhibitors may positively influence exercise capacity due to their vasodilatory characteristics. Early studies demonstrated that the use of ACE inhibitors improved the peak oxygen consumption.[54] This finding, however, was not supported by other authors who only saw a decrease in the ventilatory slope whereas the peak VO_2 remained unchanged.[55] The positive effects of the administration of ACE inhibitors and angiotensin receptor blockers were not seen in heart failure with a preserved ejection fraction.[56]

A greater availability of nitric oxide (NO) due to phosphodiesterase 5 inhibition with sildenafil, is a relatively novel treatment strategy in chronic heart failure. Sildenafil has been shown to improve cardiac output (CO), to reduce the pulmonary vasomotor tone and to improve the diffusion capacity, resulting in an increase in peak VO_2 with a concomitant decrease of the ventilatory inefficiency and a reversal of the oscillatory breathing pattern.[57, 58] Whether sildenafil influences the ventilatory reflex mechanisms, has not been fully investigated. However, one author revealed that an improvement in endothelial activity and muscle perfusion through phosphodiesterase 5 inhibition, resulted in a decrease in ergoreflex activity which was related to an improvement in aerobic capacity and ventilatory efficiency.[59, 60] These improvements in exercise capacity, however, have not been confirmed in heart failure patients with preserved ejection fraction.[61]

3.2   Exercise training

Physical training has become an important part of heart failure management since it has been demonstrated to improve exercise tolerance and quality of life, and to reduce hospitalisation in heart failure. There is also limited evidence that exercise training reduces mortality.[62] An increase in peak oxygen consumption and a consonant decrease in the VE/VCO_2 slope has been widely recognized.[63] A recently published study has provided evidence that exercise training may also decrease or even reverse exercise oscillatory ventilation.[64] Literature concerning the influence of exercise training on $P_{ET}CO_2$ in heart failure is lacking. A study in patients following physical training after acute myocardial infarction, however, suggests that improvement in $P_{ET}CO_2$ with a concomitant increase in cardiac index is possible.[65] Despite some improvements in left ventricular function, peripheral adaptations are thought to be primarily responsible for the enhanced exercise tolerance in heart failure after exercise training.

A reduction in both muscle mass and muscle quality has been observed in heart failure patients, commonly referred as 'heart failure myopathy' and is related to an impaired exercise capacity. This myopathy is characterized by apoptosis, a shift towards glycolytic type-II fibres with a concomitant rise in lactate and lactate dehydrogenase activity, a depressed oxidative enzyme capacity and a lower mitochondrial volume.[28, 66] In addition, insulin resistance and a pro-inflammatory state which are typically seen in heart failure, contribute to the anabolic/catabolic imbalance.[67] Physical training has been shown to counteract several features of this myopathy with a shift towards type-I fibre distribution, an increase in oxidative enzyme capacity and mitochondrial density.[68] A reduction in local expression of inflammatory cytokines has also been demonstrated after exercise training.[69] The shift towards an aerobic metabolism may result in a decreased ergoreflex and chemoreflex activity, with a concomitant decrease in hyperventilation, exercise oscillatory ventilation and sympathetic outflow.[64, 70]

Endothelial dysfunction, due to a decreased nitric oxide (NO) bioavailability, is another key feature in chronic heart failure. Exercise training improves the endothelium mediated vasodilation with a concomitant increase in leg blood flow and exercise capacity. In addition, by decreasing peripheral vascular resistance and ventricular afterload, small but significant improvements in stroke volume and a reduction in cardiomegaly has been demonstrated.[71]

Besides these peripheral changes, training also induces alterations that occur at the lung level with an increase in alveolar-capillary membrane diffusion capacity which may contribute to an improved ventilatory efficiency.[72]

3.3   Devices

Cardiac resynchronization therapy (CRT) was introduced in order to restore the abnormal electrical activation which is frequently seen in patients with advanced heart failure. Conduction abnormalities, such as a left bundle-branch block, are known to be responsible for mechanical dyssynchrony with an impaired ejection fraction and mitral regurgitation as a result. Besides these haemodynamic consequences, conduction disturbances also take part in the ventricular remodelling process.[73] Implantation of a CRT device has been demonstrated to improve ventricular function, symptoms, exercise tolerance and quality of life and to substantially reduce the risk for mortality and hospitalisation.[74]

Although several studies reported an improvement of peak oxygen consumption and the distance walked in six minutes, fewer studies evaluated the ventilatory slope. However, trials which also included the VE/VCO_2 slope consistently reported an improvement in both aerobic capacity and ventilatory efficiency.[75] According to Piepoli and his colleagues, improvement in exercise capacity occurs 12 months after implantation whereas cardiac indices restore already after 6 months, indicating the importance of peripheral changes.[76] These peripheral changes include the restoration of the neurohormonal reflex control with a particular emphasis on the ergoreflex.[76, 77] An additional beneficial effect on exercise tolerance is seen when CRT implantation is followed by exercise training.[78] This finding further emphasizes the importance of the peripheral adaptations.

4   Conclusions

Cardiopulmonary exercise testing is a well recognised instrument for the evaluation of exercise intolerance in CHF. Besides the peak VO_2 and the VE/VCO_2 slope, other exercise variables – EOV and $P_{ET}CO_2$ - should gain attention in the interpretation of CPET. As mentioned in this review, VE/VCO_2 slope and EOV have been demonstrated to be superior in providing prognostic information. Although less known in literature, $P_{ET}CO_2$ seems to be also a promising variable. Given the different physiological origin of these 4 exercise variables, a multivariate assessment with the inclusion of all the aforementioned parameters should be encouraged , not only for diagnostic and prognostic purposes but also for evaluating the effect of interventions.

5 References

1. Cowie MR, Mosterd A, Wood DA, et al. The epidemiology of heart failure. *Eur Heart J.* 1997; 18: 208-25.

2. Stringer WW, Hansen JE and Wasserman K. Cardiac output estimated noninvasively from oxygen uptake during exercise. *J Appl Physiol.* 1997; 82: 908-12.

3. Franciosa JA, Park M and Levine TB. Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. *Am J Cardiol.* 1981; 47: 33-9.

4. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH, Jr. and Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation.* 1991; 83: 778-86.

5. Task force of the Italian Working Group on Cardiac Rehabilitation and Prevention (Gruppo Italiano di Cardiologia Riabilitativa e Prevenzione, GICR), Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology. Statement on cardiopulmonary exercise testing in chronic heart failure due to left ventricular dysfunction: recommendations for performance and interpretation Part III: Interpretation of cardiopulmonary exercise testing in chronic heart failure and future applications. E*ur J Cardiovasc Prev Rehabil.* 2006; 13: 485-94.

6. Kao W, Winkel EM, Johnson MR, Piccione W, Lichtenberg R and Costanzo MR. Role of maximal oxygen consumption in establishment of heart transplant candidacy for heart failure patients with intermediate exercise tolerance. *Am J Cardiol.* 1997; 79: 1124-7.

7. Corra U, Mezzani A, Giordano A, et al. Peak oxygen consumption and prognosis in heart failure 14mL/kg/min is not a "gender-neutral" reference. *Int J Cardiol.* 2013; 167: 157-61.

8. O'Neill JO, Young JB, Pothier CE and Lauer MS. Peak oxygen consumption as a predictor of death in patients with heart failure receiving beta-blockers. *Circulation.* 2005; 111:2313-8.

9. Arena RA, Guazzi M, Myers J and Abella J. The prognostic value of ventilatory efficiency with beta-blocker therapy in heart failure. *Med Sci Sports Exerc.* 2007; 39:213-9.

10. Guazzi M, Adams V, Conraads V, et al. EACPR/AHA Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation*. 2012; 126: 2261-74.

11. Tabet JY, Beauvais F, Thabut G, Tartiere JM, Logeart D and Cohen-Solal A. A critical appraisal of the prognostic value of the VE/VCO2 slope in chronic heart failure. *Eur J Cardiovasc Prev Rehabil.* 2003; 10: 267-72.

12. Ingle L, Goode K, Carroll S, et al. Prognostic value of the VE/VCO2 slope calculated from different time intervals in patients with suspected heart failure. *Int J Cardiol.* 2007; 118: 350-5.

13. Tumminello G, Guazzi M, Lancellotti P and Pierard LA. Exercise ventilation inefficiency in heart failure: pathophysiological and clinical significance. *Eur Heart J.* 2007; 28: 673-8.

14. Guazzi M. Alveolar-capillary membrane dysfunction in heart failure: evidence of a pathophysiologic role. *Chest.* 2003;124(3):1090-102.

15. Wasserman K, Zhang YY, Gitt A, et al. Lung function and exercise gas exchange in chronic heart failure. *Circulation.* 1997; 96: 2221-7.

16. Guazzi M, Reina G, Tumminello G and Guazzi MD. Alveolar-capillary membrane conductance is the best pulmonary function correlate of exercise ventilation efficiency in heart failure patients. *Eur J Heart Fail.* 2005; 7: 1017-22.

17. Wada O, Asanoi H, Miyagi K, et al. Importance of abnormal lung perfusion in excessive exercise ventilation in chronic heart failure. *Am Heart J.* 1993; 125: 790-8.

18. Guazzi M, Reina G, Tumminello G and Guazzi MD. Exercise ventilation inefficiency and cardiovascular mortality in heart failure: the critical independent prognostic value of the arterial CO2 partial pressure. *Eur Heart J.* 2005; 26: 472-80.

19. Dampney RA, Coleman MJ, Fontes MA, et al. Central mechanisms underlying short- and long-term regulation of the cardiovascular system. *Clin Exp Pharmacol Physiol.* 2002; 29: 261-8.

20. Chua TP, Clark AL, Amadi AA and Coats AJ. Relation between chemosensitivity and the ventilatory response to exercise in chronic heart failure.*J Am Coll Cardiol.* 1996; 27: 650-7.

21. Ponikowski P, Chua TP, Anker SD, et al. Peripheral chemoreceptor hypersensitivity: an ominous sign in patients with chronic heart failure. *Circulation.* 2001; 104: 544-9.

22. Kaufman MP, Longhurst JC, Rybicki KJ, Wallach JH and Mitchell JH. Effects of static muscular contraction on impulse activity of groups III and IV afferents in cats. *J Appl Physiol.* 1983; 55: 105-12.

23. Scott AC, Wensel R, Davos CH, et al. Skeletal muscle reflex in heart failure patients: role of hydrogen. *Circulation.* 2003; 107:300-6.

24. Scott AC, Wensel R, Davos CH, et al. Chemical mediators of the muscle ergoreflex in chronic heart failure: a putative role for prostaglandins in reflex ventilatory control. *Circulation*. 2002; 106: 214-20.

25. Guazzi M, Berti M, Belletti S, Reina G and Guazzi MD. Exercise metaboreflex activation and endothelial function impairment in atrial fibrillation. *Am J Physiol Heart Circ Physiol.* 2006; 291: H2396-402.

26. Ponikowski PP, Chua TP, Francis DP, Capucci A, Coats AJ and Piepoli MF. Muscle ergoreceptor overactivity reflects deterioration in clinical status and cardiorespiratory reflex control in chronic heart failure. *Circulation.* 2001; 104:2324-30.

27. Lykidis CK, Kumar P and Balanos GM. The respiratory responses to the combined activation of the muscle metaboreflex and the ventilatory chemoreflex. *Adv Exp Med Biol.* 2009; 648: 281-7.

28. Schaufelberger M, Eriksson BO, Grimby G, Held P and Swedberg K. Skeletal muscle alterations in patients with chronic heart failure. *Eur Heart J.* 1997; 18: 971-80.

29. Clark AL, Poole-Wilson PA and Coats AJ. Exercise limitation in chronic heart failure: central role of the periphery. *J Am Coll Cardiol.* 1996; 28: 1092-102.

30. Wensel R, Georgiadou P, Francis DP, et al. Differential contribution of dead space ventilation and low arterial pCO2 to exercise hyperpnea in patients with chronic heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol.* 2004; 93: 318-23.

31. Arena R, Myers J and Guazzi M. The clinical and research applications of aerobic capacity and ventilatory efficiency in heart failure: an evidence-based review. *Heart Fail Rev*. 2008; 13: 245-69.

32. Arena R, Myers J, Abella J, et al. Defining the optimal prognostic window for cardiopulmonary exercise testing in patients with heart failure. *Circ Heart Fail.* 2010; 3: 405-11.

33. Corra U, Mezzani A, Bosimini E, Scapellato F, Imparato A and Giannuzzi P. Ventilatory response to exercise improves risk stratification in patients with chronic heart failure and intermediate functional capacity. *Am Heart J.* 2002; 143: 418-26.

34. Guazzi M, Myers J and Arena R. Cardiopulmonary exercise testing in the clinical and prognostic assessment of diastolic heart failure. *J Am Coll Cardiol.* 2005; 46: 1883-90.

35. Chua TP, Ponikowski P, Harrington D, et al. Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol.* 1997; 29: 1585-90.

36. Ingle L, Isted A, Witte KK, Cleland JG and Clark AL. Impact of different diagnostic criteria on the prevalence and prognostic significance of exertional oscillatory ventilation in patients with chronic heart failure. *Eur J Cardiovasc Prev Rehabil.* 2009; 16: 451-6.

37. Corra U, Giordano A, Bosimini E, et al. Oscillatory ventilation during exercise in patients with chronic heart failure: clinical correlates and prognostic implications. *Chest.* 2002; 121: 1572-80.

38. Leite JJ, Mansur AJ, de Freitas HF, et al. Periodic breathing during incremental exercise predicts mortality in patients with chronic heart failure evaluated for cardiac transplantation. *J Am Coll Cardiol.* 2003; 41: 2175-81.

39. Murphy RM, Shah RV, Malhotra R, et al. Exercise oscillatory ventilation in systolic heart failure: an indicator of impaired hemodynamic response to exercise. *Circulation.* 2011; 124: 1442-51.

40. Hall MJ, Xie A, Rutherford R, Ando S, Floras JS and Bradley TD. Cycle length of periodic breathing in patients with and without heart failure. *Am J Respir Crit Care Med.* 1996; 154: 376-81.

41. Agostoni P, Apostolo A and Albert RK. Mechanisms of periodic breathing during exercise in patients with chronic heart failure. *Chest.* 2008; 133: 197-203.

42. Ponikowski P, Anker SD, Chua TP, et al. Oscillatory breathing patterns during wakefulness in patients with chronic heart failure: clinical implications and role of augmented peripheral chemosensitivity. *Circulation.* 1999; 100: 2418-24.

43. Guazzi M, Myers J, Peberdy MA, Bensimhon D, Chase P and Arena R. Exercise oscillatory breathing in diastolic heart failure: prevalence and prognostic insights. *Eur Heart J.* 2008; 29: 2751-9.

44. Sun XG, Hansen JE, Beshai JF and Wasserman K. Oscillatory breathing and exercise gas exchange abnormalities prognosticate early mortality and morbidity in heart failure. *J Am Coll Cardiol.* 2010; 55: 1814-23.

45. Guazzi M, Boracchi P, Labate V, et al. Exercise oscillatory breathing and NT-proBNP levels in stable heart failure provide the strongest prediction of cardiac outcome when combining biomarkers with cardiopulmonary exercise testing. *J Card Fail.* 2012; 18: 313-20.

46. Guazzi M, Raimondo R, Vicenzi M, et al. Exercise oscillatory ventilation may predict sudden cardiac death in heart failure patients. *J Am Coll Cardiol.* 2007; 50: 299-308.

47. Guazzi M, Arena R, Ascione A, Piepoli M and Guazzi MD. Exercise oscillatory breathing and increased ventilation to carbon dioxide production slope in heart failure: an unfavorable combination with high prognostic value. *Am Heart J.* 2007; 153: 859-67.

48. Matsumoto A, Itoh H, Eto Y, et al. End-tidal CO2 pressure decreases during exercise in cardiac patients: association with severity of heart failure and cardiac output reserve. *J Am Coll Cardiol*. 2000; 36: 242-9.

49. Arena R, Peberdy MA, Myers J, Guazzi M and Tevald M. Prognostic value of resting end-tidal carbon dioxide in patients with heart failure. *Int J Cardiol*. 2006; 109: 351-8.

50. Wasserman K, Zhang YY and Riley MS. Ventilation during exercise in chronic heart failure. *Basic Res Cardiol.* 1996; 91 Suppl 1:1-11.

51. Agostoni P, Guazzi M, Bussotti M, De Vita S and Palermo P. Carvedilol reduces the inappropriate increase of ventilation during exercise in heart failure patients. *Chest.* 2002; 122: 2062-7.

52. Agostoni P, Contini M, Magini A, et al. Carvedilol reduces exercise-induced hyperventilation: A benefit in normoxia and a problem with hypoxia. *Eur J Heart Fail*. 2006; 8: 729-35.

53. Agostoni P, Contini M, Cattadori G, et al. Lung function with carvedilol and bisoprolol in chronic heart failure: is beta selectivity relevant? *Eur J Heart Fail*. 2007; 9: 827-33.

54. Guazzi M, Marenzi G, Alimento M, Contini M and Agostoni P. Improvement of alveolar-capillary membrane diffusing capacity with enalapril in chronic heart failure and counteracting effect of aspirin. *Circulation.* 1997; 95: 1930-6.

55. Kitaoka H, Takata J, Hitomi N, et al. Effect of angiotensin-converting enzyme inhibitor (enalapril or imidapril) on ventilation during exercise in patients with chronic heart failure secondary to idiopathic dilated cardiomyopathy. *Am J Cardiol.* 2000; 85: 658-60.

56. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med.* 2008; 359: 2456-67.

57. Guazzi M, Vicenzi M, Arena R, et al. Phosphodiesterase 5 inhibition with sildenafil reverses exercise oscillatory breathing in chronic heart failure: a long-term cardiopulmonary exercise testing placebo-controlled study. *Eur J Heart Fail.* 2012; 14: 82-90.

58. Guazzi M, Tumminello G, Di Marco F, Fiorentini C and Guazzi MD. The effects of phosphodiesterase-5 inhibition with sildenafil on pulmonary hemodynamics and diffusion capacity, exercise ventilatory efficiency, and oxygen uptake kinetics in chronic heart failure. *J Am Coll Cardiol* 2004; 44: 2339-48.

59. Guazzi M, Casali M, Berti F, Rossoni G, Colonna VD and Guazzi MD. Endothelium-mediated modulation of ergoreflex and improvement in exercise ventilation by acute sildenafil in heart failure patients. *Clin Pharmacol Ther*. 2008; 83: 336-41.

60. Guazzi M, Samaja M, Arena R, Vicenzi M and Guazzi MD. Long-term use of sildenafil in the therapeutic management of heart failure. *J Am Coll Cardiol.* 2007; 50: 2136-44.

61. Redfield MM, Chen HH, Borlaug BA, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA.* 2013; 309: 1268-77.

62. Flynn KE, Pina IL, Whellan DJ, et al. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA.* 2009; 301: 1451-9.

63. Pina IL, Apstein CS, Balady GJ, et al. Exercise and heart failure: A statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. *Circulation*. 2003; 107: 1210-25.

64. Zurek M, Corra U, Piepoli MF, Binder RK, Saner H and Schmid JP. Exercise training reverses exertional oscillatory ventilation in heart failure patients. *Eur Respir J*. 2012; 40: 1238-44.

65. Eto Y, Koike A, Matsumoto A, et al. Early aerobic training increases end-tidal CO2 pressure during exercise in patients after acute myocardial infarction. *Circ J.* 2004; 68: 778-83.

66. Vescovo G, Volterrani M, Zennaro R, et al. Apoptosis in the skeletal muscle of patients with heart failure: investigation of clinical and biochemical changes. *Heart*. 2000; 84: 431-7.

67. Conraads VM, Van Craenenbroeck EM, De Maeyer C, Van Berendoncks AM, Beckers PJ and Vrints CJ. Unraveling new mechanisms of exercise intolerance in chronic heart failure: role of exercise training. *Heart Fail Rev*. 2013; 18:65-77.

68. Hambrecht R, Fiehn E, Yu J, et al. Effects of endurance training on mitochondrial ultrastructure and fiber type distribution in skeletal muscle of patients with stable chronic heart failure. *J Am Coll Cardiol.* 1997; 29: 1067-73.

69. Gielen S, Adams V, Mobius-Winkler S, et al. Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. *J Am Coll Cardiol*. 2003; 42: 861-8.

70. Piepoli M, Clark AL, Volterrani M, Adamopoulos S, Sleight P and Coats AJ. Contribution of muscle afferents to the hemodynamic, autonomic, and ventilatory responses to exercise in patients with chronic heart failure: effects of physical training. *Circulation.* 1996; 93: 940-52.

71. Hambrecht R, Gielen S, Linke A, et al. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: A randomized trial. *JAMA.* 2000; 283: 3095-101.

72. Guazzi M, Reina G, Tumminello G and Guazzi MD. Improvement of alveolar-capillary membrane diffusing capacity with exercise training in chronic heart failure. *J Appl Physiol.* 2004; 97: 1866-73.

73. Holzmeister J and Leclercq C. Implantable cardioverter defibrillators and cardiac resynchronisation therapy. *Lancet.* 2011; 378: 722-30.

74. McAlister FA, Ezekowitz J, Hooton N, et al. Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systematic review. *JAMA.* 2007; 297: 2502-14.

75. Varma C, Sharma S, Firoozi S, McKenna WJ and Daubert JC. Atriobiventricular pacing improves exercise capacity in patients with heart failure and intraventricular conduction delay. *J Am Coll Cardiol.* 2003; 41: 582-8.

76. Piepoli MF, Villani GQ, Corra U, Aschieri D and Rusticali G. Time course of effects of cardiac resynchronization therapy in chronic heart failure: benefits in patients with preserved exercise capacity. *Pacing Clin Electrophysiol.* 2008; 31: 701-8.

77. Jaussaud J, Aimable L, Bordachar P, et al. Cardiac resynchronization therapy reduces metaboreflex contribution to the ventilatory response in heart failure population. *Cardiol Res Pract.* 2012; 2012:914071.

78. Patwala AY, Woods PR, Sharp L, Goldspink DF, Tan LB and Wright DJ. Maximizing patient benefit from cardiac resynchronization therapy with the addition of structured exercise training: a randomized controlled study. *J Am Coll Cardiol.* 2009; 53: 2332-9.

Chapter 3.

Activation of the ergoreceptors in cardiac patients with and without heart failure

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Abstract

Background: The presence of ergoreflex activity and its current relation to hyperventilation and prognosis in cardiac patients is unclear. Therefore, we evaluated ergoreflex activity in cardiac patients with and without heart failure (CHF) as well as in healthy subjects, and we examined how strong ergoreceptor activity was related to a mortality risk score in CHF (MAGGIC).

Methods and results: Twenty-five healthy subjects and 76 patients were included, among whom were 25 with ischemic heart disease (IHD), 24 with stable CHF, and 27 with unstable CHF. Ergoreflex activity was measured with a dynamic handgrip exercise, followed by post-handgrip regional circulatory occlusion (PH-RCO). Ergoreflex activity contributed significantly to ventilation (median [interquartile range] %V) in unstable CHF (81 [73 − 91] %V without PH-RCO, 92 [82 − 107] %V with PH-RCO, and 11 [6 − 20] difference in %V, $p < 0.001$) and was positively correlated with the MAGGIC risk score (Spearman $\rho = 0.431$, p=0.002). No ergoreflex activity was observed in healthy subjects (-4 [-10 to 5] difference in %V), IHD (0 [-8 to 3] difference in %V) and stable CHF (-3 [-11 to 6] difference in %V).

Conclusions: Ergoreflex activity contributes to hyperventilation, but only in CHF patients with persistent symptoms and is closely related to the MAGGIC risk score. Ergoreflex activity was not present in patients with IHD or stable CHF, suggesting other reasons for the increased ventilatory drive in those patients.

Keywords: ergoreflex, ventilation, MAGGIC risk score, heart failure, ischemic heart disease, healthy subjects

1   Introduction

Chronic heart failure (CHF) has been mainly characterized by exercise intolerance with symptoms of fatigue and breathlessness,[1] with the latter being expressed by ventilatory inefficiency during exercise. A steep ventilatory slope has not only been demonstrated with CHF, but also with ischemic heart disease (IHD) [2] with a similar prognostic value.[3]

Overactivity of the ergoreceptors, i.e. skeletal muscle afferents, has been shown to contribute to the excessive ventilatory response in CHF, with a detrimental impact on prognosis.[4-8] Pharmacological treatment has changed over the last decades, with neurohormonal agents being recommended in CHF with reduced left ventricular ejection fraction (LVEF) because of their beneficial effect on hospitalization and premature death.[9] Despite their obvious effect on survival, their influence on exercise intolerance and its determinants is less clear.

Notwithstanding the presence of an increased ventilatory slope in a substantial number of patients with IHD, information on the ergoreflex is currently lacking. Also in healthy subjects, the role of the ergoreflex in ventilatory control remains rather unclear, with some studies reporting a contribution of the ergoreflex to ventilation and others stating there is no involvement.[4, 5, 7, 10]

Therefore, the primary aim of this study was to evaluate the presence of ergoreflex activity and its current relation to the ventilatory response to exercise and exercise intolerance in a broad spectrum of subjects, ranging from healthy subjects and patients with IHD to stable and unstable CHF patients. In addition, we examined how activity of the ergoreceptors was related to a recently validated prognostic risk score in CHF patients, developed by the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC).[11]

2   Methods

2.1   Study population

Twenty-nine healthy subjects and 76 patients were prospectively included from April 2011 to March 2013. Healthy subjects were free from clinical signs or history of heart disease, diabetes, or pulmonary disease. A 1st patient group consisted of patients who had an ischemic event without signs of heart failure >1 month preceding the study (IHD, n=25), a 2nd group were stable heart failure patients with reduced LVEF (≤45%) who had an episode of decompensation >1 month preceding the

study and had no signs of fluid retention on the moment of testing (stable CHF, n=24). A third group consisted of heart failure patients with reduced LVEF (≤45%) who were recently decompensated (<1 mo) and were still symptomatic despite optimal medical treatment (unstable CHF, n=27). Heart failure patients with ischemic or nonischemic heart disease and who were treated according to the recommendations of the European Society of Cardiology (ESC) regarding medication -β-blocker, angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and mineralocorticoid receptor antagonist (MRA)- and devices[9] were included. Seriously limiting musculoskeletal or neurologic disorders such as recent orthopedic surgery (<6 mo), rheumatoid arthritis or a cerebrovascular accident (CVA) with potential influence of the performance of the tests, were considered to be exclusion criteria.

2.2 Ethics

This study protocol was approved by the local ethical committees of the two participating hospitals (AZ Maria Middelares, Ghent, and Onze-Lieve-Vrouw Hospital, Aalst) and each of the participants gave informed consent. The clinical investigations were conducted according to the principles of the Declaration of Helsinki.

2.3 Risk score calculation

An integer risk score for predicting mortality was calculated in CHF patients (n=51), with the use of the online calculator from the MAGGIC group.[11] The following predictors were included in the risk calculation: age, sex, diabetes, chronic obstructive pulmonary disease (COPD), time since diagnosis, current smoker, New York Heart Association (NYHA) class, the use of β blockers and ACE inhibitors or ARB, body mass index (BMI), systolic blood pressure at rest, serum creatinine, and LVEF. A progressively higher risk score identified an increased risk for mortality within 1 and 3 years, expressed as the median [interquartile range]. According to the cumulative mortality risk over 3 years, patients were categorized into 6 risk groups in the original study.[11] Because of the small sample in the present study, CHF patients were classified into 3 risk groups: 24 patients were classified as having a low risk with a score ≤20 (1-y risk 6% [4% - 9%], 3-y risk 15% [11% - 22%]), 14 patients had a medium risk with a score 21 – 28 (1-y risk 15% [12% - 18%], 3-y risk 36% [29% - 40%]) and 13 patients had a high risk with a score >28 (1-y risk 32% [25% - 46%], 3-y risk 63% [52% - 79%]).

2.4 Ergoreflex activity

Before the test, maximal handgrip force was measured with the nondominant arm as the greatest of the peak forces produced by 3 brief maximal handgrip contractions with a Baseline pneumatic squeeze dynamometer. Ergoreflex activity was evaluated with the post-handgrip regional circulatory occlusion (PH-RCO) method, consisting of 2 parts which were performed in random order. Ventilatory parameters were measured (Cortex Metalyzer 3B breath-by-breath analysis) during 3 minutes of resting, followed by a rhythmic handgrip exercise at 50% of the predetermined maximal capacity until exhaustion (30 squeezes/min) and a recovery period of 3 minutes. After a pause of 30 minutes, the same exercise protocol was used, but followed by 3 minutes of blood flow stasis in the exercising arm by inflation of a forearm tourniquet 30mmHg above systolic pressure (PH-RCO). After the cuff was inflated, the subject was instructed to relax. Four of the 29 healthy subjects complained of pain or serious discomfort and were excluded from further analysis. This protocol has been shown to isolate the metabolic state of the muscle and to prolong the activation of the ergoreceptors.[10, 12] Because the performance was not equal during the 2 parts of the tests with a difference in peak exercise, ergoreflex activity was expressed as the percentage exercise response that was maintained during PH-RCO (2nd and 3rd minutes) compared with the percentage exercise response maintained during normal recovery (2nd and 3rd minutes).[4] The difference between these 2 percentages represents the contribution of the ergoreflex activity to the ventilatory parameters (Fig 1).

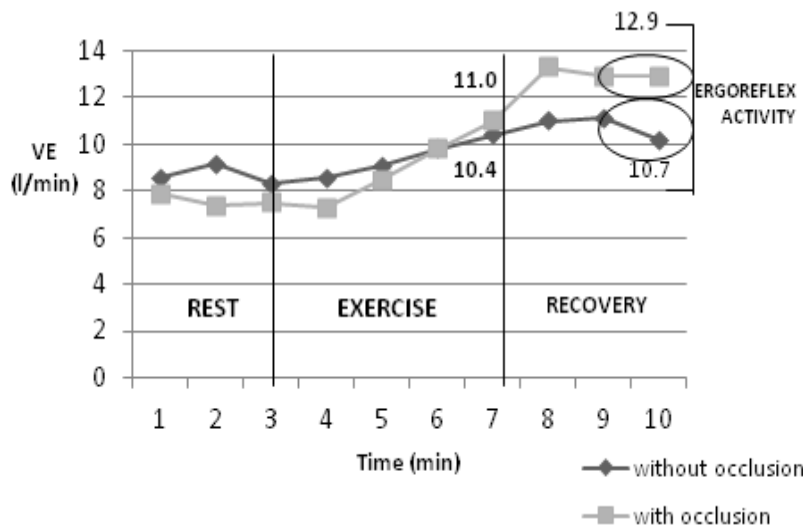**Figure 1.** Measurement of ergoreflex activity. Ergoreflex activity is expressed as the percentage exercise response that is maintained during recovery with occlusion (12.9/11.0 = 117%) compared with the percentage exercise response maintained during recovery without occlusion (10.7/10.4 = 103%). The difference between these 2 percentages represents the contribution of the ergoreflex activity to ventilation (difference in %V = 14%)

2.5   Exercise testing

Cardiopulmonary exercise testing was performed on a cyclo-ergometer with the use of a protocol adapted to the subjects' physical status. Ventilatory and respiratory gas measurements were obtained on a breath-by-breath basis with the use of an Oxycon Pro spirometer (Jaeger – Viasys Healthcare, Germany). Heart rate (HR) was continuously registered with the use of a 12-lead electrocardiography, and blood pressure was noninvasively measured, with the use of a manual sphygmanometer every 2 minutes during the exercise test. Patients and healthy subjects exercised to the limits of their functional capacities or until the physician stopped the test because of adverse events, such as chest pain, dizziness, potentially life-threatening arrhythmias, ST segment deviations, and marked systolic hypotension or hypertension. The maximal achieved load during incremental exercise was recorded. Peak oxygen consumption (peak VO_2) was defined as the mean of the last 30 seconds of peak exercise and was expressed as $ml.min^{-1}.kg^{-1}$. The slope of the linear relation between VE (y-axis) and VCO_2 (x-axis), the VE/VCO_2 slope, was calculated by including all data points to the end of exercise. A classification according to tertiles of peak VO_2 (<14 – 14-17 – ≥ 18 $ml.min^{-1}.kg^{-1}$) and to ventilatory classes of VE/VCO_2 slope [13] (<30 – 30-35 – 36-44 – ≥ 45) was made for evaluating ergoreflex activity by measures of exercise tolerance.

2.6   Statistical methods

Statistical analysis was performed with the use of IBM SPSS Statistics for Windows, Version 21.0 (IBM, Armonk, New York). Overall differences in clinical characteristics and exercise capacity between the three patient groups were assessed with the χ^2 test or Fisher exact test for proportions and Kruskal Wallis test for continuous variables. A level of alpha of 0.05 was used to indicate statistical significance. The Mann-Whitney U test was used to further evaluate differences in continuous variables between the individual patient groups. In the latter analyses, the inflation of type I error due to multiple comparisons was taken into account by considering an alpha level of 0.01 to indicate statistical significance. Ergoreflex activity within healthy subjects and in each patient group separately was evaluated with the use of the Wilcoxon matched-pairs signed-ranks test. Differences in ergoreflex activity between the patient groups were compared with the use of the Kruskal-Wallis test and Mann-Whitney U test. No comparison with healthy subjects was made, because this was not a matched control group. Because age was significantly different between the individual patient groups, ergoreflex activity was further evaluated in patient groups stratified by the median age (64 y). A similar analysis was performed to assess the influence of COPD on ergoreflex activity in unstable CHF patients. The Kruskal-Wallis test and the Mann-Whitney U test were also

used to evaluate ergoreflex activity according to groups of MAGGIC score, peak VO_2 and VE/VCO_2 slope. The relationship between ergoreflex activity and prognostic parameters was assessed with Spearman bivariate correlations.

3 Results

3.1 Clinical characteristics

Clinical characteristics of the patient groups are presented in Table 1; 85% of the total patient population were men and their median age was 64 [interquartile range 53 – 72] years. Unstable CHF patients were older than stable CHF and IHD patients (overall p<0.001) and had a lower BMI (p<0.01) than patients with IHD. LVEF was significantly different among the 3 groups (overall p<0.001), with the lowest values in the group with unstable CHF. The group with unstable CHF was also more symptomatic, with 45% of the patients in NYHA functional class III or IV (p<0.01). Calculation of the MAGGIC risk score in heart failure patients resulted in a significantly higher risk score (median [interquartile range]) in unstable CHF (26 [22 – 33] vs 15 [11 – 20], p<0.001). Worse exercise capacity was also seen in unstable CHF, as expressed by a progressively lower load and peak VO_2 and a higher VE/VCO_2 slope (overall p<0.001). Of the healthy subjects, 56% were men and their median age was 45 years. Only a small number of them had cardiovascular risk factors; 4% had hypertension, 17% had hyperlipidemia and 1 (4%) was an active smoker on the moment of testing. None of the healthy subjects took heart disease-related medication, except for 1 who took aspirin. Exercise capacity was found to be normal with a median peak VO_2 of 33 $ml.min^{-1}.kg^{-1}$ and a VE/VCO_2 slope of 28.

3.2 Ergoreflex activity in healthy subjects and patients

As presented in Table 2, ergoreflex activity was present only in unstable CHF, with a significant contribution of the ergoreflex to ventilation (p<0.001). Ventilation during recovery with PH-RCO was 11% higher than during normal recovery and this was likely the result of the higher breathing frequency (p=0.001). Healthy subjects and IHD and stable CHF patients showed no sign of ergoreflex contribution to their ventilatory pattern. Similar results were obtained when patients were first stratified according to their age. Ergoreflex activity was present only in unstable CHF, both in patients younger and older than 64 years (Supplement 1). Supplementary analyses in unstable CHF according to the presence of COPD showed ergoreflex activation in both patient groups regardless of COPD (Supplement 2).

Table 1. Clinical characteristics

	Healthy subjects n=25	IHD n=25	Stable CHF n=24	Unstable CHF n=27	Diff between patient groups: P value
Age (years)	45 [35,57]	62 [55,68]	55 [48,64]	71 [65,79][a,d]	<0.001
Men (%)	56	84	91	85	0.761
BMI (kg/m²)	24 [23,26]	28 [26,30]	27 [25,30]	25 [24,28][a]	0.010
CAD (%)		100	71[e]	67[a]	0.007
Etiology CHF (%)					0.813
Ischemic			62	59	
Non ischemic			38	41	
LVEF (%)		67 [62,73]	30 [24,37][f]	25 [17,30][b,c]	<0.001
NYHA class (%)					<0.001
I		92	25[f]	0[b,d]	
II		8	75	55	
III		0	0	41	
IV		0	0	4	
Risk factors & comorbidities (%)					
Hypertension	4	76	50	56	0.142
Hyperlipidemia	17	96	75	78	0.092
Diabetes	0	28	29	37	0.746
Smoking	4	16	29	7	0.026
COPD	0	0	8	30[a]	0.003
AF during hospitalisation		20	42	41	0.188
Systolic BP at rest (mmHg)	130 [120,140]	125 [120,130]	110 [110,124][e]	110 [105,120][a]	0.005
Creatinine (mg/dl)		0.99 [0.89,1.13]	1 [0.90,1.43]	1.33 [1.02,1.67][a]	0.007
HF diagnosed last 18 months (%)			54	37	<0.001
Medication (%)					
Aspirin	4	100	38[f]	52[b]	<0.001
B blockers	0	88	88	70	0.194
ACE-inhibitors/ ARB	0	60	83	82	0.106
Diuretics	0	12	67[f]	89[b]	<0.001
Spironolacton	0	0	88[f]	93[b]	<0.001
Antiarrhythmic drugs	0	4	17	11	0.374
Digoxin	0	0	17	22	0.035
Exercise capacity					
Maximal load (Watt)	168 [147,250]	125 [108,153]	110 [88,143]	74 [51,80][b,d]	<0.001
Peak VO$_2$ (ml.min^{-1}.kg^{-1})	33 [26,38]	19 [17,22]	17 [12,20]	12 [10,14][b,c]	<0.001
VE/VCO$_2$ slope	28 [25,30]	33 [28,36]	35 [32,39]	44 [36,50][a,c]	0.001

Continuous variables are presented as median [interquartile range], categorical variables are presented as percentage.

IHD, ischemic heart disease; CHF, chronic heart failure; Diff, difference; BMI, body mass index; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; BP, blood pressure; HF, heart failure; ACE-inhibitors, Angiotensin Converting Enzyme inhibitors; ARB, Angiotensin Receptor Blockers; peak VO$_2$, peak oxygen consumption

[a]p<0.01 [b]p<0.001, unstable CHF vs IHD patients
[c]p<0.01 [d]p<0.001, unstable CHF vs stable CHF patients
[e]p<0.01 [f]p<0.001, stable CHF vs IHD patients

Table 2. Ergoreflex activity in healthy subjects and patients

	Healthy subjects n=25	IHD n=25	Stable CHF n=24	Unstable CHF n=27	Diff in % exercise response between the patient groups: P value
Ventilation (V)					
% without PH-RCO	84 [79,95]	85 [76,88]	86 [81,91]	81 [73,91]	
% with PH-RCO	83 [78,90]	81 [76,86]	85 [75,93]	92 [82,107]	
P value	0.174	0.326	0.458	<0.001	
Diff in %V	-4 [-10,5]	0 [-8,3]	-3 [-11,6]	11 [6,20][a,c]	<0.001
Breathing frequency (BF)					
% without PH-RCO	90 [72,96]	84 [74,100]	90 [81,100]	85 [76,83]	
% with PH-RCO	81 [68,92]	88 [79,95]	85 [79,93]	95 [83,117]	
P value	0.069	0.427	0.376	0.001	
Diff in %BF	-5 [-12,1]	5 [-9,15]	-5[-9,6]	8 [0,18][b]	0.013
Tidal volume (VT)					
% without PH-RCO	97 [88,118]	97 [86,104]	95 [89,104]	96 [84-103]	
% with PH-RCO	100 [91,123]	94 [84,100]	97 [83,106]	96 [83-109]	
P value	0.397	0.122	0.932	0.719	
Diff in %VT	4 [-8,13]	-1 [-19,5]	2 [-12,14]	5 [-12,10]	0.235

Variables are presented as median [interquartile range]. IHD, ischemic heart disease; CHF, chronic heart failure; Diff, difference; PH-RCO, post-handgrip regional circulatory occlusion; V, ventilation; Diff in %V, difference in percentage ventilation; BF, breathing frequency; Diff in %BF, difference in percentage breathing frequency; VT, tidal volume; Diff in %VT, difference in percentage tidal volume.
[a] p<0.001 unstable CHF vs. IHD [b]p<0.01 unstable CHF vs. stable CHF [c]p<0.001 unstable CHF vs. stable CHF

When patients were subdivided according to their peak VO_2, a difference in ergoreflex activity was found between patients who had a peakVO$_2$ ≥14 ml.min^{-1}.kg^{-1} and patients with a peak VO_2 <14 ml.min^{-1}.kg^{-1} (overall p<0.05). A classification according to the ventilatory classes of the VE/VCO$_2$ slope, revealed a difference in the activity of the ergoreceptors between patients who had a ventilatory slope ≥45 and those with a VE/VCO$_2$ slope below this value (overall p<0.05). Ergoreflex activity according to diagnosis, peak VO_2, and VE/VCO$_2$ slope is represented in Figure 2.

In the total patient group, ergoreflex contribution to ventilation was negatively correlated with LVEF (Spearman ρ=-0.298, p=0.018) and peak VO_2 (Spearman ρ=-0.276, p=0.028). No correlation was found with the VE/VCO$_2$ slope. When the patient population was subdivided according to the VE/VCO$_2$ slope (≤34 and >34), correlations were more pronounced in patients with an elevated VE/VCO$_2$ slope compared with the total patient group (LVEF, Spearman ρ=-0.353; p=0.030, peak VO_2, Spearman ρ=-0.588, p<0.001; VE/VCO$_2$ slope, Spearman ρ=0.455, p=0.004). In contrast, in patients with a VE/VCO$_2$ slope <34, no significant correlations with LVEF, peak VO_2, or VE/VCO$_2$ slope were demonstrated. These findings are shown in Figure 3.
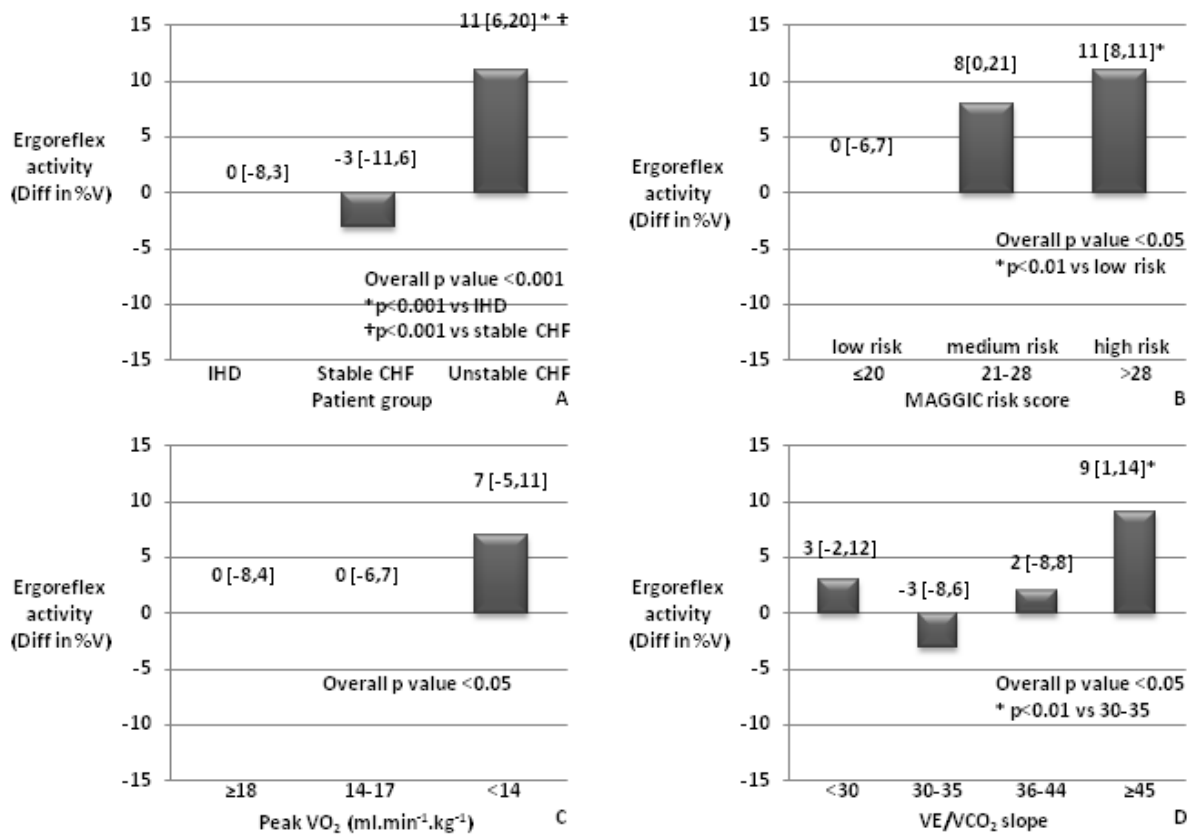
Figure 2. Ergoreflex activity according to (A) diagnosis, (B) MAGGIC mortality risk score, (C) peak oxygen consumption (peak VO_2) and (D) VE/VCO_2 slope and expressed as the median value with the interquartile range [Q1, Q3] on top of each bar. *Significant difference.

3.3   Ergoreflex activity and the MAGGIC risk score

The overall MAGGIC score (median [interquartile range]) in CHF patients was 21 [14 – 29] with estimated 1-year and 3-year all-cause mortality risk of 11% [6% - 23%] and 27% [15% - 49%] respectively. Unstable CHF patients had a considerably higher MAGGIC score and associated mortality risk (26 [22 – 33], 1-y risk 18% [12% - 32%], 3-y risk 40% [29% - 63%]) than stable CHF patients (15 [11 – 20], 1-y risk 6% [4% - 10%], 3-y risk 16% [11% - 24%]) (all p<0.001).

Ergoreflex was evaluated in 3 risk groups with a clear activation in patients with a score >20 (overall p<0.05; Fig 2). A positive correlation was found between ergoreflex activity and the MAGGIC risk score (Spearman ρ=0.431, p=0.002).
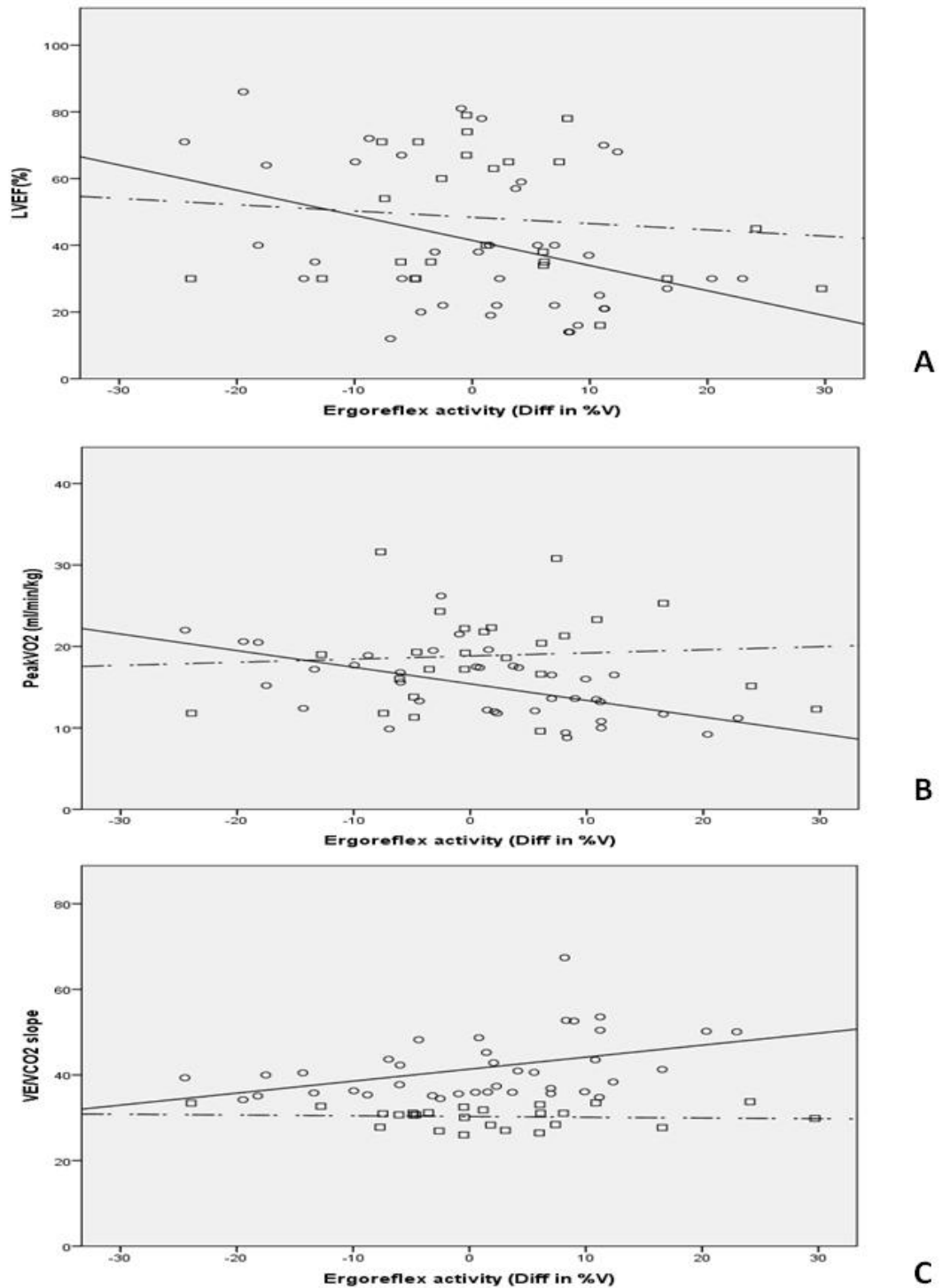
Figure 3. Relationship between ergoreflex activity and (A) left ventricular ejection fraction (LVEF), (B) peak oxygen consumption (peak VO_2), and (C) VE/VCO$_2$ slope, represented in scatterplots according to the ventilatory slope (≤34 and >34). Patients with a VE/VCO$_2$ slope ≤34 are indicated with squares and the relationship with a dashed line. Patients with a VE/VCO$_2$ slope >34 are indicated with circles and the relationship with a solid line.

4   Discussion

The major finding of this study is that in a broad spectrum of subjects including healthy subjects and patients with IHD and heart failure, ergoreflex activation contributes to hyperventilation and exercise intolerance, but only in those heart failure patients with persistent symptoms. In contrast, activation of the ergoreceptors is not present in healthy subjects nor in patients with IHD or stable CHF. In addition, ergoreflex activity is clearly associated with the recently developed MAGGIC mortality risk score, thereby emphasizing the link with the severity of heart failure.

No ergoreflex activity was found in patients with IHD or stable CHF nor in healthy subjects. Conflicting results have been reported regarding ergoreflex activity in healthy subjects.[4, 5, 7] Our findings are in agreement with those reports stating there is no ergoreflex activity in healthy subjects, suggesting that in physiologic conditions mechanisms other than ergoreflex activity may play a major role in ventilatory control.[7] The ventilatory response to exercise was elevated in IHD, which supports earlier studies demonstrating that an increased VE/VCO_2 slope is not exclusively seen in the state of heart failure.[2] Several mechanisms are thought to underlie this phenomenon with an enhanced chemoreceptor activity being the most plausible determinant.[2] To date, the role of the ergoreceptors in the ventilatory control has not been investigated yet in IHD, although overactivation has been suggested owing to physical deconditioning.[2] Our results demonstrate for the first time that activation of the ergoreflex is not involved in the increased ventilatory drive that is seen in a substantial proportion of patients with IHD. Nor could ergoreflex activity be demonstrated in stable CHF patients despite a similar level of exercise intolerance as in earlier studies.[5, 7, 14, 15] Similar to IHD, their aberrant VE/VCO_2 slope may indicate that other systems than ergoreflex activity are responsible for the increased ventilatory drive, including chemoreceptor activity or pulmonary dysfunction.[2, 16]

Only recently decompensated CHF patients who were still symptomatic showed signs of ergoreflex activation, but to a lesser extent than was formerly assumed. A plausible explanation could be found in the introduction of ACE inhibitors and β-blockers as a standard of care. ACE inhibitors may positively influence exercise capacity and ventilatory efficiency owing to their vasodilatory characteristics driven by prostaglandins and their impact on diffusion capacity.[17-19] However, prostaglandins may also stimulate ergoreflex overactivity and subsequent hyperventilation,[20, 21] which could in turn be counteracted by aspirin.[22] Nevertheless, prostaglandin inhibition alone is unlikely to have a clinically significant influence on the ventilatory abnormalities seen in CHF.[23] In this study, a high percentage of patients was on ACE inhibitors. Activation of the ergoreflex, however, was lower than in earlier investigations with a similar proportion of patients on this treatment.[5, 6, 21,]

[22] A decrease in the ventilatory slope has already been demonstrated after β blocker therapy, [24, 25] but the influence of β blockers on ergoreflex activity has not been investigated yet. In contrast to earlier studies with a low percentage of patients on β blockers, i.e. 20% - 30% on average, [5, 7, 15, 22] 88% of stable CHF and 70% of unstable CHF patients had β blocker therapy in the present study. Bisoprolol was mainly prescribed in stable CHF (73%) with an average daily dose of 4mg, whereas carvedilol was primarily used in unstable CHF patients (36%) with an average daily dose of 12.5mg. The dosages reached in our study population extended the starting doses recommended by the ESC,[9] although the suggested target doses were rarely reached. β blocker therapy may have decreased ergoreflex activation, [24] but these findings should be interpreted with caution because this study was not aimed to investigate the impact of these medications on ergoreflex activity.

Regardless of the diagnosis, ergoreflex activity was also evaluated according to measures of exercise tolerance. With a decrease in peak VO_2 to < 14 ml.min^{-1}.kg^{-1} and a rise in the VE/VCO$_2$ slope to > 45, a progressive increase in ergoreflex contribution to the ventilatory response was observed. In earlier investigations, ergoreflex activity has also been demonstrated in patients who had a preserved exercise capacity and a normal VE/VCO$_2$ slope,[5, 6] but this could not be confirmed by our results. Similarly, correlations were significant only in those patients with an abnormally elevated VE/VCO$_2$ slope (>34), suggesting a later onset of ergoreflex activation under current medical management strategies. [4-6, 14] Although our findings of a reduced ergoreflex activity might be encouraging, this reflex mechanism still contributes to hyperventilation and subsequent prognosis in an important subset of heart failure patients with persistent symptoms despite the current medical approach.

In this study, ergoreflex activity was most pronounced in those patients with a VE/VCO$_2$ slope > 45, a value that is indicative of a particularly high risk for adverse events within 2 years.[13] In the past, activation of the ergoreceptors had already been related to a deterioration in clinical status, suggesting a link with prognosis.[5, 6] Our study provides evidence for this hypothesis by demonstrating a clear relation with the MAGGIC mortality risk score, a risk calculator integrating 13 clinical factors and comorbidities to quantify individual patients' prognosis in CHF.[11] This link suggests that ergoreflex activity is a marker of the severity of heart failure and further emphasizes the importance of peripheral reflex mechanisms in the progression of heart failure disease.

4.1   Study limitations

The activity of the ergoreceptors has already been widely studied, but mainly focused on CHF. In addition, pharmacological treatment has changed over the past decades with a beneficial effect on survival but a less clear impact on exercise intolerance and its determinants. Therefore, novel studies are necessary to provide new clinical insights on this topic and to evaluate its current prognostic value. The present study was not aimed to investigate the effect of the pharmacological treatment itself, but rather to provide a clinical update on the presence of ergoreflex activity and its current relationship to prognosis. The sample size in this study did not allow us to assess outcome; therefore, the MAGGIC risk score was used. Nevertheless, this should be subject of larger studies. Because unstable CHF patients were older than IHD and stable CHF patients, age may have had a potential confounding effect on these results. Additional analyses according to age, however, revealed similar results in both younger and older patient groups. Similarly, COPD a comorbidity whose influence on ergoreflex activity is not entirely clear,[26, 27] seemed not to influence the presence of ergoreflex activity in unstable CHF. A small number of patients in some subgroups may have led to underpowered results, in particular in the analyses according to age. Therefore, these results should be interpreted with caution.

5   Conclusions

In a broad spectrum of subjects including healthy subjects and patients with IHD and heart failure, ergoreflex activation contributes to hyperventilation, but only in those heart failure patients with persistent symptoms, and is closely related to the MAGGIC mortality risk score. In contrast, no signs of ergoreflex activation were found in patients with IHD or stable CHF which may suggest that other mechanisms are involved in the increased ventilatory drive in these patients.

6   References

1. Clark AL, Poole-Wilson PA and Coats AJ. Exercise limitation in chronic heart failure: central role of the periphery. *J Am Coll Cardiol*. 1996; 28: 1092-102.

2. Tomita T, Takaki H, Hara Y, et al. Attenuation of hypercapnic carbon dioxide chemosensitivity after postinfarction exercise training: possible contribution to the improvement in exercise hyperventilation. *Heart (British Cardiac Society)*. 2003; 89: 404-10.

3. Tsurugaya H, Adachi H, Kurabayashi M, Ohshima S and Taniguchi K. Prognostic impact of ventilatory efficiency in heart disease patients with preserved exercise tolerance. *Circ J*. 2006; 70: 1332-6.

4. Piepoli M, Ponikowski P, Clark AL, Banasiak W, Capucci A and Coats AJ. A neural link to explain the "muscle hypothesis" of exercise intolerance in chronic heart failure. *Am Heart J*. 1999; 137: 1050-6.

5. Ponikowski PP, Chua TP, Francis DP, Capucci A, Coats AJ and Piepoli MF. Muscle ergoreceptor overactivity reflects deterioration in clinical status and cardiorespiratory reflex control in chronic heart failure. *Circulation*. 2001; 104: 2324-30.

6. Ponikowski P, Francis DP, Piepoli MF, et al. Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. *Circulation*. 2001; 103: 967-72.

7. Scott AC, Francis DP, Davies LC, Ponikowski P, Coats AJ and Piepoli MF. Contribution of skeletal muscle 'ergoreceptors' in the human leg to respiratory control in chronic heart failure. *J Physiol*. 2000; 529 Pt 3: 863-70.

8. Scott AC, Francis DP, Coats AJ and Piepoli MF. Reproducibility of the measurement of the muscle ergoreflex activity in chronic heart failure. *Eur J Heart Fail*. 2003; 5: 453-61.

9. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2012; 14: 803-69.

10. Piepoli M, Clark AL and Coats AJ. Muscle metaboreceptors in hemodynamic, autonomic, and ventilatory responses to exercise in men. *Am J Physiol*. 1995; 269: H1428-36.

11. Pocock SJ, Ariti CA, McMurray JJ, et al. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. *Eur Heart J*. 2013; 34: 1404-13.

12. Alam M and Smirk FH. Observations in man upon a blood pressure raising reflex arising from the voluntary muscles. *J Physiol*. 1937; 89: 372-83.

13. Arena R, Myers J, Abella J, et al. Development of a ventilatory classification system in patients with heart failure. *Circulation*. 2007; 115: 2410-7.

14. Piepoli MF, Kaczmarek A, Francis DP, et al. Reduced peripheral skeletal muscle mass and abnormal reflex physiology in chronic heart failure. *Circulation*. 2006; 114: 126-34.

15. Scott AC, Davies LC, Coats AJ and Piepoli M. Relationship of skeletal muscle metaboreceptors in the upper and lower limbs with the respiratory control in patients with heart failure. *Clin Sci (Lond)*. 2002; 102: 23-30.

16. Tumminello G, Guazzi M, Lancellotti P and Pierard LA. Exercise ventilation inefficiency in heart failure: pathophysiological and clinical significance. *Eur Heart J*. 2007; 28: 673-8.

17. Guazzi M, Marenzi G, Alimento M, Contini M and Agostoni P. Improvement of alveolar-capillary membrane diffusing capacity with enalapril in chronic heart failure and counteracting effect of aspirin. *Circulation*. 1997; 95: 1930-6.

18. Kitaoka H, Takata J, Hitomi N, et al. Effect of angiotensin-converting enzyme inhibitor (enalapril or imidapril) on ventilation during exercise in patients with chronic heart failure secondary to idiopathic dilated cardiomyopathy. Am J Cardiol. 2000; 85: 658-60, A10.

19. Guazzi M, Melzi G, Marenzi GC and Agostoni P. Angiotensin-converting enzyme inhibition facilitates alveolar-capillary gas transfer and improves ventilation-perfusion coupling in patients with left ventricular dysfunction. *Clin Pharmacol Ther*. 1999; 65: 319-27.

20. Schwieler JH and Hjemdahl P. Influence of angiotensin-converting enzyme inhibition on sympathetic neurotransmission: possible roles of bradykinin and prostaglandins. *J Cardiovasc Pharmacol*. 1992; 20 Suppl 9: S39-46.

21. Scott AC, Wensel R, Davos CH, et al. Putative contribution of prostaglandin and bradykinin to muscle reflex hyperactivity in patients on Ace-inhibitor therapy for chronic heart failure. *Eur Heart J.* 2004; 25: 1806-13.

22. Scott AC, Wensel R, Davos CH, et al. Chemical mediators of the muscle ergoreflex in chronic heart failure: a putative role for prostaglandins in reflex ventilatory control. *Circulation*. 2002; 106: 214-20.

23. Witte KK and Clark AL. The effect of aspirin on the ventilatory response to exercise in chronic heart failure. *Eur J Heart Fail*. 2004; 6: 745-8.

24. Agostoni P, Guazzi M, Bussotti M, De Vita S and Palermo P. Carvedilol reduces the inappropriate increase of ventilation during exercise in heart failure patients. *Chest*. 2002; 122: 2062-7.

25. Agostoni P, Contini M, Magini A, et al. Carvedilol reduces exercise-induced hyperventilation: A benefit in normoxia and a problem with hypoxia. *Eur J Heart Fail*. 2006; 8: 729-35.

26. Nakamoto FP, Neder JA, Maia J, Andrade MS and Silva AC. Skeletal muscle ergoreflex overactivity is not related to exercise ventilatory inefficiency in non-hypoxaemic patients with COPD. *Eur J Appl Physiol*. 2007; 101: 705-12.

27. Sharma S, Gupta R, Nautiyal A and Sindhwani G. Effects of ergoreflex on respiration and other efferent effects in adult male patients with chronic obstructive pulmonary disease. *Indian J Physiol Pharmacol*. 2012; 56: 201-12.

Supplement 1. Ergoreflex activity in patients according to age

	≤64 years			P value Diff in % exercise response between the patient groups	>64 years			P value Diff in % exercise response between the patient groups
	IHD N=15	Stable CHF N=19	Unstable CHF N=5		IHD N=10	Stable CHF N=5	Unstable CHF N=22	
Ventilation (V)								
% without PH-RCO	85 [77,86]	87 [84,94]	70 [61,92]		88 [75,92]	83 [69,86]	82 [74,91]	
% with PH-RCO	77 [72,85]	84 [77,94]	107 [68,118]		85 [79,88]	86 [71,91]	92 [83,105]	
P value	0.125	0.136	0.043		0.878	0.500	<0.001	
Diff in %V	-1 [-8,1]	-4 [-13,2]	11 [1,45][a,b]	0.034	1 [-6,6]	6 [-4,11]	10[6,18][a]	0.014
Breathing frequency (BF)								
% without PH-RCO	84 [83,94]	93 [85,102]	79 [63,103]		86 [67,101]	80 [69,93]	85 [78,94]	
% with PH-RCO	88 [71,94]	86 [79,101]	104 [83,118]		89 [79,100]	82 [77,89]	94 [83,110]	
P value	0.776	0.314	0.080		0.386	0.686	0.006	
Diff in %BF	5 [-11,11]	-5 [-9,4]	18 [2,36]	0.087	4 [-8,20]	-5 [-5,13]	7 [0,17]	0.481
Tidal volume (VT)								
% without PH-RCO	95 [86,101]	97 [89,104]	97 [78,113]		99 [85,116]	90 [83,116]	96 [85,100]	
% with PH-RCO	90 [82,99]	97 [85,104]	94 [83,103]		94 [87,101]	105 [81,115]	97 [82,111]	
P value	0.281	0.968	0.893		0.285	0.893	0.390	
Diff in %VT	-1 [-19,3]	1 [-13,14]	-11 [-21,20]	0.680	-10 [-29,8]	6 [-13,15]	6 [-8,8]	0.294

Variables are presented as median [interquartile range]. IHD, ischemic heart disease; CHF, chronic heart failure; Diff, difference; PH-RCO, post-handgrip regional circulatory occlusion; V, ventilation; Diff in %V, difference in percentage ventilation; BF, breathing frequency; Diff in %BF, difference in percentage breathing frequency; VT, tidal volume; Diff in %VT, difference in percentage tidal volume.

[a]p<0.01, unstable CHF vs IHD patients [b]p<0.01 , unstable CHF vs stable CHF patients

Supplement 2. Ergoreflex activity in unstable CHF according to the presence of COPD

COPD	No	Yes	P value
	N=19	N=8	Diff in % exercise response
			between the patient groups
Ventilation (V)			
% without PH-RCO	81 [73,91]	79 [67,90]	
% with PH-RCO	95 [81,106]	89 [85,108]	
P value	<0.001	0.025	
Diff in %V	9 [6,20]	11 [3,23]	0.791
Breathing frequency (BF)			
% without PH-RCO	86 [78,95]	80 [70,86]	
% with PH-RCO	96 [85,118]	91 [79,104]	
P value	0.002	0.161	
Diff in %BF	7 [0,17]	17 [-2,22]	0.396
Tidal volume (VT)			
% without PH-RCO	96 [77,99]	96 [87,114]	
% with PH-RCO	94 [79,105]	103 [93,114]	
P value	0.748	0.779	
Diff in %VT	5 [-12,7]	5 [-20,20]	0.559

Variables are presented as median [interquartile range]. CHF, chronic heart failure; Diff, difference; PH-RCO, post-handgrip regional circulatory occlusion; V, ventilation; Diff in %V, difference in percentage ventilation; BF, breathing frequency; Diff in %BF, difference in percentage breathing frequency; VT, tidal volume; Diff in %VT, difference in percentage tidal volume.

Part 2.

Outcome and the key role of exercise training in heart failure

Chapter 4.

Clinical characteristics and short-term outcome of patients admitted with heart failure in Belgium: results from the BIO-HF registry

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Abstract

Objective: Hospitalization for acute heart failure (HF) is associated with poor outcome. As specific data for Belgium are not available, the aim of the Belgian BIO-HF registry is to evaluate the clinical characteristics, in-hospital mortality and outcomes after discharge of patients hospitalized for acute HF.

Methods and results: This is a prospective observational cohort study in 2 Belgian hospitals. For the current analysis, the first 904 patients enrolled between 2008 and 2012 were analyzed to evaluate clinical characteristics and short-term outcome (all-cause mortality and all-cause mortality + rehospitalization 3 months after discharge). Mean age of patients was 77 years, 44% were women and 64% had an eGFR <60 ml/min/1.73m². Mean LVEF was 42% with only 40% with LVEF≤35%. In-hospital mortality was 7.1% with a mortality of 22% in the subgroup of patients with a creatinine ≥ 2mg/dl and systolic blood pressure ≤110 mmHg on admission. Three months after discharge, the all-cause mortality rate was 7.6% and the all-cause mortality or hospitalization for HF 18.3%. Multivariate Cox regression analysis revealed eGFR, COPD, absence of β blockers and atrial fibrillation at discharge (all p<0.05) as independent predictors of all-cause mortality.

Conclusions: In this Belgian registry of mainly elderly patients admitted with acute HF, a relatively preserved LVEF and a reduced kidney function were present in the majority of patients. In-hospital and short-term mortality after discharge remain high and are mainly related to the presence of comorbidities such as renal failure and COPD. Comorbidities should be the focus for future efforts to improve the dire outcome of these patients.

Keywords: acute heart failure, mortality, hospitalization, comorbidities

1   Introduction

Heart failure (HF) is a global world-wide public health problem with an estimated prevalence of 15 million patients alone in the countries represented by the European Society of Cardiology (ESC).[1-3] Hospitalizations for acute HF represent currently 1% to 2% of all hospitalizations in the Western world and remain associated with a high early post-discharge mortality and readmission rate.[4-7] Data from hospitalized HF registries are useful to better understand the clinical characteristics, patient management and outcomes after discharge. Also, data from the "real-world" may help to develop quality improvement initiatives and ultimately improve patient outcomes.[3, 8] Several international registries have shown that important geographic variations in patient characteristics and treatment exist.[3, 9] Even for Europe, data from the ESC-HF Pilot survey indicate that differences across countries exist and may be due to different local medical practice as well to differences in healthcare systems.[10] Thus, country specific data remain important to monitor and guide public policy at all levels. For Belgium, no specific clinical and outcome data on acute HF admissions have been published thus far and Belgium was also not part of the ESC-HF Pilot survey or ESC-HF Long-Term registry.[10, 11]

Therefore, the current analysis of the BIO-Heart Failure (BIO-HF) registry aims to report the specific clinical characteristics as well as the in-hospital course and 3 months outcome after discharge for acute decompensated HF in 2 Belgian hospitals. Also a comparison is made with other recent European and international HF registries that have reported on clinical characteristics and short-term outcomes after hospitalization for HF.[10, 12-14]

2   Methods

2.1   Study population

The BIO-HF registry is an ongoing prospective HF registry evaluating all patients admitted with NYHA class III-IV HF in 2 hospitals in Belgium (AZ Maria Middelares Hospital Ghent and University Hospital Brussels).[15] The departments of cardiology of both hospitals provide on-site interventional cardiology and electrophysiology/device implantation as well as cardiac surgery but do not perform heart transplantation. The objective of the registry is to prospectively collect data regarding baseline characteristics, in-hospital treatments, medication at discharge and outcome for consecutive patients admitted with acute HF. For the present analysis, we included all patients that entered the database

between 2008 and May 2012 at the AZ Maria Middelares Hospital Ghent and the patients that entered the database in 2008 at the University Hospital Brussels. Clinical data as well as data on risk factors and comorbidities (including the presence of ischemic heart disease, atrial fibrillation, hypertension, diabetes, smoking, COPD, peripheral artery disease, stroke and malignancy) were collected. Also laboratory results on admission (including creatinine and sodium levels and estimated glomerular filtration rate, eGFR) as well as medication on admission and discharge were documented. Echocardiography was performed with a measurement of left ventricular ejection fraction (LVEF, Simpson's method) within the first two days of admission. QRS duration was measured from the surface electrocardiogram on admission. NT-proBNP levels on admission were also collected but were not available in all patients (54% of the total population).

In total 960 patients admitted with acute HF were included (838 at the AZ Maria Middelares Hospital Ghent and 122 at the University Hospital Brussels). Echocardiography and LVEF measurements were lacking in 56 patients (6%) and they were excluded for further analysis. Thus, in total 904 patients formed the study population. During the index hospitalisation 64 patients (7%) died, leaving 840 patients who were discharged alive. These patients were followed for the endpoints of all-cause mortality and the combined endpoint of all-cause mortality or hospitalisation for HF at 3 months (91 days) after discharge. Of these 840 patients, 46 patients (5%) were lost to follow-up, leaving 794 patients for the outcome analysis.

2.2   Outcome data

In hospital mortality was recorded in all patients as well as in-hospital length of stay. In-hospital mortality was further evaluated according to the results of the ADHERE registry[7] with 2 predictors : admission creatinine <2 mg/dl versus ≥2 mg/dl and admission systolic blood pressure ≤110 mmHg versus >110 mmHg. The primary outcome measure for the 3 months follow-up post discharge was all-cause mortality. The secondary endpoint was the combination of all-cause mortality and hospitalisation for HF.

2.3   Statistical analysis

Data are expressed as mean ± SD or median (interquartile range) for continuous variables and as percentage (%) for categorical variables. Student's t-test, ANOVA or Wilcoxon-rank sum test for continuous variables and X^2 test for categorical variables were used to examine the difference between groups. For the comparison of medication on admission versus discharge, the non-

parametric McNemar test for comparison of related samples was used. Kaplan-Meier analysis with Cox proportional hazards regression was used for time-to-event analysis, for both the evaluation of the primary and secondary endpoints after 3 months follow-up. Multivariate Cox proportional hazards regression was based on the variables that were associated with the endpoint in univariate analysis (p<0.1). The variables evaluated included age, LVEF, ischemic heart disease, acute coronary syndrome on admission, left bundle branch block, atrial fibrillation at discharge, comorbidities including renal function, hypertension, diabetes, COPD, active smoking, stroke and malignancy, as well as medication at discharge (β blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers (ACE-I/ARB), mineralocorticoid receptor antagonist (MRA)). Odds ratios (ORs) with 95% confidence intervals (CIs) are reported. Survival was also evaluated using the Kaplan-Meier method and compared among groups using the log-rank test. Statistical significance was defined as p<0.05 or 95% CI for OR not including 1.0. All statistical analyses were performed with the use of SPSS Version 19.0 for Windows (SPSS Inc., Chicago, IL, USA).

2.4 Ethics

The study complied with the Declaration of Helsinki. The BIO-HF registry was approved by the Central Ethical Committee of the University Hospital Brussels and the AZ Maria Middelares Hospital Ghent (2010/262). Written informed consent was obtained from all patients or their legal representatives.

3 Results

3.1 General characteristics

The clinical characteristics of the total study population are shown in table 1. Average age was high (77 years) and 51% of all patients were 80 years or older. A preserved LVEF ≥50% was noted in 40% of patients while another 40% had a LVEF ≤35%. Importantly, 20% of patients had an intermediate LVEF of 36-49%. Patients with preserved LVEF were older, more frequently women and had more frequently a history of hypertension. On admission, they presented with higher blood pressures, more frequently with atrial fibrillation and less frequently with an acute coronary syndrome. Creatinine levels were significantly higher in patients with reduced LVEF, but overall eGFR was comparable in the 3 groups. Mean QRS duration on the surface ECG as well as the presence of LBBB were significantly higher in patients with reduced LVEF. NT-proBNP values on admission (available in 54% of all patients) were high in the 3 groups. Although patients with preserved LVEF presented with significantly lower NT-proBNP values, their admission values were still high (median NT-proBNP 5210

pg/ml). In contrast, sodium levels on admission were remarkably comparable between the 3 groups. The prevalence of implanted pacemakers was comparable between the 3 groups. The overall prevalence of implanted devices (ICD and/or CRT) was however low (1%-2% of all patients) and, as expected, almost completely restricted to patients with reduced LVEF.

Table 1. Clinical characteristics on admission

	Total group N=904	LVEF ≤ 35% N=361 (40%)	LVEF 36-49% N=182 (20%)	LVEF ≥ 50% N=361 (40%)	Overall p-value
Age (years)	77±11	74±12	78±10	79±10	<0.001
Age ≥ 80 years (%)	51	41	51	60	<0.001
Women (%)	44	31	42	57	<0.001
LVEF (%)	42±17	25±6	42±3	60±7	<0.001
AF on admission (%)	48	41	51	52	0.008
AF at discharge (%)	21	18	21	25	0.100
Ischemic heart disease (%)	45	52	57	33	<0.001
ACS on admission (%)	17	22	19	11	0.001
Comorbidities (%)					
Hypertension	62	52	67	70	<0.001
Diabetes	27	27	34	24	0.077
Current smoking	12	16	12	9	0.009
COPD	19	18	19	19	0.875
PAOD	17	14	21	17	0.064
Stroke	11	11	12	11	0.985
Malignancy	12	9	14	14	0.098
Devices (%)					
Pacemaker	9	9	10	8	0.797
ICD	2	4	3	0.3	0.004
CRT	1	3	0.5	0.3	0.016
CRTD	0.3	0.8	0	0	0.104
Lab-values					
Sodium (mmol/l)	138±4	138±4	138±4	138±4	0.779
Creatinine (mg/dl)	1.4±0.9	1.4±1.1	1.4±0.8	1.3±0.6	0.017
eGFR (ml/min/1.73m²)	54±21	54±20	54±21	54±21	0.954
NT-proBNP(pg/ml) (n=487)	6500 (3216,11800)	8919 (4150,17398)	6563 (2987,13147)	5210 (2907,9105)	<0.001
Clinical parameters					
Heart rate (beats/min)	93±28	97±28	93±28	89±28	0.002
SBP (mmHg)	141±30	134±27	142±30	147±30	<0.001
DBP (mmHg)	81±19	81±15	81±20	81±18	0.944
ECG parameters					
QRS duration (ms)	115±34	123±35	114±34	107±31	<0.001
Typical LBBB (%)	17	24	17	11	<0.001

Data are presented as mean±SD, median (interquartile range) or %.
P-value: overall significance between the 3 groups of left ventricular ejection fraction (LVEF). AF, atrial fibrillation; ACS, acute coronary syndrome; COPD, chronic obstructive pulmonary disease; PAOD, peripheral arterial occlusive disease; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro brain natriuretic peptide; SBP, systolic blood pressure; DBP, diastolic blood pressure; LBBB, left bundle branch block.

3.2 In-hospital mortality and in-hospital length of stay

Of the 904 patients, 64 died during the hospitalization (overall in hospital mortality 7.1%). Patients who died were older (80±10 vs. 77±11 years, p=0.02), had a lower blood pressure on admission (systolic blood pressure 134±31 vs. 141±29 mmHg, p=0.04) and higher creatinine levels on admission (1.7±0.8 vs. 1.3±0.9 mg/dl, p<0.001). Admission heart rate was comparable (95±26 vs. 93±28 beats/min, p=0.48) as well as sodium levels (137±5 vs. 138± 4 mmol/l, p=0.44). There was a trend towards higher in-hospital mortality in patients with LVEF ≤35% (9% mortality) and LVEF 36-49% (8.8% mortality) as compared to patients with LVEF ≥50% (4.7% mortality) (overall p-value = 0.076). The average LVEF of patients who died versus those who were discharged alive was also significantly lower (37±15% vs. 43±17%, p=0.01).

Figure 1 shows the in-hospital mortality according to admission creatinine levels and systolic blood pressure. Patients with a creatinine <2 mg/dl and a systolic blood pressure >110 mmHg had the lowest in-hospital mortality (30/670, 4.5%), followed by patients with a creatinine <2mg/dl and systolic blood pressure ≤110 mmHg (10/108, 9.3%) and patients with a creatinine ≥2 mg/dl and systolic blood pressure >110 mmHg (18/99, 18.2%). The highest in-hospital mortality was noted in patients with a creatinine ≥2 mg/dl and systolic blood pressure ≤110 mmHg (6/27, 22.2%) (overall p-value <0.01).

Median in-hospital length of stay was 9 days (IQR 5,14) and this was comparable in patients with LVEF ≤35% (median 9 days, IQR 5,15), LVEF 36-49% (median 8 days, IQR 6,13) and LVEF ≥50% (median 8 days, IQR 5,15) (overall p-value = 0.44). Patients who died during hospitalization had a significantly higher median in-hospital length of stay of 15 days (IQR 9,31) (p<0.01 as compared to patients discharged alive).

3.3 Medication on admission and discharge

Table 2 shows the medical treatment of the patients who were discharged alive (n=794). Both their medication on admission and at discharge are shown according to LVEF. As compared with medication on admission, a significant increase in the prescription of β blockers, ACE-I/ARB and MRA at discharge can be noted in all groups, except for the use of ACE-I/ARB in patients with LVEF≥50% . Also at discharge, patients with a preserved ejection fraction were significantly less treated with β blockers, ACE-I/ARB and MRA.
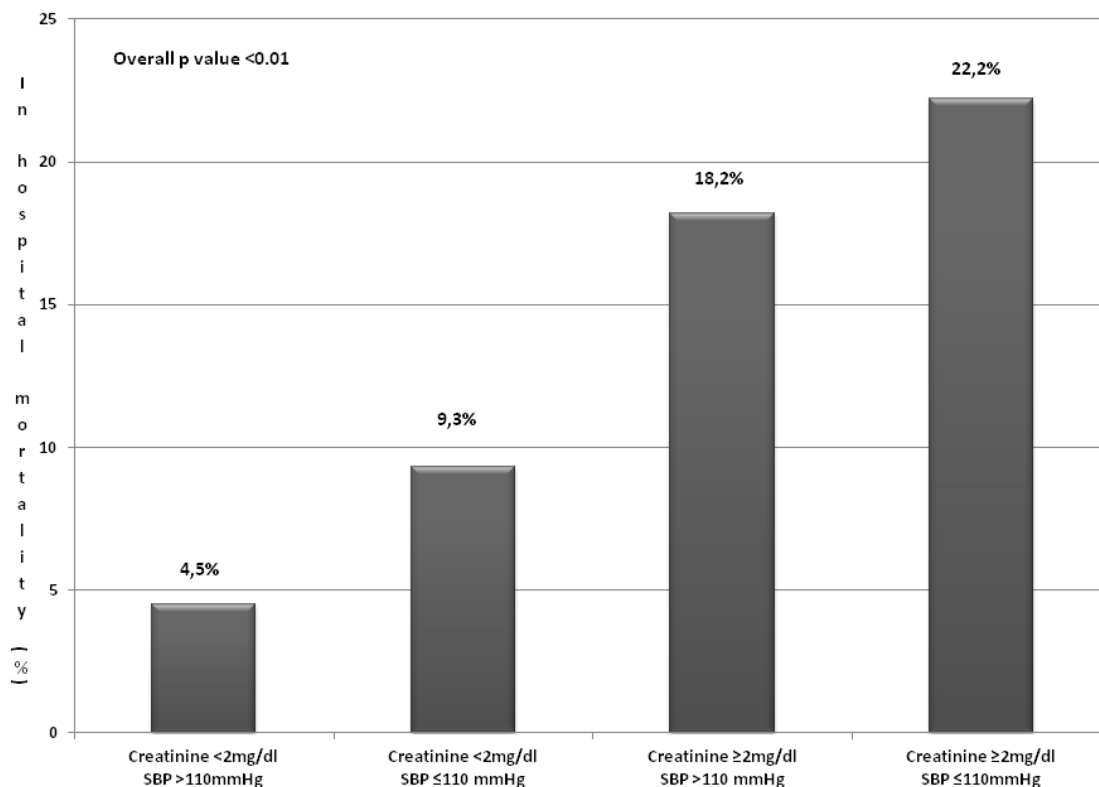
Figure 1. In-hospital mortality according to renal function (creatinine < 2 mg/dl versus ≥ 2 mg/dl) and systolic blood pressure (≤ 110 mmHg versus > 110 mmHg) on admission.

Table 2. Medication on admission and discharge according to LVEF in the patients who were discharged alive

	Total group N=794	LVEF ≤ 35% N=310 (39%)	LVEF 36-49% N=152 (19%)	LVEF ≥ 50% N=332 (42%)	Overall p-value
Admission (%)					
β blockers	52	46	61	53	0.005
ACE-I/ARB	53	54	53	52	0.930
MRA	15	15	19	14	0.291
Discharge (%)					
β blockers	77*	82*	84*	70*	<0.001
ACE-I/ARB	66*	76*	68*	55	<0.001
MRA	33*	38*	38*	25*	0.001

Data are expressed as %. P-value indicates overall significance between the 3 groups of LVEF, * indicates p-value < 0.01 for the comparison between admission and discharge. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

3.4   Follow-up

After a follow-up of 3 months, 60 patients had died (7.6%) and 145 had died or were rehospitalized for heart failure (18.3%). Univariate predictors of all-cause mortality at 3 months after discharge are

presented in the supplementary table 1. Parameters associated with p-values <0.1 are used for the multivariate Cox regression analysis that is shown in table 3. As age, creatinine and eGFR were significantly related, only eGFR was used for multivariate regression analysis. The absence of β blockers at discharge, the presence of atrial fibrillation at discharge, a history of COPD as well as eGFR remained as independent predictors of short-term all-cause mortality after discharge. Figure 2 (A-D) shows the Kaplan-Meier plots for all-cause mortality during follow-up according to LVEF (A: Log-Rank 0.059, p=0.808), use of β blockers at discharge (B: Log-Rank 7.33, p=0.007), history of COPD (C: Log-Rank 7.82, p=0.005) and eGFR (>60, 60-30 and <30 ml/min/1.73m²)(D: Log-Rank 21.8, p<0.001). As can be noted from panel A, there was no difference in short-term mortality at 3 months between patients with preserved (≥ 50%) and reduced (<50%) LVEF and patients with eGFR<30 ml/min/1.73m² had a very high death rate of 18% at 3 months.

Similar results were found for the combined end-point of all-cause mortality or rehospitalization for heart failure at 3 months after discharge (see supplementary tables 2 and 3). For this endpoint, a history of COPD as well as eGFR and a history of stroke remained as independent predictors.

Table 3. Multivariate Cox regression analysis of all-cause mortality at 3 months after discharge

	OR	95% CI	p-value
eGFR	0.97	0.96-0.99	<0.001
COPD	2.35	1.27-4.36	0.006
β Blocker at discharge	0.50	0.26-0.94	0.032
ACE-I/ARB at discharge	0.67	0.35-1.27	0.219
Stroke	1.51	0.70-3.26	0.298
AF at discharge	2.06	1.08-3.91	0.028

OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AF, atrial fibrillation.
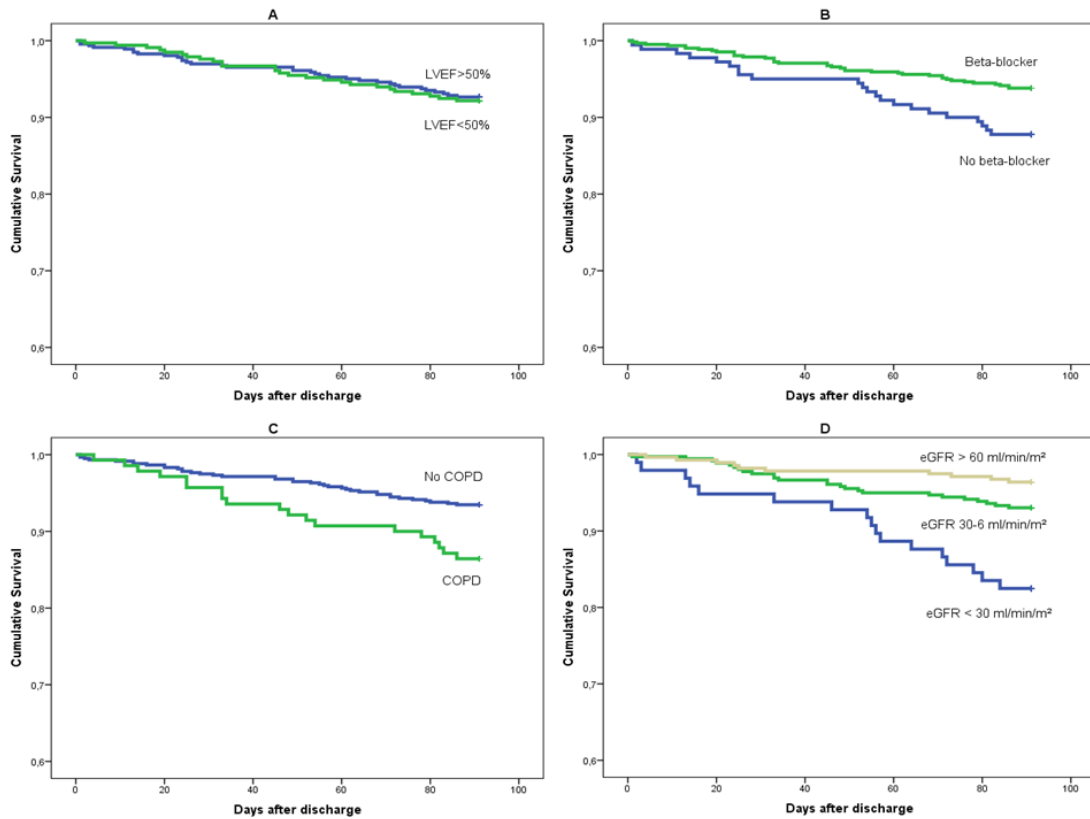
Figure 2. Kaplan-Meier plots for all-cause mortality during 3 months follow-up according to LVEF (A), use of beta-blockers at discharge (B), history of COPD (C) and eGFR (>60, 60-30 and <30 ml/min/1.73m²)(D).

4   Discussion

In this larger contemporary hospital registry, we describe in detail the clinical characteristics and short-term outcome of patients admitted with HF in 2 Belgian hospitals. A comparison with other recent registries that reported outcome after hospital discharge for acute decompensated HF is presented in table 4. Overall, our patients were older (mean age 77 years) and presented less frequently with a reduced LVEF. The difference in age might be explained by many factors including differences in the prevalence of underlying risk factors, life expectancy and standard of living and probably also reflects the continuous aging of the heart failure patients.[3]

One of the strengths of this registry is that LVEF was measured in all patients with echocardiography during index admission. This allowed us to describe in detail the prevalence of HF according to LVEF. Strikingly, not only 40% of patients presented with a preserved LVEF (HFPEF patients with LVEF ≥50%), but also another 20% showed only a moderately reduced LVEF between 35 and 50%. As a result, 60% of patients presented with a LVEF >35%, a population of patients for who scientific evidence regarding optimal treatment is limited. As expected, patients with a more preserved LVEF

were in general older, were more frequently women and presented more frequently with hypertension or atrial fibrillation and less frequently with ischemic heart disease. Similar as in several previous reports,[10, 14, 16] LVEF did not predict outcome after discharge with a similar event rate for both all-cause mortality and all-cause mortality or HF rehospitalization. Despite the fact that average LVEF was somewhat higher than in previous registries, admission NT-proBNP values were higher than reported in e.g. the IN-HF and ESC-HF Pilot registries.[10, 14] This might be explained by the older age and more advanced renal dysfunction in the present registry. Although patients with preserved LVEF presented with significantly lower NT-proBNP values, their admission values were still high (median NT-proBNP 5210 pg/ml).

4.1   In-hospital mortality and length of in hospital stay

The median length of stay in our registry was 9 days and this was comparable across the range of LVEF. As recently reviewed by Ambrosy et al,[3] global heart failure hospitalization registries show that the median length of stay ranges from 4 to 20 days. Geographical differences (with shorter length of stay in US registries) can be largely explained by differences in clinical practice and reimbursement issues. We report an in-hospital mortality of 7.1% which is comparable to the in-hospital mortality of the IN-HF and KorAF registries[12, 14] but somewhat higher than the ESC-HF Pilot or OPTIMIZE-HF results.[10, 13] Differences in clinical characteristics including the higher age of our patients might partly explain these differences. Importantly, in line with the findings of the ADHERE registry,[7] a set of simple parameters including systolic blood pressure and renal function on admission can help to discriminate hospital survivors and non-survivors (figure 1). However, even patients with a creatinine <2 mg/dl and a systolic blood pressure >110 mmHg on admission still had an in-hospital mortality of 4.5%.

4.2   Medication at discharge

Overall we noted a significant increase in the prescription of β blockers, ACE-I/ARB and MRA at discharge as compared to admission. This was documented in all groups of LVEF, except for the use of ACE-I/ARB in patients with LVEF≥50%. The global use of β blockers was comparable to other registries (see table 4), but the use of ACE-I/ARB and MRA tended to be somewhat lower for the overall population as well as for the patients with a reduced LVEF. This might be partly explained by the more advanced age and renal dysfunction in our patients (eGFR<60 ml/min/1.73m² in 64%) but will also be explored in future studies within the BIO-HF study framework. Of note, even in patients

with preserved LVEF, β blockers were described in 70%, ACE-I/ARB in 55% and MRA in 25% although current evidence for using these medications in HFPEF patients is lacking.[1]

4.3   Outcome after discharge

Rather few HF hospital registries have collected data on post discharge mortality and readmissions for HF (see table 4). In general, they noticed a high mortality and morbidity rate early after hospitalization of acute HF. We also report a comparable all-cause mortality of 7.6% and a combined all-cause mortality or heart failure rehospitalization of 18.3%. To the best of our knowledge these are the first reported outcome data for Belgian patients. The ESC-HF Pilot survey reported a 1-year all-cause mortality of 17.4% and all-cause mortality of rehospitalization for heart failure of 35.8%. Of note, only 218 of the 1892 patients came from Western Europe (Austria, France, Germany and The Netherlands) with similar event rates (respectively 18.4% and 33.9% at 1 year).[14]

The short-term outcome in our registry was mainly driven by the absence of the use of β blockers at discharge and the presence of different comorbidities. Comorbidities are prevalent in patients with HF and contribute to an increased morbidity and mortality and an impairment of quality of life.[17-19] The prevalence of different comorbidities in the present registry are generally similar to the data reported by other registries on acute HF (see table 4). They are also in line with data in patients with chronic HF, for example for diabetes (27% in the present survey vs. 29% in the European Heart Failure Pilot Survey for chronic HF), hypertension (62% vs. 58%), COPD (19% vs. 15%) and stroke (11% vs. 11%).[20] Especially impaired renal function and COPD emerged as important independent prognostic parameters for both short-term all-cause mortality and the combined endpoint of all-cause mortality and hospitalization for HF. The prognostic value of renal dysfunction is in line with several other registries[10, 13, 14, 21] although our patients showed in general more advanced kidney impairment with a mean creatinine of 1.4 mg/dl and a GFR<60 ml/min/1.73m² in 64% of patients. Our present data regarding COPD are in agreement with previous reports showing that COPD is an independent predictor of all-cause mortality in HF patients.[22-26] COPD in HF patients has not only been associated with a low-grade systemic inflammation,[23] increased myocardial damage and arterial stiffness[25, 26] but also with increased other comorbidities and less use of evidence-based heart failure medications.[27] Importantly, the use of β blockers had a positive effect on the short-term outcome, independent of the presence of COPD. This finding further supports the notion that selective beta-1 blockade or combined nonselective beta- and alpha-adrenergic blockade should not be denied to HF patients with concomitant stable COPD who do not have reversible airway obstruction.[1, 27] Although diabetes was highly prevalent in our study, its prevalence was lower than in other registries and it

was not associated with outcome measurements in multivariate analysis. Most studies have shown that diabetes is associated with a poorer prognosis in acute HF, although this relationship is less clear in patients with chronic HF.[20, 28, 29] Our findings regarding diabetes can probably be explained by the short-term follow-up, the older age of the patients and the fact that systematic screening for diabetes was not performed.

4.4   Limitations

This study has some limitations. First, this is not a nationwide register but a register limited to 2 hospitals. However, because of the large sample size, the consecutive inclusion during a longer time period and the fact that the general results are comparable to other large American or European registries, we believe that our data reflect the real-life situation in Belgium. Secondly, as it is the case for most hospital based heart failure registries, medical comorbidities such as hypertension, COPD and diabetes were self-recorded or extracted from chart review and lacked formal diagnostic criteria. Other potential important comorbidities such as body mass index, anemia, sleep disorders or depression were not recorded in all patients and were therefore not used for further analysis. Also, NT-proBNP levels on admission were only available in 54% of the patients and were therefore not included for further statistical analysis. Thirdly we only recorded all-cause and not cause-specific mortality during a short term (3 months) follow-up. Finally, we did not record reasons why certain evidence based medications were not given. These last 2 limitations are however part of an ongoing heart failure quality improvement project within the BIO-HF framework.

5   Conclusion

In this contemporary registry of mainly elderly patients admitted with acute HF, a relatively preserved LVEF and a reduced kidney function are present in the majority of patients. In-hospital and short-term mortality and rehospitalization after discharge remain high and are mainly related to the presence of comorbidities such as renal failure and COPD. Comorbidities should be the focus for future efforts to improve the dire outcome of these patients.

Table 4. Comparison of the BIO-HF clinical characteristics and outcome results to other registries that reported outcome after hospital discharge for acute decompensated heart failure

	BIO-HF	IN-HF (14)	ESC-HF Pilot (10)	KorAHF (12)	OPTIMIZE-HF (13)
Region	Belgium	Italy	Europe	Korea	USA
Time period	2008-2012	2007-2009	2009-2010	2011-2012	2003-2004
Sample Size	904	1855	1892	2066	4402
Age (years)	77±11	72±12	69±13	69±14	72±14
Women (%)	44	40	37	45	49
History of CAD/IHD (%)	45	42	51	38	50
LVEF (%)	42±17	38±11	38±14	40±18	37±17
LVEF <40 (%)	42	58	65 (LVEF <45%)	56	49
NT-proBNP (pg/ml) on admission	6500 (3216,11800)	5168 (2518,11583)	4007 (2043,9487)	NA	NA
Hypertension (%)	62	58	62	59	72
Diabetes (%)	27	40	35	36	42
COPD (%)	19	30	15	11	31
Creatinine (mg/dl)	1.4±0.9	1.2 (1, 1.6)	NA	1.5±1.6	1.3 (1.0, 1.8)
eGFR <60 ml/min/1.73m² (%)	64	55	49	NA	NA
eGFR<30 ml/min/1.73m² (%)	15	13	10	NA	NA
Discharge medication (%)					
ACE-I/ARB	66	78	78	65	68
β blockers	77	61	81	44	67
MRA	33	55	37	40	NA
Median length of stay (days)	9	10	8	8	4
In-hospital mortality (%)	7.1	6.4	3.8	6.1	1.6
All-cause mortality after discharge (%)	7.6 (3 months)	12.3 (3 months)		9.2 (6 months)	8.6 (60-90 days)
		24 (1 year)	17 (1 year)		
All-cause mortality or rehospitalization for heart failure after discharge (%)	18.3 (3 months)	NA	36 (1 year)	28 (6 months)	36.2 (60-90 days)

Data are presented as mean ± SD, median (IQR range) or %. CAD, coronary artery disease; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; NA not available.

6   References

1. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2012; 14: 803-69.

2. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail*. 2013; 6: 606-19.

3. Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol*. 2014; 63: 1123-33.

4. Mosterd A and Hoes AW. Clinical epidemiology of heart failure. *Heart*. 2007; 93: 1137-46.

5. Jhund PS, Macintyre K, Simpson CR, et al. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. *Circulation*. 2009; 119: 515-23.

6. Rudiger A, Harjola VP, Muller A, et al. Acute heart failure: clinical presentation, one-year mortality and prognostic factors. *Eur J Heart Fail*. 2005; 7: 662-70.

7. Fonarow GC, Adams KF, Jr., Abraham WT, Yancy CW and Boscardin WJ. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. *Jama*. 2005; 293: 572-80.

8. Jonsson A, Edner M, Alehagen U and Dahlstrom U. Heart failure registry: a valuable tool for improving the management of patients with heart failure. *Eur J Heart Fail*. 2010; 12: 25-31.

9. Ventura HO and Gaddam KK. Geographic variations of acute heart failure syndromes: the importance of clinical registries. *Am Heart J*. 2011; 162: 1-2.

10. Maggioni AP, Dahlstrom U, Filippatos G, et al. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail*. 2013; 15: 808-17.

11. Maggioni AP, Anker SD, Dahlstrom U, et al. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2013; 15: 1173-84.

12. Lee SE, Cho HJ, Lee HY, et al. A multicentre cohort study of acute heart failure syndromes in Korea: rationale, design, and interim observations of the Korean Acute Heart Failure (KorAHF) registry. *Eur J Heart Fail*. 2014; 16: 700-8.

13. O'Connor CM, Abraham WT, Albert NM, et al. Predictors of mortality after discharge in patients hospitalized with heart failure: an analysis from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J*. 2008; 156: 662-73.

14. Tavazzi L, Senni M, Metra M, et al. Multicenter prospective observational study on acute and chronic heart failure: one-year follow-up results of IN-HF (Italian Network on Heart Failure) outcome registry. *Circ Heart Fail*. 2013; 6: 473-81.

15. De Sutter J, Weytjens C, Van de Veire N, et al. Prevalence of potential cardiac resynchronization therapy candidates and actual use of cardiac resynchronization therapy in patients hospitalized for heart failure. *Eur J Heart Fail*. 2011; 13: 412-5.

16. Fonarow GC, Stough WG, Abraham WT, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. *J Am Coll Cardiol*. 2007; 50: 768-77.

17. Braunstein JB, Anderson GF, Gerstenblith G, et al. Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. *J Am Coll Cardiol*. 2003; 42: 1226-33.

18. Ather S, Chan W, Bozkurt B, et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. *J Am Coll Cardiol*. 2012; 59: 998-1005.

19. Saczynski JS, Go AS, Magid DJ, et al. Patterns of comorbidity in older adults with heart failure: the Cardiovascular Research Network PRESERVE study. *J Am Geriatr Soc*. 2013; 61: 26-33.

20. van Deursen VM, Urso R, Laroche C, et al. Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. *Eur J Heart Fail*. 2014; 16: 103-11.

21. Damman K, Voors AA, Hillege HL, et al. Congestion in chronic systolic heart failure is related to renal dysfunction and increased mortality. *Eur J Heart Fail*. 2010; 12: 974-82.

22. Kwon BJ, Kim DB, Jang SW, et al. Prognosis of heart failure patients with reduced and preserved ejection fraction and coexistent chronic obstructive pulmonary disease. *Eur J Heart Fail*. 2010; 12: 1339-44.

23. Staszewsky L, Wong M, Masson S, et al. Clinical, neurohormonal, and inflammatory markers and overall prognostic role of chronic obstructive pulmonary disease in patients with heart failure: data from the Val-HeFT heart failure trial. *J Card Fail*. 2007; 13: 797-804.

24. Rusinaru D, Saaidi I, Godard S, Mahjoub H, Battle C and Tribouilloy C. Impact of chronic obstructive pulmonary disease on long-term outcome of patients hospitalized for heart failure. *Am J Cardiol*. 2008; 101: 353-8.

25. Mentz RJ, Fiuzat M, Wojdyla DM, et al. Clinical characteristics and outcomes of hospitalized heart failure patients with systolic dysfunction and chronic obstructive pulmonary disease: findings from OPTIMIZE-HF. *Eur J Heart Fail*. 2012; 14: 395-403.

26. Yoshihisa A, Takiguchi M, Shimizu T, et al. Cardiovascular function and prognosis of patients with heart failure coexistent with chronic obstructive pulmonary disease. *J Cardiol*. 2014.

27. Le Jemtel TH, Padeletti M and Jelic S. Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. *J Am Coll Cardiol*. 2007; 49: 171-80.

28. Berry C, Brett M, Stevenson K, McMurray JJ and Norrie J. Nature and prognostic importance of abnormal glucose tolerance and diabetes in acute heart failure. *Heart*. 2008; 94: 296-304.

29. Tomova GS, Nimbal V and Horwich TB. Relation between hemoglobin a(1c) and outcomes in heart failure patients with and without diabetes mellitus. *Am J Cardiol*. 2012; 109: 1767-73.

Supplement 1. Univariate predictors of all-cause mortality at 3 months after discharge

	Alive N=734	Deceased N=60	p-value
Age (years)	76±11	79±10	0.048
Women (%)	44	43	0.985
LVEF (%)	43±17	43±16	0.995
LVEF ≥ 50 (%)	42	43	0.804
Ischemic heart disease (%)	43	49	0.383
ACS on admission (%)	16	16	0.948
LBBB (%)	16	10	0.180
AF at discharge (%)	22	34	0.037
Creatinine (mg/dl)	1.3±0.9	1.6±0.8	0.008
eGFR (ml/min/1.73m²)	56±20	43±20	<0.001
Hypertension (%)	62	63	0.837
Diabetes (%)	27	25	0.706
COPD (%)	18	33	0.005
Smoking (%)	12	17	0.258
Stroke (%)	11	18	0.069
Malignancy (%)	12	14	0.665
β Blocker at discharge (%)	79	63	0.007
ACE-I/ARB at discharge (%)	67	43	<0.001
MRA at discharge (%)	33	28	0.461

Data are presented as mean±SD or %. LVEF, left ventricular ejection fraction; ACS, acute coronary syndrome; LBBB, left bundle branch block; AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; ACE-I, angiotensin-converting enzyme inhibitor; ARB angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

Supplement 2. Univariate predictors of the combined endpoint of all-cause mortality and hospitalization for heart failure at 3 months after discharge

	Alive N=649	Deceased N=145	p-value
Age (years)	76±11	78±10	0.060
Women (%)	43	46	0.459
LVEF (%)	43±17	43±16	0.762
LVEF ≥ 50 (%)	42	41	0.804
Ischemic heart disease (%)	42	50	0.115
ACS on admission (%)	15	19	0.211
LBBB (%)	16	16	0.925
AF at discharge (%)	21	28	0.101
Creatinine (mg/dl)	1.3±0.9	1.5±0.7	0.043
eGFR (ml/min/1.73m²)	57±20	48±20	<0.001
Hypertension (%)	61	66	0.258
Diabetes (%)	27	30	0.440
COPD (%)	17	28	0.004
Smoking (%)	13	10	0.476
Stroke (%)	10	17	0.024
Malignancy (%)	13	10	0.426
β Blocker at discharge (%)	79	70	0.026
ACE-I/ARB at discharge (%)	67	58	0.031
MRA at discharge (%)	35	24	0.016

Data are presented as mean±SD or %. LVEF, left ventricular ejection fraction; ACS, acute coronary syndrome; LBBB, left bundle branch block; AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; COPD, chronic obstructive pulmonary disease; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

Supplement 3. Multivariate Cox regression analysis of the combined endpoint of all-cause mortality and hospitalization for heart failure at 3 months after discharge

	OR	95% CI	p-value
eGFR	0.98	0.97-0.99	<0.001
COPD	1.66	1.12-2.44	0.011
β Blocker at discharge	0.75	0.51-1.11	0.152
ACE-I/ARB at discharge	0.99	0.69-1.45	0.990
MRA at discharge	0.65	0.42-1.00	0.051
Stroke	1.58	1.01-2.50	0.045

OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; COPD, chronic obstructive pulmonary disease; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

Chapter 5.

Exercise capacity and training effects according to neurohormonal activation in patients with coronary artery disease

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Abstract

Purpose: The relation between exercise capacity and neurohormonal activation is unclear in coronary artery disease (CAD) patients. Therefore, we evaluated whether exercise capacity was related to neurohormonal activation in CAD patients with a wide range of left ventricular ejection fraction (LVEF) and NT-proBNP as well as whether the functional improvement after exercise training depends on LVEF or NT-proBNP.

Methods: 581 patients who were referred for cardiac rehabilitation after a coronary event, were stratified according to LVEF (<50%, n=94 and ≥50%, n=487) and to tertiles of NT-proBNP (≤279, >279 and ≤656, >656pg/ml). Six-minute walking distance (6MWD) before and after cardiac rehabilitation was available in all patients, spiro-ergometry was performed in 285 patients. Baseline exercise capacity and the benefit from exercise training were compared between the groups.

Results: Patients with reduced and preserved LVEF showed a similar decrease in baseline exercise capacity with increasing NT-proBNP, as expressed by a lower load (all $p<0.05$), peakVO_2, 6MWD, and a higher VE/VCO_2 slope (all $p<0.001$ in preserved LVEF). In the upper tertile of NT-proBNP, exercise intolerance was comparable in patients with reduced and preserved LVEF. Exercise training resulted for each level of NT-proBNP in an overall improvement in exercise capacity and this gain was comparable for all levels of NT-proBNP, both for patients with reduced and preserved LVEF.

Conclusions: Exercise capacity shows a similar decrease with increasing NT-proBNP, irrespective of left ventricular function in CAD. Exercise training improves exercise capacity regardless of left ventricular function or neurohormonal activation.

Keywords: exercise capacity, exercise training, natriuretic peptide, left ventricular function, coronary artery disease

1   Introduction

Biomarkers such as natriuretic peptides, brain natriuretic peptide or N-terminal pro brain natriuretic peptide (NT-proBNP), have become increasingly important for the diagnosis and prognosis of heart failure patients, both with reduced and preserved ejection fraction.[1, 2] In addition to their role in heart failure, natriuretic peptides have also been demonstrated to be predictive for cardiac events and mortality in other clinical settings such as acute coronary syndrome, coronary artery bypass graft, valvular heart disease and even in patients without coronary artery disease (CAD) at baseline.[1, 3-7]

Previous research has already shown that neurohormonal activation, as assessed by NT-proBNP, is associated with an impaired exercise capacity and ventilatory inefficiency in heart failure with reduced [8-11] and preserved ejection fraction.[12] Nevertheless, studies investigating this relation in CAD patients with a wide range of left ventricular ejection fraction (LVEF) and neurohormonal activation are lacking. Exercise training has been demonstrated to improve both exercise intolerance[13-17] and neurohormonal activation,[18-20] but whether the functional improvement after exercise training is related to the baseline level of neurohormonal activation is currently unknown.

In this study, we wanted to evaluate whether exercise capacity was related to neurohormonal activation in CAD patients with a wide range of LVEF and NT-proBNP as well as whether the functional improvement after exercise training depends on left ventricular function or neurohormonal activation.

2   Patients and methods

2.1   Study population

A total of 581 patients who were referred for cardiac rehabilitation after a coronary event (acute coronary syndrome n=283 or coronary artery bypass graft n=298) were prospectively included in the study. According to tertiles of NT-proBNP, 3 groups were defined with 194 patients having NT-proBNP ≤279 pg/ml (T1), 194 patients with a value >279 and ≤656 pg/ml (T2) and 193 patients with NT-proBNP >656 pg/ml (T3). The study population was further classified according to their LVEF, 94 patients had a LVEF<50% and 487 patients had a LVEF≥50%. CAD and LVEF were assessed with coronary angiography. This study protocol was approved by the local ethical committee of AZ Maria

Middelares Ghent and all patients gave informed consent. The clinical investigations were conducted according to the principles of the declaration of Helsinki.

2.2 Exercise testing

Prior to the rehabilitation program, cardiopulmonary exercise testing was performed on a cyclo-ergometer using a ramp protocol adapted at the patients' physical status approximately 3 weeks after discharge from the hospital (median 20 days [7, 28] for the total patient group, 7 days [4,10] after acute coronary syndrome and 27 days [22,31] after coronary artery bypass graft). Ventilatory and respiratory gas measurements were obtained on a breath-by-breath basis using an Oxycon Pro spirometer (Jaeger – Viasys Healthcare, Germany). Heart rate was continuously registered by a 12-lead electrocardiogram and blood pressure was non-invasively measured, using a manual sphygmanometer every 2 minutes during the exercise test. Patients exercised to the limits of their functional capacities established by a respiratory exchange ratio >1.15 or until the physician stopped the test because of adverse signs and/or symptoms, such as chest pain, dizziness, potentially life-threatening arrhythmias, ST segment deviations (≥1mm), and marked systolic hypotension or hypertension. The maximal achieved load during incremental exercise was recorded. Peak oxygen consumption (peak VO_2) was defined as the mean of the last 30 seconds of peak exercise and was expressed as $ml.min^{-1}.kg^{-1}$. The slope of the linear relation between VE (y-axis) and VCO_2 (x-axis), the VE/VCO_2 slope, was calculated by including all data points to the end of exercise. The anaerobic threshold was defined as the exercise level at which ventilation starts to increase exponentially, relative to the increase in VO_2[21].

At the beginning of the exercise training program, a six-minute walk test was also performed in a 30m hallway. The distance a patient could quickly walk on a flat hard surface in a period of 6 minutes, was measured (6MWD).

This protocol, both the cardiopulmonary exercise testing and six-minute walk test, were repeated at the end of the rehabilitation program. The six-minute walk test before and after cardiac rehabilitation was available in all patients (n=581), spiroergometry was performed in 285 patients. The gain in exercise capacity was expressed as a percentage of improvement and calculated as follows for the aforementioned exercise parameters: (exercise parameter$_{end}$ − exercise parameter$_{start}$)/ (exercise parameter$_{start}$) *100.

2.3   Exercise training

Rehabilitation was initiated at the first day after hospital admission and focused on respiration in combination with low-intensity aerobic exercises. After discharge, patients were encouraged to continue low-intensity aerobic exercises at home until they were referred for outpatient cardiac rehabilitation approximately 4 weeks after discharge from the hospital (median 29 days [interquartile range 20, 41] for the total patient group, 23 days [14, 31] after acute coronary syndrome and 38 days [28, 50] after coronary artery bypass graft). Patients trained 2 or 3 times weekly during 60 minutes for a period of 3 to 5 months with a maximum of 45 sessions. The exercise training program consisted of a combination of aerobic and strengthening exercises. Aerobic training mainly included cycling, treadmill walking and stepping and was performed at an intensity of the heart rate at the anaerobic threshold with an evaluation of the rating of perceived exertion. Strengthening exercises targeted both lower and upper body muscles at 60%1RM for 2 sets of 15 to 20 repetitions. Upper body strength training was started in a later phase in coronary artery bypass graft patients after the sternum was healed. Every training session was initiated and terminated with 5 minutes warm-up and cool-down period.

2.4   Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 21.0 (Armonk, New York, USA: IBM Corp). Clinical characteristics and exercise capacity were assessed according to LVEF, thereafter the same parameters were analyzed according to the NT-proBNP level within each group of LVEF separately. Chi², Fisher exact and Kruskal Wallis test were used to evaluate these parameters. A Wilcoxon matched – pairs signed – ranks test was used to evaluate the improvement after exercise training within each group separately. Differences in training effects were then compared between the tertiles of NT-proBNP within each class of LVEF, using the Kruskal Wallis test. Within the patient group with the highest level of NT-proBNP, clinical characteristics and training effects were also compared between patients with preserved and reduced LVEF, using the aforementioned statistical tests. For all analyses, the level of significance was set at $p < 0.05$.

3   Results

3.1   Patient characteristics

Clinical characteristics according to LVEF are given in supplement 1. Table 1 summarizes the clinical characteristics according to NT-proBNP, stratified by LVEF. 82% of the total patient population (n=581) were men and this ratio was similar between patients with reduced and preserved LVEF. The highest percentage of women was found in the upper tertile of NT-proBNP. Patients, both with reduced and preserved LVEF, had a mean age of 63 years. Within the group with a preserved LVEF separately, patients were older with increasing NT-proBNP (p<0.001). In both groups of left ventricular function, a worse clinical status was seen with increasing NT-proBNP, as reflected by a decrease in LVEF, worse renal function and more patients in NYHA class II or III (all p<0.001 in preserved LVEF). Hypertension was significantly more present in the upper tertile of NT-proBNP, but only in patients with preserved LVEF (p<0.05). B-blockers, diuretics and spironolacton were more frequently used in the highest NT-proBNP level (all p<0.05 in preserved LVEF).

3.2   Baseline exercise capacity and training effects according to LVEF and tertiles of NT-proBNP

Exercise capacity and functional improvement after attending cardiac rehabilitation was assessed according to LVEF and neurohormonal activation (figure 1, 2 and 3). In general, patients with a reduced LVEF had a worse exercise capacity after their event as compared with patients with preserved LVEF. Both patients with reduced and preserved LVEF showed a similar decrease in baseline exercise capacity with increasing NT-proBNP, as expressed by a progressively lower maximal achieved load (all p<0.05), peak VO_2, 6MWD and a higher VE/VCO_2 slope (p<0.001 in preserved LVEF). Patients attended 38 training sessions on average and this number was comparable for both groups of left ventricular function and each level of neurohormonal activation. Exercise training resulted for each level of NT-proBNP in an overall improvement in load (all p<0.05), 6MWD (all p<0.01) and peak VO_2 (all p<0.05 except for tertile 1 in LVEF<50%). This gain in exercise capacity was comparable for the three levels of NT-proBNP, both for patients with reduced and preserved LVEF. Only in patients with preserved ejection fraction and the highest level of NT-proBNP, a small but significant effect on the VE/VCO_2 slope was found (p<0.001).

3.3   Patient characteristics and training effects in patients with an increased NT-proBNP

In patients with an increased neurohormonal activation (>656pg/ml), patients with preserved LVEF were approximately 5 years older than those with reduced LVEF (p<0.01). Although patients with reduced LVEF had a higher NT-proBNP and more frequently a history of diabetes than patients with preserved LVEF (all p<0.05), no other signs for a worse clinical status were found. The percentage of patients in NYHA class II/III was similar as well as renal function and other comorbidities. Heart failure related medication such as ACE-inhibitors/angiotensin receptor blockers and diuretics was more frequently prescribed in patients with reduced LVEF (all p<0.05) (table 1). Patients with preserved LVEF showed a similar level of exercise intolerance as patients with reduced LVEF, with a decreased maximal achieved load, 6MWD, peak VO_2 and an increased VE/VCO_2 slope. Exercise training resulted in a comparable improvement in the aforementioned parameters, both in patients with reduced and preserved LVEF (figure 1, 2 and 3).

Table 1. Clinical characteristics according to LVEF and tertiles of NT-proBNP

Tertiles of NT-proBNP		LVEF<50%				LVEF≥50%			
		T1	T2	T3	P	T1	T2	T3	P
		N=12	N=24	N=58		N=182	N=170	N=135	
Age (years)		61±9	62±9	63±10	0.510	58±10	63±10	68±8[**]	<0.001
Men (%)		75	88	74	0.419	89	87	72	<0.001
BMI (kg/m²)		28±3	25±3	27±4	0.092	28±4	27±4	27±4	0.053
LVEF (%)		41±5	42±5	37±10	0.123	69±8	68±9	64±9[***]	<0.001
NT-proBNP (pg/ml)		192 (126-242)	453 (389-561)	1854 (1141-2757)	<0.001	144 (64-221)	434 (363-516)	1070 (872-1623)[***]	<0.001
GFR (ml/min/1.73m²)		75±11	78±15	69±22	0.344	79±12	77±13	67±18	<0.001
NYHA (%)	I	73	62	41	0.214	78	65	48	<0.001
	II-III	27	38	59		22	35	52	
Risk factors & comorbidities (%)									
Hypertension		50	25	52	0.080	42	53	58	0.012
Diabetes		8	17	28	0.318	13	19	15[*]	0.331
Smoking		17	4	10	0.454	4	6	7	0.664
COPD		0	0	10	0.512	5	3	5	0.835
AF at start cardiac rehabilitation		8	0	7	0.398	0	2	9	<0.001
Medication (%)									
Antiplatelets		100	96	98	0.622	100	99	99	1
Lipid lowering drugs		83	100	93	0.105	97	98	90	0.003
β blockers		92	96	97	0.757	86	95	94	0.003
ACE inhibitors/ ARB		92	79	83	0.726	39	30	42[***]	0.085
Diuretics		8	17	36	0.070	7	8	22[*]	<0.001
Spironolacton		8	21	14	0.691	2	1	5	0.029

Categorical variables are presented as percentages, normally distributed continuous variables are presented as mean ± standard deviation, non normally continuous variables are presented as median (interquartile range).

LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro Brain Natriuretic Peptide; BMI, body mass index; GFR, glomerular filtration rate; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; ACE inhibitors, Angiotensin Converting Enzym inhibitor; ARB, Angiotensin Receptor Blocker.

Difference between LVEF<50 and ≥50% within the highest NT-proBNP level (T3): *p<0.05 **p<0.01 ***p<0.001

LVEF<50%
n.s
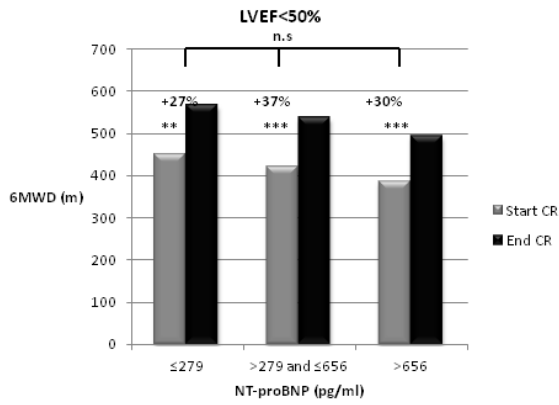
6MWD (m)	≤279 pg/ml (n=12)	>279 and ≤656 pg/ml (n=24)	>656 pg/ml (n=58)
Start CR	449±106	419±99	384±96
End CR	566±114	536±94	492±120

LVEF≥50%
n.s
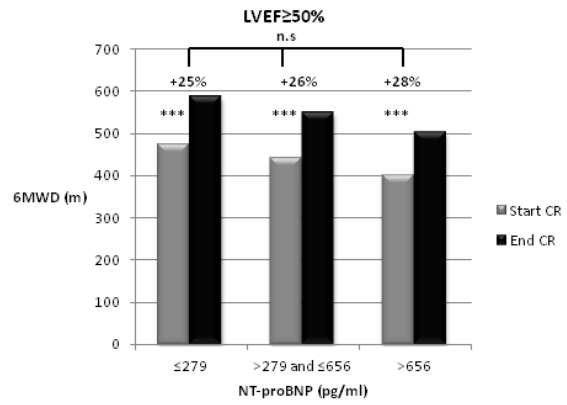
6MWD (m)	≤279 pg/ml (n=182)	>279 and ≤656 pg/ml (n=170)	>656 pg/ml (n=135)
Start CR	471±73	440±69	400±79
End CR	586±86	549±81	501±86

LVEF<50%
n.s.
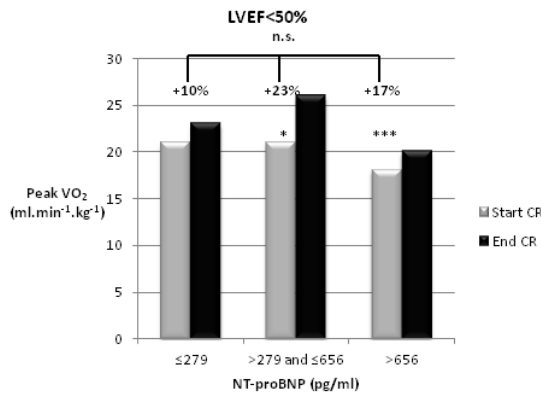
Peak VO$_2$ (ml.min^{-1}.kg^{-1})	≤279pg/ml (n=10)	>279 and ≤656 pg/ml (n=11)	>656 pg/ml (n=29)
Start CR	21±7	21±6	18±5
End CR	23±9	26±6	20±6

LVEF≥50%
n.s.
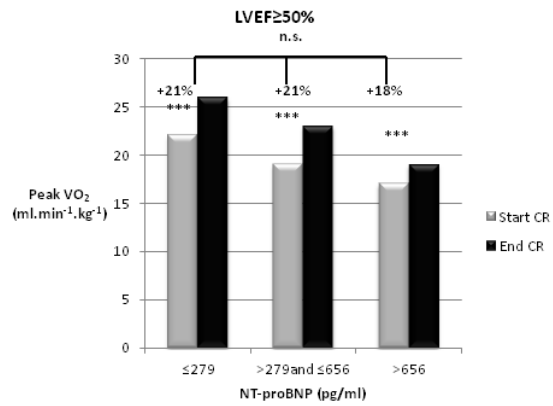
Peak VO$_2$ (ml.min^{-1}.kg^{-1})	≤279pg/ml (n=96)	>279 and ≤656 pg/ml (n=71)	>656 pg/ml (n=68)
Start CR	22±6	19±5	17±4
End CR	26±7	23±5	19±5

LVEF<50%
n.s.
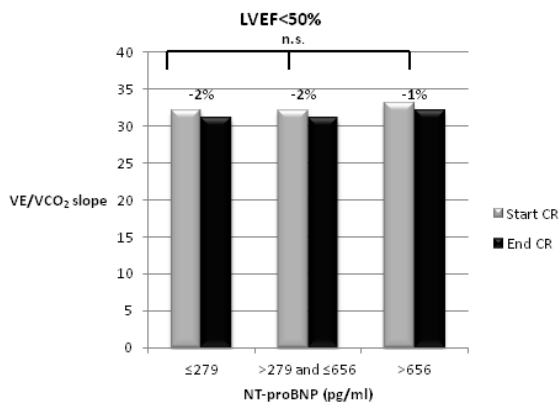
VE/VCO$_2$ slope	≤279 pg/ml (n=10)	>279 and ≤656 pg/ml (n=11)	>656 pg/ml (n=29)
Start CR	32±7	32±7	33±5
End CR	31±6	31±6	32±6

LVEF≥50%
n.s.
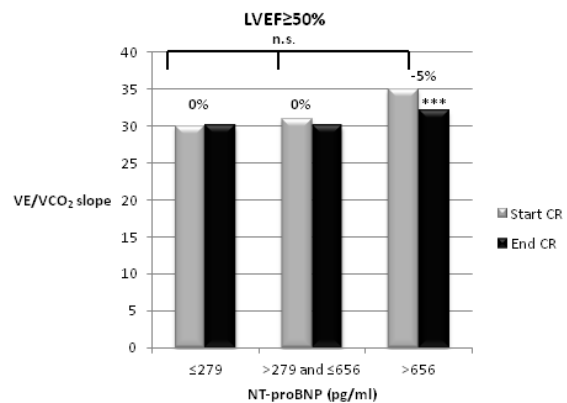
HRR (%)	≤279 pg/ml (n=96)	>279 and ≤656 pg/ml (n=71)	>656 pg/ml (n=68)
Start CR	30±5	31±5	35±6
End CR	30±5	30±5	32±5

Figure 1, 2 & 3. Six-minute walking distance, peak oxygen consumption and VE/VCO$_2$ slope according to NT-proBNP, stratified by left ventricular function

Six-minute walking distance, peak oxygen consumption and the VE/VCO$_2$ slope are shown at the start and end of the cardiac rehabilitation program, according to the level of NT-proBNP. Variables are presented as the mean ± standard deviation in the table under the figure. The improvement in exercise capacity is presented as a percentage (%) above the bars in each group separately, significance levels are indicated with an asterisk (*p <0.05, **p <0.01, and ***p <0.001). Differences in training benefits between the tertiles of NT-proBNP are shown on top of the figure.

CR, cardiac rehabilitation; 6MWD, six-minute walking distance; peak VO$_2$, peak oxygen consumption.

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4   Discussion

The primary finding of this study was that both in CAD patients with reduced and preserved LVEF a similar decrease in exercise capacity was observed as neurohormonal activation increased. Furthermore, exercise training resulted in an improvement in exercise tolerance, irrespective of the left ventricular function or the level of neurohormonal activation.

As already previously mentioned in literature, a worse clinical status is seen in patients with increased plasma concentrations of NT-proBNP. Apart from this clinical status, we have demonstrated a progressive decline in exercise capacity as neurohormonal activation increased. In the past, the link between exercise capacity and NT-proBNP has been mainly investigated in heart failure.[8-12] Our study provides a broader perspective by analysing CAD patients with a wide range of neurohormonal activation both with reduced and preserved LVEF. In general, exercise capacity is slightly more impaired in patients with reduced LVEF as compared with patients with preserved LVEF, which supports previous findings in heart failure.[22] Nevertheless, there is a similar decrease in exercise capacity, as expressed by the 6MWD, for elevating levels of NT-proBNP in both groups of left ventricular function. The maximal achieved load and the peakVO$_2$ describe a similar course as the 6MWD whereas the VE/VCO$_2$ slope tends to increase with elevating neurohormonal activation. Our findings are in agreement with Guazzi et al. [12] who recently demonstrated comparable correlations between NT-proBNP and peak VO$_2$ and VE/VCO$_2$ slope in a matched heart failure population with reduced and preserved LVEF of 68 patients. However, the relation in CAD has not been investigated so far and neither the link between training benefits and baseline neurohormonal activation.

This study has shown an overall improvement in exercise capacity after exercise training, regardless of left ventricular function or level of neurohormonal activation. Numerous studies have already

demonstrated the beneficial effect of exercise training on peak VO_2.[13, 18, 19, 23, 24] The average progression in peak VO_2 in this study, ranging from 10 to 23%, is consistent with previous investigations both focusing on heart failure and other cardiac pathologies.[24, 25] In contrast to the aforementioned variables, we only saw a modest decrease in the VE/VCO_2 slope, which was only significant in the upper tertile of NT-proBNP in patients with preserved LVEF. Currently, there is no consensus on the effect of exercise training on ventilatory inefficiency.[14, 19, 23, 24] A relatively healthy patient population in the lower tertiles of NT-proBNP with a baseline VE/VCO_2 slope below 34, may be a plausible explanation for this finding. However, also the intensity and type of exercise training may have been insufficient to influence ventilatory inefficiency. Addition of inspiratory muscle therapy may result in an additional improvement in cardiorespiratory responses to exercise.[26]

Patients with CAD in the highest level of NT-proBNP had a poor clinical status, both in patients with preserved and reduced LVEF. Also their level of exercise intolerance was generally comparable, which may indicate they have a comparable disease severity and associated prognosis. Van Veldhuisen et al.[2] has provided evidence for this presumption in a HF population by demonstrating a similar risk of all cause mortality and heart failure related hospitalisation in patients with a reduced and preserved LVEF for a given BNP level. Therefore, neurohormonal activation may be the primary driver of outcome, whereas adding LVEF has limited value in prognostication.[2] In addition, our study shows equal training benefits, irrespective of the left ventricular function. Consequently, more attention is needed for exercise intolerance and the beneficial role of exercise training, particularly in those patients with an increased neurohormonal activation.

This study has several limitations. A small number of patients in some subgroups may have led to underpowered results, in particular in the lower tertiles of NT-proBNP for patients with a reduced LVEF. Therefore, these results should be interpreted with caution. NT-proBNP was not measured at the end of cardiac rehabilitation, hence potential improvements in neurohormonal activation after exercise training and the relation to changes in exercise tolerance could not be assessed. However, literature has already shown that neurohormonal activation may also improve after exercise training and that this change may be related to the progression in exercise capacity and ventilatory efficiency.[18, 19]

## 5	Conclusions

In CAD patients, exercise capacity shows a similar decrease with increasing neurohormonal activation, irrespective of left ventricular function. Exercise training improves exercise capacity regardless of left ventricular function or the level of neurohormonal activation.

6   References

1. Daniels LB and Maisel AS. Natriuretic peptides. *J Am Coll Cardiol*. 2007; 50: 2357-68.

2. 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. *J Am Coll Cardiol*. 2013; 61: 1498-506.

3. Schnabel RB, Schulz A, Messow CM, et al. Multiple marker approach to risk stratification in patients with stable coronary artery disease. *Eur Heart J*. 2010; 31: 3024-31.

4. Holm J, Vidlund M, Vanky F, Friberg O, Hakanson E and Svedjeholm R. Preoperative NT-proBNP independently predicts outcome in patients with acute coronary syndrome undergoing CABG. *Scand Cardiovasc J Suppl*. 2013; 47: 28-35.

5. Gibson PH, Croal BL, Cuthbertson BH, et al. Use of preoperative natriuretic peptides and echocardiographic parameters in predicting new-onset atrial fibrillation after coronary artery bypass grafting: a prospective comparative study. *Am Heart J*. 2009; 158: 244-51.

6. Omland T, Persson A, Ng L, et al. N-terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes. *Circulation*. 2002; 106: 2913-8.

7. Leistner DM, Klotsche J, Pieper L, et al. Prognostic value of NT-pro-BNP and hs-CRP for risk stratification in primary care: results from the population-based DETECT study. *Clin Res Cardiol*. 2013; 102: 259-68.

8. Kruger S, Graf J, Kunz D, Stickel T, Hanrath P and Janssens U. brain natriuretic peptide levels predict functional capacity in patients with chronic heart failure. *J Am Coll Cardiol*. 2002; 40: 718-22.

9. Passino C, Poletti R, Bramanti F, Prontera C, Clerico A and Emdin M. Neuro-hormonal activation predicts ventilatory response to exercise and functional capacity in patients with heart failure. *Eur J Heart Fail*. 2006; 8: 46-53.

10. Kallistratos MS, Dritsas A, Laoutaris ID and Cokkinos DV. N-terminal prohormone brain natriuretic peptide as a marker for detecting low functional class patients and candidates for cardiac transplantation: linear correlation with exercise tolerance. *J Heart Lung Transplant*. 2007; 26: 516-21.

11. 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. *Am Heart J*. 2009; 158: S37-44.

12. Guazzi M, Labate V, Cahalin LP and Arena R. Cardiopulmonary exercise testing reflects similar pathophysiology and disease severity in heart failure patients with reduced and preserved ejection fraction. *Eur J Prec Cardiol*. 2013; 21:847-54.

13. Coats AJ, Adamopoulos S, Radaelli A, et al. Controlled trial of physical training in chronic heart failure. Exercise performance, hemodynamics, ventilation, and autonomic function. *Circulation*. 1992; 85: 2119-31.

14. Zurek M, Corra U, Piepoli MF, Binder RK, Saner H and Schmid JP. Exercise training reverses exertional oscillatory ventilation in heart failure patients. *Eur Respir J*. 2012.

15. Belardinelli R, Paolini I, Cianci G, Piva R, Georgiou D and Purcaro A. Exercise training intervention after coronary angioplasty: the ETICA trial. *J Am Coll Cardiol*. 2001; 37: 1891-900.

16. Lan C, Chen SY, Hsu CJ, Chiu SF and Lai JS. Improvement of cardiorespiratory function after percutaneous transluminal coronary angioplasty or coronary artery bypass grafting. *Am J Phys Med Rehabil*. 2002; 81: 336-41.

17. Currie KD, Dubberley JB, McKelvie RS and MacDonald MJ. Low-volume, high-intensity interval training in patients with CAD. *Med Sci Sports Exerc*. 2013; 45: 1436-42.

18. Passino C, Severino S, Poletti R, et al. Aerobic training decreases B-type natriuretic peptide expression and adrenergic activation in patients with heart failure. *J Am Coll Cardiol*. 2006; 47: 1835-9.

19. Guazzi M, Vitelli A and 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. *Int J Cardiol*. 2012; 158: 290-1.

20. Lara Fernandes J, Serrano CV, Jr., Toledo F, et al. Acute and chronic effects of exercise on inflammatory markers and B-type natriuretic peptide in patients with coronary artery disease. *Clin Res Cardiol*. 2011; 100: 77-84.

21. Conraads VM and Beckers PJ. Exercise training in heart failure: practical guidance. *Heart*. 2010; 96: 2025-31.

22. Moore B, Brubaker PH, Stewart KP and Kitzman DW. VE/VCO2 slope in older heart failure patients with normal versus reduced ejection fraction compared with age-matched healthy controls. *J Card Fail*. 2007; 13: 259-62.

23. Cipriano G, Jr., Cipriano VT, da Silva VZ, et al. Aerobic exercise effect on prognostic markers for systolic heart failure patients: a systematic review and meta-analysis. *Heart Fail Rev*. 2013.

24. Myers J, Gademan M, Brunner K, Kottman W, Boesch C and Dubach P. Effects of high-intensity training on indices of ventilatory efficiency in chronic heart failure. *J Cardiopulm Rehabil Prev*. 2012; 32: 9-16.

25. Temfemo A, Chlif M, Mandengue SH, Lelard T, Choquet D and Ahmaidi S. Is there a beneficial effect difference between age, gender, and different cardiac pathology groups of exercise training at ventilatory threshold in cardiac patients? *Cardiology journal*. 2011; 18: 632-8.

26. Winkelmann ER, Chiappa GR, Lima CO, Viecili PR, Stein R and Ribeiro JP. Addition of inspiratory muscle training to aerobic training improves cardiorespiratory responses to exercise in patients with heart failure and inspiratory muscle weakness. *Am Heart J*. 2009; 158: 768 e1-7.

Supplement 1. Clinical characteristics according to LVEF

		LVEF<50%	LVEF≥50%	P
		N=94	N=487	
Age (years)		63±10	63±10	0.887
Men (%)		78	83	0.201
BMI (kg/m²)		27±4	27±4	0.108
LVEF (%)		39±8	67±9	<0.001
NT-proBNP (pg/ml)		1056 (440-2125)	393 (188-744)	<0.001
GFR (ml/min/1.73m²)		72±20	75±15	0.506
NYHA (%)	I	50	65	0.019
	II-III	50	35	
Risk factors and comorbidities (%)				
	Hypertension	45	50	0.336
	Diabetes	22	16	0.109
	Smoking	10	6	0.138
	COPD	7	4	0.410
AF at start cardiac rehabilitation		5	3	0.361
Medication (%)				
	Antiplatelets	98	99	0.186
	Lipid lowering drugs	94	95	0.609
	β blockers	96	91	0.151
	ACE inhibitors/ ARB	83	36	<0.001
	Diuretics	28	12	<0.001
	Spironolacton	15	2	<0.001

Categorical variables are presented as percentages, normally distributed continuous variables are presented as mean ± standard deviation, non normally continuous variables are presented as median (interquartile range). LVEF, left ventricular ejection fraction; BMI, body mass index; NT-proBNP, N-terminal pro Brain Natriuretic Peptide; GFR, glomerular filtration rate; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; ACE inhibitors, Angiotensin Converting Enzym inhibitor; ARB, Angiotensin Receptor Blocker.

Part 3.

Barriers in the implementation

of cardiac rehabilitation

Chapter 6.

Participation in cardiac rehabilitation after hospitalization for heart failure: a report from the BIO-HF registry

Pardaens Sofie, Willems Anne-Marie, Vande Kerckhove Barbara, De Sutter Johan

Abstract

Objective: Participation in cardiac rehabilitation (CR) after hospitalisation for heart failure (HF) is estimated to be low, but specific data for Belgium are lacking. Therefore, we wanted to evaluate attendance after HF hospitalisation compared to patients after cardiac surgery or acute coronary syndrome (ACS). Moreover, the improvement in exercise capacity was compared with the other patient groups.

Methods and results: Patients who were hospitalized for HF (n=428), cardiac surgery (n=358) or ACS (n=467) in a single hospital, were prospectively included between January 2010 and May 2012. After hospitalisation for HF only 9% participated, compared to 29% after ACS and 56% after cardiac surgery. Non-participants in HF were older, more frequently women (p<0.01) and had a better left ventricular ejection fraction (p<0.05). In addition, they had more frequently atrial fibrillation and problems to walk independently (p<0.01). At start of CR, HF patients had a worse clinical status and exercise capacity than patients after cardiac surgery or ACS (all p<0.001). However, exercise training resulted in a significant improvement in each group separately (all p<0.001) and the relative improvement in exercise capacity in HF was comparable with the other groups.

Conclusions: Only 9% of HF patients participates in CR after hospitalisation. Age, female gender, a relatively well preserved ventricular function and atrial fibrillation seem to impede attendance to CR. However, HF patients can have as much improvement in exercise capacity as other patient populations, suggesting that more effort is needed to increase participation in CR among HF patients.

Keywords: cardiac rehabilitation, participation, heart failure, exercise capacity

1   Introduction

Cardiac rehabilitation (CR) has been recommended as an effective tool in the prevention and treatment of cardiovascular diseases.[1] Nevertheless, figures on participation in CR are disappointing with less than 50% attendance of the eligible patients. In addition, mainly coronary heart disease patients are referred, whereas only a minority of heart failure (HF) patients is estimated to participate in CR.[2]

In Belgium, general figures regarding participation in CR are varying [2, 3] and specific data among the different patient groups and in HF in particular, are lacking. Therefore, we wanted to evaluate attendance in CR after hospitalisation for HF in comparison with patients after hospitalisation for cardiac surgery or acute coronary syndrome (ACS). Potential differences in clinical characteristics at discharge from the hospital between HF patients who participated and those who did not participate, were assessed. Moreover, the benefit of exercise training in HF patients was compared with the results in the other patient groups.

2   Methods

2.1   Study population

This study was performed in a single hospital (AZ Maria Middelares Ghent) providing on-site interventional cardiology, cardiac surgery and outpatient CR. Patients who were hospitalized for HF (n=428), cardiac surgery (n=358) or ACS (n=467) between January 2010 and May 2012 were prospectively included. Data on HF patients were based on the ongoing BIO-HF registry.[4] During the same time period, attendance to CR in the different patient groups was also registered. This study protocol was approved by the ethical committee of AZ Maria Middelares Ghent and all patients gave informed consent. The clinical investigations were conducted according to the principles of the Declaration of Helsinki.

2.2   Exercise testing

Cardiopulmonary exercise testing (CPET) was performed 21 days [interquartile range 7-29] after hospitalisation on a cyclo-ergometer using a ramp protocol adapted to the patient's physical status. Ventilatory and respiratory gas measurements were obtained on a breath-by-breath basis using an

Oxycon Pro spirometer (Jaeger – Viasys Healthcare, Germany). Heart rate was continuously registered by a 12-lead electrocardiogram and blood pressure was non-invasively measured, using a manual sphygmanometer every 2 minutes during the exercise test. Patients exercised to the limits of their functional capacities established by a respiratory exchange ratio >1.15 or until the physician stopped the test because of adverse signs and/or symptoms, such as chest pain, dizziness, potentially life-threatening arrhythmias, ST segment deviations (≥1mm), and marked systolic hypotension or hypertension. The maximal achieved load during incremental exercise was recorded. Peak oxygen consumption (peak VO_2) was defined as the mean of the last 30 seconds of peak exercise and was expressed as $ml.min^{-1}.kg^{-1}$. The slope of the linear relation between VE (y-axis) and VCO_2 (x-axis), the VE/VCO_2 slope, was calculated by including all data points to the end of exercise. The anaerobic threshold (AT) was defined as the exercise level at which ventilation starts to increase exponentially, relative to the increase in VO_2.[5] The distance a patient could quickly walk on a flat hard surface in a period of 6 minutes, was also measured (6MWD). This protocol, both CPET and 6MWT, was repeated at the end of the rehabilitation program. The gain in exercise capacity was expressed as a percentage of improvement and calculated as follows for the aforementioned exercise parameters: (exercise parameter$_{end}$ – exercise parameter$_{start}$)/ (exercise parameter$_{start}$) *100.

2.3   Exercise training

Patients trained 2 or 3 times weekly during 60 minutes for a period of 3 to 5 months with a maximum of 45 sessions. The exercise training program consisted of a combination of aerobic and strengthening exercises. Aerobic training mainly included cycling, treadmill walking and stepping and was performed at an intensity of the heart rate at the anaerobic threshold. Strengthening exercises targeted both lower and upper body muscles at 60%1RM for 2 sets of 15 to 20 repetitions. Upper body strength training was started in a later phase in cardiac surgery patients after the sternum was healed. Every training session was initiated and terminated with 5 minutes warm-up and cool-down period.

2.4   Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 21.0 (Armonk, New York, USA: IBM Corp). Clinical characteristics were assessed in patients hospitalized for HF according to their participation in CR using the Chi^2, Fisher exact, Independent Samples T test and Mann Whitney U test as appropriate. Same statistical tests were used to evaluate the difference in clinical characteristics and baseline exercise capacity between patients who started CR after hospitalisation

for HF, cardiac surgery or ACS and to assess the difference in functional improvement after exercise training. A Wilcoxon matched – pairs signed – ranks test was used to evaluate the improvement after exercise training within each group separately. For all analyses, the level of significance was set at $p < 0.05$.

3   Results

3.1   Participation in CR

After hospitalisation for HF only 9% participated in CR, compared to 56% in patients hospitalized for cardiac surgery and 29% after ACS with a remarkable difference between patients who had a myocardial infarction with ST elevation (STEMI, 40%) and those without ST elevation (NSTEMI, 16%) (Figure 1).
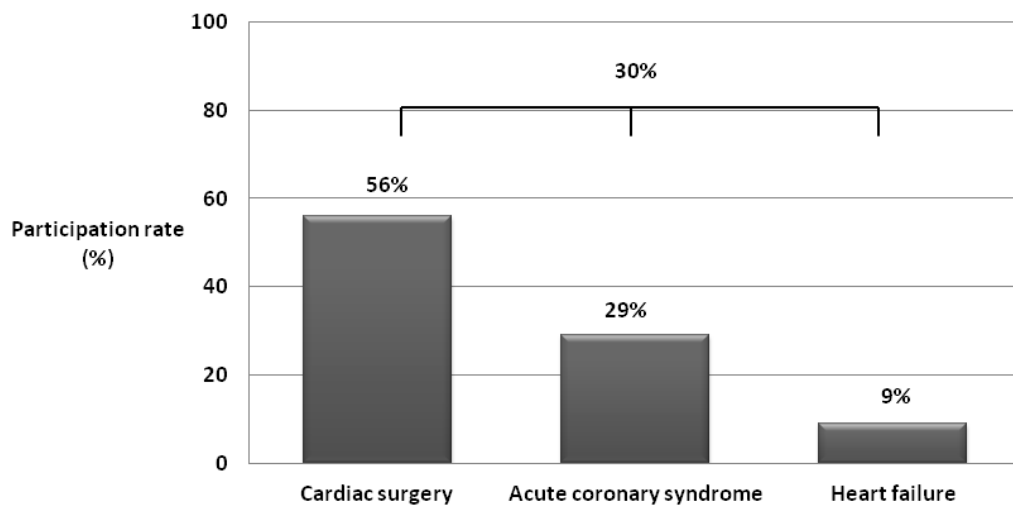
	Cardiac surgery	Acute coronary syndrome	Heart failure
Hospitalisation	358	467	428
Attendance CR	201	133	37
Participation rate (%)	56	29	9

Figure 1. Participation in CR among the different patient groups.

Table 1. Clinical characteristics of the hospitalized heart failure population

		Total population N=428	Participation CR N=37	Non participation CR N=391	P
Age (years)		78±10	65±10	79±10	<0.001
Men (%)		54	76	52	0.005
BMI at discharge (kg/m²)		26±4	27±5	26±4	0.419
LVEF (%)		43±17	36±15	44±17	0.011
LVEF≥50 (%)		40	23	42	0.030
NT-proBNP (pg/ml) on admission		5728 (2985-11441)	5569 (2014-8474)	5744 (3008-11663)	0.266
Creatinin (mg/dl) on admission		1.1 (0.9-1.5)	1.2 (1.0-1.5)	1.1 (0.9-1.5)	0.416
Creatinin (mg/dl) at discharge		1.2 (0.9-1.6)	1 (0.8-1.3)	1.2 (0.9-1.6)	0.077
GFR on admission		53 (41-73)	62 (44-78)	53 (41-73)	0.363
NYHA at discharge n=354	I	20	19	20	0.808
	II	69	75	68	
	III	11	6	11	
	IV	1	0	2	
Ischemic heart disease (%)		45	57	44	0.128
Risk factors & comorbidities (%)	Hypertension	63	49	65	0.053
	Hyperlipidemia (n=376)	52	72	50	0.012
	Diabetes	29	27	29	0.810
	Smoking	12	35	10	<0.001
	COPD	17	14	18	0.525
	CVA	12	5	13	0.292
	PAD	18	11	19	0.222
	AF	44	19	46	0.001
Sinus rhythm at discharge		52	92	49	<0.001
Able to walk independently at discharge		76	100	73	0.002
Medication (%)	Antiplatelets	52	65	51	0.110
	β blockers	79	95	78	0.015
	ACE inhibitors/ ARB	60	73	59	0.093
	Diuretics	82	81	82	0.909
	Spironolacton	36	38	36	0.781

Categorical variables are presented as percentages, normally distributed continuous variables are presented as mean ± standard deviation, non normally continuous variables are presented as median (interquartile range). BMI, body mass index; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro Brain Natriuretic Peptide; GFR, glomerular filtration rate; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; PAD, peripheral arterial disease; AF, atrial fibrillation; ACE inhibitors, Angiotensin Converting Enzym inhibitor, ARB, Angiotensin Receptor Blocker.

Table 2. Clinical characteristics of patients at start of cardiac rehabilitation

		Cardiac Surgery N=201	Acute Coronary Syndrome N=133	Heart failure N=37	P
Age (years)		65±10	58±11	64±10	<0.001
Men (%)		79	79	76	0.909
BMI (kg/m²)		27±4	29±5	26±5	0.001
LVEF (%)		65±12	59±13	37±16	<0.001
NT-proBNP (pg/ml)		487 (274-940)	321 (141-767)	1651 (843-2336)	<0.001
Creatinin (mg/dl)		0.9 (0.8-1.1)	1 (0.8-1.1)	1 (0.9-1.5)	0.073
GFR		77 (62-90)	78 (65-90)	68 (42-83)	0.011
NYHA	I	63	76	38	<0.001
	II	32	22	30	
	III	5	2	32	
Risk factors & comorbidities (%)					
	Hypertension	53	39	41	0.029
	Hyperlipidemia	43	47	57	0.311
	Diabetes	20	13	22	0.166
	Smoking	2	13	16	<0.001
	COPD	4	3	6	0.700
	CVA	6	2	3	0.313
	PAD	7	4	11	0.233
	AF	9	2	11	0.017
Medication (%)					
	Antiplatelets	98	100	73	<0.001
	β blockers	93	90	92	0.755
	ACE inhibitors/ ARB	23	68	70	<0.001
	Diuretics	16	9	70	<0.001
	Spironolacton	3	4	35	<0.001

Categorical variables are presented as percentages, normally distributed continuous variables are presented as mean ± standard deviation, non normally continuous variables are presented as median (interquartile range).

BMI, body mass index; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro Brain Natriuretic Peptide; GFR, glomerular filtration rate; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; PAD, peripheral arterial disease; AF, atrial fibrillation; ACE inhibitors, Angiotensin Converting Enzym inhibitor, ARB, Angiotensin Receptor Blocker.

3.2 Clinical characteristics of the hospitalized HF patients

Patients not attending CR after hospitalisation for HF, were significantly older and more female (both p<0.01), and they had a higher left ventricular function than HF patients who participated in CR (p<0.05). In addition, almost half of them had atrial fibrillation during hospitalisation and 27% reported problems to walk independently at discharge from the hospital (p<0.01). Clinical risk factors for CAD (hyperlipidemia and smoking) were less frequent in non-participants (both p<0.05). The medication use was comparable between the groups, except for β blockers which were less used in those not attending CR (p<0.05) (Table 1).

3.3 Clinical characteristics of patients participating in cardiac rehabilitation

In total, 371 patients attended CR of whom HF patients were the smallest group (10%). Patients participating after ACS were on average younger and had a higher BMI than patients after cardiac surgery or HF (p<0.001). HF patients had a lower left ventricular ejection fraction, a higher NT-proBNP level, a higher NYHA class (p<0.001) and a worse renal function (p<0.05). Almost none of the patients who had cardiac surgery were smoking at the start of CR, whereas 13 to 16% did after ACS or HF respectively (p<0.001). Atrial fibrillation was present in 9% of patients after cardiac surgery and 11% of HF patients which is significantly more than in ACS (p<0.05). HF related medications such as ACE inhibitors or ARB, diuretics and spironolacton, were significantly more prescribed in HF patients (p<0.001), whereas antiplatelets were prescribed in almost all patients after ACS or cardiac surgery (p<0.001) (Table 2).

3.4 Exercise capacity and exercise training among the different patient groups

At the start of CR, HF patients had the worst exercise capacity with a significantly lower maximal achieved load, peak VO_2, 6MWD and a higher VE/VCO_2 slope (all p<0.001). Exercise training resulted in a significant improvement in these exercise parameters in each patient group separately (all p<0.001), except for the VE/VCO_2 slope which only decreased slightly in patients after cardiac surgery and HF (both p<0.05). Furthermore, the percentage of improvement after exercise training seen in HF, was comparable with patients after cardiac surgery or ACS (Figure 2).
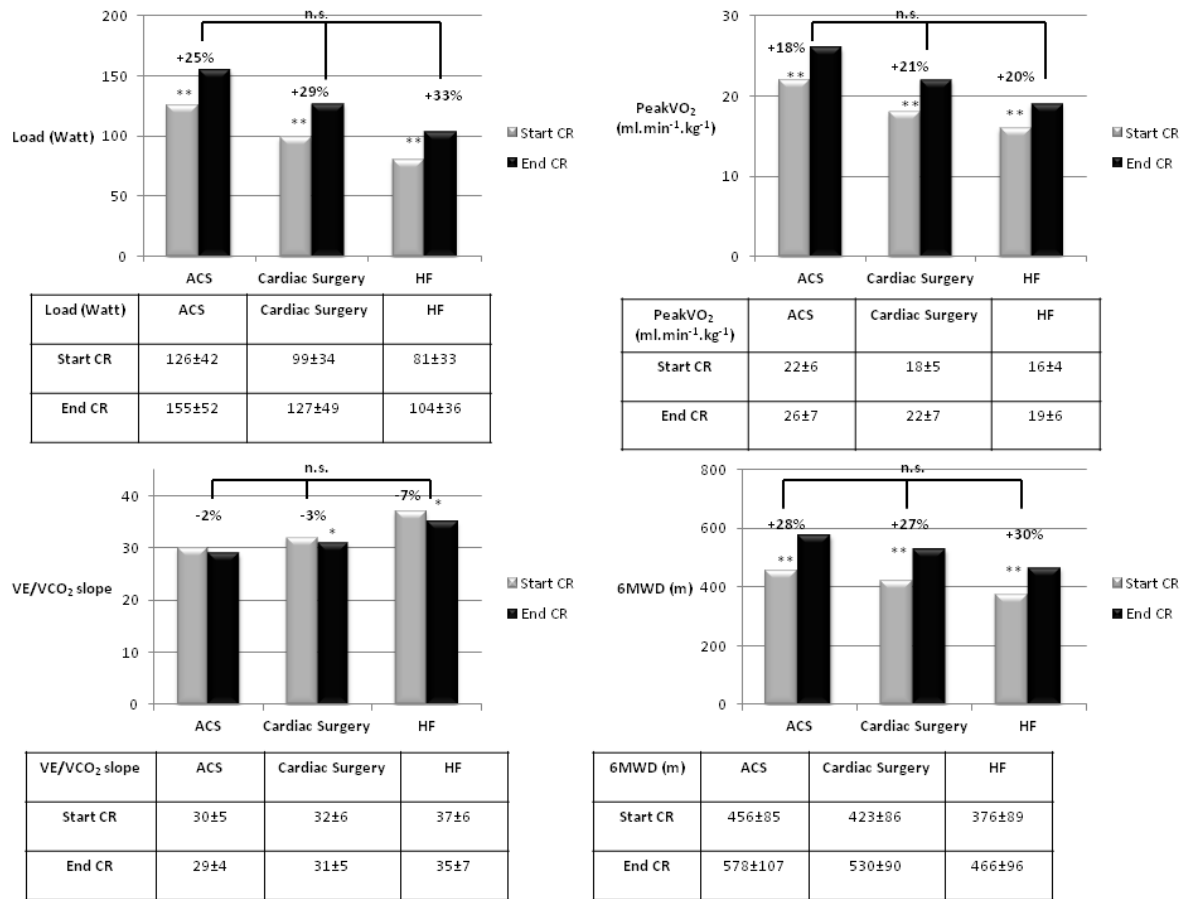
Figure 2. Exercise capacity and improvement after exercise training among the different patient groups. Exercise capacity – expressed as the load, peakVO$_2$, VE/VCO$_2$ slope, and 6MWD – is shown at the start and end of the cardiac rehabilitation program. Variables are presented as the mean ±SD in the table. The improvement in exercise capacity is presented in percentage (%) above the bars in each group separately. Significance levels are indicated with an asterisk (*p <0.05, **p <0.001). Differences in training benefits between the patient groups are shown on top of the figure.

CR, cardiac rehabilitation; ACS, acute coronary syndrome; HF, heart failure; peak VO$_2$, peak oxygen consumption; 6MWD, six-minute walking distance.

4 Discussion

Overall, one third of eligible patients attended CR after discharge from the hospital, but large differences were found between patient groups. Only 9% of hospitalized HF patients participated in CR, which is far below the achieved rates in ACS and cardiac surgery. Higher participation rates were already previously demonstrated in CABG patients and may be due to a greater perceived need for CR.[2, 6, 7] In addition, ACS patients have a shorter stay in hospital making it difficult to adequately refer to outpatient CR.[6] Although not assessed in our study, literature has shown that NSTEMI patients are

older and have more frequently comorbidities[8,9] which may result in a lower participation rate than in STEMI patients.

Despite the increasing number of patients with HF and the efficacy of exercise training to reduce mortality and hospitalisation in HF,[10, 11] barely one out of ten HF patients took part in CR. Neurohormonal activation, renal function and NYHA class were equal in both groups of HF, suggesting that disease severity did not have a major impact on participation in CR. Non-participants had a better left ventricular function, indicating the presence of heart failure with preserved ejection fraction (HFPEF). Also the higher age, the larger number of women and the presence of atrial fibrillation, which were all more frequently seen in non-participants, may be related to HFPEF.[12] This high rate of non-attendance to CR among HFPEF is likely due to the national government guidelines restricting reimbursement for CR to HF patients with reduced ejection fraction (HFREF). The gap between men and women may also be related to differences in social status, but this could not be assessed in our study.[6] Comorbidities, whether they are related to a higher age or not,[6] may also underlie the lower participation rate. One quarter of non-participants reported problems to walk independently at discharge from the hospital, which is a major barrier in daily life. Individual-tailored exercise programs should be offered to these patients at discharge from the hospital. The presence of cardiovascular risk factors for coronary artery disease, such as hyperlipidemia and smoking, resulted in a higher participation rate in CR. In this case, both physicians and patients may be aware of the importance of lifestyle modification thereby encouraging attendance to CR. Although our findings regarding hyperlipidemia were in agreement with the study of Worcester et al.,[6] this author reported that smoking appeared to reduce participation in CR. Other studies indicated that risk factor status did have little influence on CR participation.[13]

In comparison with patients participating after cardiac surgery or ACS, HF patients had obviously a worse clinical status which may explain their lower baseline exercise capacity at the start of CR. However, their benefit of exercise training was equal with substantial improvements in exercise capacity and to a lesser extent in ventilatory efficiency, which may have important prognostic implications. In addition to the high-tech therapies that have emerged in recent years, clinicians and patients should also be aware of the potential of cardiac rehabilitation in the treatment of this vulnerable population. Future studies and guidelines should adequately address potential barriers to CR in order to increase the participation in cardiac rehabilitation among heart failure patients.

4.1   Limitations

Our study was performed in a single-hospital making generalisation of our data difficult. However, to our knowledge these are the first data on attendance to CR in HF for Belgium. Due to the differences in reimbursement guidelines, these data are not applicable to other countries. In addition to clinical characteristics, psychosocial factors and exercise capacity at discharge from the hospital may have influenced the decision for (non-)participation in HF patients and this should be subject of further investigation.

5   Conclusion

Only 9% of HF patients participates in CR after hospitalisation. Age, female gender, a relatively well preserved ventricular function and atrial fibrillation seem to impede attendance to CR. However, HF patients can have as much improvement in exercise capacity as other patient populations, suggesting that more effort is needed to increase participation in CR among HF patients.

6   References

1. Piepoli MF, Corra U, Benzer W, et al. Secondary prevention through cardiac rehabilitation: from knowledge to implementation. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc Prev Rehabil.* 2010; 17: 1-17.

2. Bjarnason-Wehrens B, McGee H, Zwisler AD, et al. Cardiac rehabilitation in Europe: results from the European Cardiac Rehabilitation Inventory Survey. *Eur J Cardiovasc Prev Rehabil.* 2010; 17: 410-8.

3. De Vos C, Li X, Van Vlaenderen I, Saska O, Dendale P, Eyssen M and Paulus D. Participating or not in a cardiac rehabilitation programme: factors influencing a patient's decision. *Eur J Prev Cardiol.* 2013; 20: 341-8.

4. De Sutter J, Weytjens C, Van de Veire N, et al. Prevalence of potential cardiac resynchronization therapy candidates and actual use of cardiac resynchronization therapy in patients hospitalized for heart failure. *Eur J Heart Fail.* 2011; 13: 412-5.

5. Conraads VM and Beckers PJ. Exercise training in heart failure: practical guidance. *Heart.* 2010; 96: 2025-31.

6. Worcester MU, Murphy BM, Mee VK, Roberts SB and Goble AJ. Cardiac rehabilitation programmes: predictors of non-attendance and drop-out. *Eur J Cardiovasc Prev Rehabil.* 2004; 11: 328-35.

7. Shanmugasegaram S, Oh P, Reid RD, McCumber T and Grace SL. Cardiac rehabilitation barriers by rurality and socioeconomic status: a cross-sectional study. *Int J Equity Health.* 2013; 12: 72.

8. Polonski L, Gasior M, Gierlotka M,et al. A comparison of ST elevation versus non-ST elevation myocardial infarction outcomes in a large registry database: are non-ST myocardial infarctions associated with worse long-term prognoses? *Int J Cardiol.* 2011; 152: 70-7.

9. Brener SJ, Weisz G, Maehara A, et al. Does clinical presentation affect outcome among patients with acute coronary syndromes undergoing percutaneous coronary intervention? Insights from the Providing Regional Observations to Study Predictors of Events in the Coronary Tree study. *Am Heart J.* 2012; 164: 561-7.

10. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA.* 2009; 301: 1439-50.

11. Taylor RS, Sagar VA, Davies EJ, et al. Exercise-based rehabilitation for heart failure. *Cochrane Database Syst Rev.* 2014; 4: Cd003331.

12. Lund LH, Donal E, Oger E, et al. Association between cardiovascular vs. non-cardiovascular co-morbidities and outcomes in heart failure with preserved ejection fraction. *Eur J Heart Fail.* 2014.

13. McKee G, Biddle M, S OD, Mooney M, O'Brien F and Moser DK. Cardiac rehabilitation after myocardial infarction: What influences patients' intentions to attend? *Eur J Cardiovasc Nurs.* 2013; 13: 329-37.

Chapter 7.

Comorbidities and psychosocial characteristics as determinants of drop-out in outpatient cardiac rehabilitation

Pardaens Sofie, De Smedt Delphine, De Bacquer Dirk, Willems Anne-Marie, Verstreken Sofie, De Sutter Johan

Abstract

Background: Despite the clear benefits of cardiac rehabilitation (CR), a considerable number of patients drop out early.

Objective: Therefore, we wanted to evaluate drop-out in CR in Belgium with a special focus on comorbidities and psychosocial background.

Methods: Patients who attended CR after acute coronary syndrome, cardiac surgery or heart failure (n=489) were prospectively included. Drop-out was defined as attending ≤50% of the training sessions (n=96, 20%). Demographic and clinical characteristics, exercise parameters and psychosocial factors were analysed according to drop-out and those with a trend towards a significant difference (p<0.10) were entered in a multivariate logistic model.

Results: The presence of chronic obstructive pulmonary disease (2.55[0.99-6.54]) or cerebrovascular accident (4.18[1.39-12.52]) involved a higher risk for drop-out as well as attending the training program only twice per week (3.76[2.23-6.35]). In contrast, patients on β blockers were less likely to withdraw prematurely (0.47[0.22-0.98]). Singles were more likely to drop out (2.89[1.56-5.35]) as well as those patients who were dependent on others to get to CR (2.01[1.16-3.47]). Finally, the reporting of severe problems on the anxiety/depression subscale of the EuroQOL-5D questionnaire involved a higher odds for drop-out (7.17[1.46-35.29]).

Conclusion: Demographic characteristics nor clinical status or exercise capacity could independently identify patients who were at risk for drop-out. The presence of comorbidities and a vulnerable psychosocial background rather seem to play a key role in drop-out.

Keywords: cardiac rehabilitation, drop-out, comorbidities, exercise capacity, psychosocial characteristics

1 Introduction

Cardiac rehabilitation (CR) has been shown to reduce the risk for mortality and hospitalisation, particularly in coronary artery disease. [1-6] Despite these clear benefits, more than half of eligible patients do not attend CR, [7, 8] mainly because of personal or logistic reasons. [8-10] In addition, a considerable number of those patients who actually attend CR, drop out prematurely varying from 22 to 65%. [11, 12] This may be partly due to personal (perception of self control of the problem, illness cognition, socioeconomic status) or financial reasons [9, 11, 13, 14] but also physical and psychological health problems may play a key role. [9, 12]

The majority of these studies have often focused on a particular subgroup of cardiac patients which may not always be representative for the total CR population. Therefore, the aim of our study was to evaluate drop-out in CR among a Belgian cardiac population consisting of patients after acute coronary syndrome, cardiac surgery and heart failure, with a focus on potential predisposing demographic and clinical characteristics, exercise parameters and psychosocial factors which could lead to drop-out.

2 Methods

2.1 Study population

489 patients who attended CR after hospitalisation for acute coronary syndrome (n=204), cardiac surgery (n=245) or heart failure (n=40) in two Belgian hospitals (AZ Maria Middelares Ghent and Onze-Lieve-Vrouw Hospital Aalst) between April 2011 and March 2013 were prospectively included. In both hospitals, a similar multidisciplinary outpatient CR program was offered to each patient with a maximum of 45 reimbursed sessions, which is further explained in this section. Since the length of phase II rehabilitation programs varies across countries, drop-out was defined as attending ≤50% of the rehabilitation program which is consistent with previous studies. [11]

2.2 Ethics

This study protocol was approved by the ethical committee of the two participating hospitals (AZ Maria Middelares Ghent and Onze-Lieve-Vrouw Hospital Aalst) and all patients gave informed

consent. The clinical investigations conform with the principles outlined in the Declaration of Helsinki.

2.3   Clinical characteristics

Demographic characteristics, medication use, risk factors and comorbidities were collected at start of CR, based on chart review. A standard blood sample was taken to measure hematological parameters, glucose metabolism, lipids, renal function and N-Terminal pro brain natriuretic peptide. Echocardiography was performed on admission to the hospital in 456 patients with a measurement of left ventricular ejection fraction (Simpson's method).

2.4   Exercise testing

Cardiopulmonary exercise testing was performed in 411 patients, 24 days after hospitalisation (median 24 interquartile range [10,34]) on a cyclo-ergometer using a ramp protocol adapted to the patient's physical status. Ventilatory and respiratory gas measurements were obtained on a breath-by-breath basis using an Oxycon Pro spirometer (Jaeger – Viasys Healthcare, Germany). Heart rate was continuously registered by a 12-lead electrocardiogram and blood pressure was non-invasively measured, using a manual sphygmanometer every 2 minutes during the exercise test. Patients exercised to the limits of their functional capacities established by a respiratory exchange ratio >1.15 or until the physician stopped the test because of adverse signs and/or symptoms, such as chest pain, dizziness, potentially life-threatening arrhythmias, significant ST segment displacement (≥1mm), and marked systolic hypotension or hypertension. The maximal achieved load during incremental exercise was recorded. Peak oxygen consumption (peak VO_2) was defined as the mean of the last 30 seconds of peak exercise and was expressed as $ml.min^{-1}.kg^{-1}$. The slope of the linear relation between VE (y-axis) and VCO_2 (x-axis), the VE/VCO_2 slope, was calculated by including all data points to the end of exercise. The anaerobic threshold (AT) was defined as the exercise level at which ventilation starts to increase exponentially, relative to the increase in VO_2. [15] At the beginning of the exercise training program, a six-minute walk test (6MWT) was also performed in a 30m hallway. The distance a patient could quickly walk on a flat hard surface in a period of 6 minutes, was measured (six-minute walking distance).

2.5 Psychosocial and logistic factors

Educational background, social and occupational status were recorded as well as the dependency for transport and the distance to the CR centre. Health-related quality of life (HRQoL) was evaluated using the EuroQoL-5D-3L (EQ-5D-3L) which consists of two parts: the EQ-5D descriptive system and the EQ-5D visual analogue scale (EQ-5D VAS). The EQ-5D-3L descriptive system includes 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with 3 levels of severity of problems for each dimension (no problems, some problems, severe problems). An index value is calculated from the answers on the aforementioned dimensions with 1 representing perfect health, 0 representing death and <0 representing a health state perceived worse than death. The EQ-5D VAS is a visual analogue scale used to record the patients self-perceived health with 0 as the worst imaginable health state and 100 as the best imaginable health state. [16, 17] The Hospital Anxiety and Depression Scale (HADS) was applied for identifying those patients with symptoms of anxiety or depression. The HADS comprises 14 items, of which 7 are related to anxiety (HADS-A) and 7 to depression (HADS-D). Each item is scored on a four-point response scale (0-3) and the total score on each subscale ranges between 0 and 21. A score <8 could be regarded as being in the normal range whereas a score of 11 or higher indicates the probable presence of a mood disorder. A score between 8 and 10 is just suggestive of the presence of the respective state. [18]

2.6 Cardiac rehabilitation program

A multidisciplinary rehabilitation program was offered to each patient 29 [19-40] days after discharge from the hospital, including exercise training, dietary counseling, smoking cessation and psychological support. Patients had the choice to train 2 or 3 times weekly for 60 minutes during a period of 3 to 5 months with a maximum of 45 reimbursed sessions. Patients who withdrew prematurely attended 17 [10,20] training sessions, compared with 44 [38-45] training sessions in the group who continued the training program. The exercise training program consisted of a combination of aerobic and strengthening exercises. Body weight and waist were measured at start and end of the rehabilitation program and dietary counselling was offered to the patient as needed. Patients with an increased risk for anxiety or depression according to the HADS were invited for further psychological support.

2.7   Statistical methods

Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 21.0 (Armonk, New York, USA: IBM Corp). Clinical characteristics, baseline exercise capacity and psychosocial factors were assessed according to drop-out using the Chi square, Fisher exact, Independent Samples T test and Mann Whitney U test as appropriate. For all analyses, the level of significance was set at $p<0.05$. Variables with an overall significance value $p<0.10$ were entered in a multivariable backward logistic regression model to identify the strongest predictors for drop-out. Nagelkerke R^2 was reported to assess the percentage of variation that was explained by the model. Since the frequency of the training program was significantly different according to drop-out, differences in clinical and psychosocial characteristics between patients who trained 2 or 3 times per week were investigated in a supplementary analysis.

3   Results

3.1   Clinical characteristics according to drop-out

Clinical characteristics are summarized in table 1. In total, 96 of the 489 patients (20%) who attended CR, dropped out in the first half of the training program. Age and BMI were comparable, but women tended to drop out earlier than men during the course of CR ($p<0.05$). A quite similar clinical status was seen in both groups with a comparable left ventricular function, renal function and level of neurohormonal activation. Patients who were referred after coronary artery bypass graft were less likely to drop out than patients after acute coronary syndrome or heart failure ($p<0.05$). Comorbidities such as chronic obstructive pulmonary disease (COPD) and cerebrovascular accident (CVA) were significantly more present in those patients who ceased in the first half of the training program and β blockers were less prescribed in the latter group (all $p<0.05$). No differences were found in exercise capacity, except for a trend towards a slightly lower maximal achieved load ($p=0.051$). Patients who chose to attend the training program 3 times weekly were clearly less likely to drop-out in the first half of CR ($p<0.001$).

Table 1. Clinical characteristics according to drop out in cardiac rehabilitation

		Total population N=489	≤23 sessions N=96	>23 sessions N=393	P
Age (years)		60±11	60±13	60±11	0.824
Men (%)		80	72	81	0.038
BMI (kg/m²)		27±4	27±5	27±4	0.548
LVEF (%)		59±16	58±16	59±16	0.785
NT-proBNP (pg/ml)		475 (211-1073)	430 (246-1611)	482 (191-999)	0.588
Creatinin (mg/dl)		1 (0.8-1.1)	1 (0.8-1.1)	1 (0.8-1.1)	0.922
GFR (ml/min/1.73m²)		76 (65-91)	75 (63-91)	76 (65-89)	0.953
Exercise training after (%)	ACS	42	48	41	0.020
	Cardiac surgery	50	39	52	
	Heart failure	8	13	7	
Risk factors & comorbidities (%)					
	Hypertension	50	52	49	0.571
	Hyperlipidemia	71	69	72	0.594
	Diabetes	18	17	18	0.792
	Smoking	7	10	6	0.087
	COPD	5	10	4	0.048
	CVA	3	7	2	0.022
	PAD	5	8	4	0.109
	AF at start CR	1	1	2	1
Medication (%)					
	Antiplatelets	89	91	88	0.517
	Lipid lowering drugs	80	78	81	0.576
	β blockers	88	81	90	0.016
	ACE inhibitors/ ARB	51	53	50	0.598
	Diuretics	20	22	20	0.699
	Spironolacton	15	18	14	0.357
Exercise capacity					
	Load (Watt)	114±38	107±43	116±37	0.051
	HR at anaerobic threshold (/min)	100±17	99±16	100±17	0.696
	Peak VO$_2$ (ml.min^{-1}.kg^{-1})	19±6	18±6	19±6	0.102
	VE/VCO$_2$ slope	32±6	32±7	32±5	0.995
	6MWD (m)	432±93	420±104	436±89	0.178
Frequency training program (%)	2x/week	38	62	32	<0.001
	3x/week	62	38	68	

Categorical variables are presented as percentages, normally distributed continuous variables are presented as mean ± standard deviation, non normally continuous variables are presented as median (interquartile range).

BMI, body mass index; ACS, acute coronary syndrome; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro Brain Natriuretic Peptide; GFR, glomerular filtration rate; CR, cardiac rehabilitation; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; PAD, peripheral arterial disease; AF, atrial fibrillation; ACE inhibitors, Angiotensin Converting Enzym inhibitor, ARB, Angiotensin Receptor Blocker; HR, heart rate; peak VO$_2$, peak oxygen consumption; VE/VCO$_2$ slope, ventilatory slope; 6WMD, six-minute walking distance.

Table 2. Psychosocial and logistic factors according to drop out in cardiac rehabilitation

		Total population N=489	≤23 sessions N=96	>23 sessions N=393	P
Education level (%)	Primary education	32	39	30	0.153
	Secondary education	36	36	36	
	High education	32	25	34	
Partner (%)		83	71	86	<0.001
Occupational status (%)	Employed	39	37	39	0.160
	Retired	47	43	48	
	Others	14	20	13	
Dependency for transport to CR (%)		27	39	24	0.004
Distance to CR (%)	≤10km	32	32	31	0.930
	>10 and ≤20km	48	47	49	
	>20km	20	21	20	
EQ-5D Mobility (%)	No problems	81	75	82	0.109
	Some problems	19	25	18	
	Severe problems	0	0	0	
EQ-5D Self-care (%)	No problems	95	90	96	0.017
	Some problems	5	10	4	
	Severe problems	0	0	0	
EQ-5D Usual activities (%)	No problems	66	62	67	0.299
	Some problems	28	34	27	
	Severe problems	6	4	6	
EQ-5D Pain/ discomfort (%)	No problems	51	53	50	0.440
	Some problems	47	44	48	
	Severe problems	2	3	2	
EQ-5D Anxiety/ depression (%)	No problems	76	76	76	0.003
	Some problems	23	18	23	
	Severe problems	1	6	1	
$EQ-5D_{index}$		0.76 (0.66-1)	0.76 (0.66-1)	0.76 (0.66-1)	0.680
EQ-5D VAS		70 (60-75)	70 (60-80)	70 (60-75)	0.667
HADS – Anxiety		5 (3-8)	6 (2-9)	5 (3-8)	0.677
	score between (%) 0-7	69	62	71	0.129
	8-10	19	21	19	
	≥11	11	17	10	0.058
HADS – Depression		4 (2-7)	5 (2-8)	4 (2-7)	0.300
	score between (%) 0-7	77	73	78	0.085
	8-10	16	15	16	
	≥11	7	12	6	0.027

Categorical variables are presented as percentages, normally distributed continuous variables are presented as mean ± standard deviation, non normally continuous variables are presented as median (interquartile range). CR, cardiac rehabilitation; EQ-5D, EuroQOL-5D; VAS, visual analogue scale; HADS, hospital anxiety and depression scale.

3.2   Psychosocial and logistic factors according to drop-out

Table 2 shows the psychosocial and logistic factors according to drop-out. Educational and occupational status were comparable but patients without a partner were significantly more present in the group which has withdrawn prematurely (p<0.05). Evaluation of logistic factors revealed that patients who were dependent on others for getting to CR were more likely to drop out than those who came on their own to the centre (p<0.01). Patients who dropped out prematurely, reported

more problems regarding HRQoL on the dimensions of self-care and anxiety/depression of the EQ-5D-3L (all p<0.05). Nevertheless, their perception of health (EQ-5D VAS) was not significantly different. Also a higher percentage of patients with an increased risk for depression (HADS-D ≥11) was seen in the group which dropped out early from CR (p<0.05) and a similar trend was seen for patients with an increased risk for anxiety (HADS-A ≥11) (p=0.058).

3.3   Logistic regression model for drop-out

Logistic backward regression was performed to identify the strongest predictors for drop-out and the remaining significant variables are shown in table 3. The presence of comorbidities involved a higher risk for early withdrawal with patients suffering from COPD being nearly three times as likely (2.55 [0.99-6.54]) to drop out and patients with CVA having four times (4.18 [1.39-12.52]) higher odds for drop out. Also attending the training program only two times per week involved a higher odds for early withdrawal (3.76 [2.23-6.35]). Patients on β blocker therapy on the other hand, were less likely to cease in the first half of the training program than patients who did not have β blocker therapy (0.47 [0.22-0.98]). Also several psychosocial characteristics remained in the final logistic regression model. Singles had a three times higher risk for drop-out (2.89 [1.56-5.35]) and being dependent on others to get to CR involved twice as much risk for drop-out (2.01 [1.16-3.47]). The reporting of severe problems on the anxiety/depression subscale of the EQ-5D was a final significant predictor for early withdrawal (7.17 [1.46-35.29]). Together, these variables explained approximately one fifth of the total variation in drop-out (Nagelkerke R^2=0.215).

Table 3. Logistic regression model for drop out in cardiac rehabilitation

	Odds ratio	95% CI	P
COPD	2.55	0.99-6.54	0.050
CVA	4.18	1.39-12.52	0.011
β blockers	0.47	0.22-0.98	0.043
Training program twice per week	3.76	2.23-6.35	<0.001
No partner	2.89	1.56-5.35	0.001
Dependency for transport to CR	2.01	1.16-3.47	0.013
EQ-5D anxiety/depression			0.009
Some problems	0.57	0.30-1.09	0.087
Severe problems	7.17	1.46-35.29	0.015

COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; CR, cardiac rehabilitation; EQ-5D, EuroQOL-5D.

3.4   Clinical, psychosocial and logistic factors according to the frequency of training program

Supplementary analyses according to the frequency of the training program are described in supplement 1 and 2. Patients who attended CR only twice per week, were slightly older and more frequently women (all p<0.001). They also had signs of a worse clinical status with a trend towards a decreased left ventricular function (p=0.052) and an increased neurohormonal activation (p<0.01). Renal function was equal in both groups. No differences in risk factors, comorbidities or medication were found, except for diuretics which were more frequently prescribed in patients who trained twice per week (p<0.05). An impaired exercise capacity was seen in patients who attended CR twice per week with a decrease in load, peak VO$_2$ and six-minute walking distance (all p<0.001).

A lower education level was seen in the group which trained twice per week as well as more singles (both p<0.05). Patients attending CR only twice per week were also more frequently professionally inactive (p<0.01). In addition, they reported more problems regarding mobility and self-care influencing HRQoL (both p<0.01).

4   Discussion

In this prospective analysis of potential determinants of drop-out, one fifth of our patient population quit in the first half of the CR program with a higher risk in patients presenting with comorbidities and a vulnerable psychosocial background.

Although demographic factors, age and gender, were predictive of drop-out in the report of Yohannes et al., [12] these were not crucial in our study. Women were slightly more represented in the group which dropped out early but this may be explained by the fact that women were more frequently single (26% vs. 15%) and dependent on others to get to CR (39% vs. 24%). Multivariate analysis revealed that being single or being dependent for transport were main drivers of drop-out rather than gender which is in line with previous findings. [11, 19] Similarly, clinical status as expressed by ventricular function, neurohormonal activation and renal function, was equal in both groups, suggesting that disease severity did not influence drop-out. On the other hand, the majority of patients participating in CR in our hospitals, were referred after cardiac surgery and they were also more likely to continue the training program than others, although this could not be confirmed in multivariate analysis. Their greater participation rate is rather due to the lack of perceived need for CR in other patient groups [11, 20] than to differences in clinical status. Surprisingly, baseline exercise capacity did neither have any influence on withdrawal, suggesting that physically impaired patients may as well successfully complete their program as patients who are fitter at the start of CR.

Traditional cardiovascular risk factors such as smoking and diabetes have been related to drop-out in the past, [11] but this was not supported by our results. Interestingly, the presence of comorbidities, in particular a history of CVA and COPD, turned out to play a key role. COPD has generally been recognized as an independent predictor of all-cause mortality in heart failure [21-24] and likewise, the presence of CVA after acute myocardial infarction has been related to a higher risk for mortality. [25] In addition, the presence of COPD may implicate a lower use of B-blockers, [26] which in turn also involves a higher risk for drop-out.

Dependency for transport was a major predictor of drop-out, but not the distance to the CR center which was previously mentioned as an important barrier to attend CR. [9, 20] In contrast to countries with rural areas, [20, 27] the majority of our patients was living within a radius of 20km of the CR centre making it unlikely that distance itself was a major issue. Since being dependent for transport and having no partner were key drivers in drop-out, this suggests that a vulnerable social situation is more important than logistic barriers.

Furthermore, HRQoL was a major determinant in our study. Patients who dropped out early, reported significantly more problems at the start of CR regarding self-care and symptoms of anxiety and depression. In coronary artery disease patients, an impaired HRQoL has been reported with problems on several dimensions of the EQ-5D except for self-care. [28] This discrepancy regarding self-care may be due to a difference in time after the event. Since our patients were in the acute phase after their event (<6months), problems regarding self-care were more likely than at a later stage as in the previous study. [28] Perhaps more important than self-care, were the reported problems on anxiety and depression. Strikingly, only the severe problems did have an impact on drop-out. HRQoL is known to be related to lifestyle risk factors and may, together with psychological distress, be improved by modifying these risk factors. [29-32] However, symptoms of depression and anxiety are associated with a less frequent modification of lifestyle [33] which is in line with our findings on drop-out. Consequently, those patients who are most likely to benefit from CR, are unfortunately just the ones who are at high risk of drop-out.

Another strong predictor of early withdrawal seemed to rely on the choice whether patients preferred to attend CR 2 or 3 times weekly. Supplementary analyses revealed differences in the patient profile. Patients who attended CR only twice per week were slightly older and more frequently women. Moreover, they had a worse clinical status and a lower exercise capacity at the start of CR and they also differed in their psychosocial profile. Taken together, these demographic, clinical and psychosocial characteristics which did not influence withdrawal independently, actually

may have an impact on drop-out by influencing the choice of the training program. However, this should be subject of further investigations.

4.1 Strengths and limitations

This study has several strengths but also limitations. First, all patients were prospectively included at the beginning of the CR program, regardless of the recruiting diagnosis. Therefore, our study population is a fairly good representation of the 'real life' CR population. Another strength may be that we did not rely on the reasons for drop-out given by the patients, but we have prospectively collected potential predictors at the beginning of CR to see what their impact was on the course of the program. In spite of the broad spectrum of included variables, some interesting variables are lacking such as information on illness cognition and perception and the influence of the income which have been demonstrated to be important in literature. [9, 12, 14, 20] Only 21% of the variation was explained, suggesting that other unknown factors are involved in this complex issue.

5 Conclusions

This study aimed to evaluate potential predisposing factors for drop-out in CR. Demographic characteristics nor clinical status or exercise capacity could independently identify patients who were at risk for drop-out. The presence of comorbidities and a vulnerable psychosocial background rather seem to play a key role in drop-out.

6   References

1. Belardinelli R, Georgiou D, Cianci G and Purcaro A. Exercise training for patients with chronic heart failure reduced mortality and cardiac events and improved quality of life. *West J Med*. 2000; 172: 28.

2. Goel K, Lennon RJ, Tilbury RT, Squires RW and Thomas RJ. Impact of cardiac rehabilitation on mortality and cardiovascular events after percutaneous coronary intervention in the community. *Circulation*. 2011; 123: 2344-52.

3. Goel K, Pack QR, Lahr B, et al. Cardiac rehabilitation is associated with reduced long-term mortality in patients undergoing combined heart valve and CABG surgery. *Eur J Prev Cardiol*. 2013.

4. Martin BJ, Arena R, Haykowsky M, et al. Cardiovascular fitness and mortality after contemporary cardiac rehabilitation. *Mayo Clin Proc*. 2013; 88: 455-63.

5. Pack QR, Goel K, Lahr BD, et al. Participation in cardiac rehabilitation and survival after coronary artery bypass graft surgery: a community-based study. *Circulation*. 2013; 128: 590-7.

6. Lewinter C, Bland JM, Crouch S, et al. The effect of referral for cardiac rehabilitation on survival following acute myocardial infarction: a comparison survival in two cohorts collected in 1995 and 2003. *Eur J Prev Cardiol*. 2014; 21: 163-71.

7. Bjarnason-Wehrens B, McGee H, Zwisler AD, et al. Cardiac rehabilitation in Europe: results from the European Cardiac Rehabilitation Inventory Survey. *Eur J Cardiovasc Prev Rehabil*. 2010; 17: 410-8.

8. Neubeck L, Freedman SB, Clark AM, Briffa T, Bauman A and Redfern J. Participating in cardiac rehabilitation: a systematic review and meta-synthesis of qualitative data. *Eur J Prev Cardiol*. 2012; 19: 494-503.

9. De Vos C, Li X, Van Vlaenderen I, et al. Participating or not in a cardiac rehabilitation programme: factors influencing a patient's decision. *Eur J Prev Cardiol*. 2013; 20: 341-8.

10. McKee G, Biddle M, S OD, Mooney M, F OB and Moser DK. Cardiac rehabilitation after myocardial infarction: What influences patients' intentions to attend? *Eur J Cardiovasc Nurs*. 2013.

11. Worcester MU, Murphy BM, Mee VK, Roberts SB and Goble AJ. Cardiac rehabilitation programmes: predictors of non-attendance and drop-out. *Eur J Cardiovasc Prev Rehabil*. 2004; 11: 328-35.

12. Yohannes AM, Yalfani A, Doherty P and Bundy C. Predictors of drop-out from an outpatient cardiac rehabilitation programme. *Clin Rehabil*. 2007; 21: 222-9.

13. Scotto CJ, Waechter D and Rosneck J. Factors affecting program completion in phase II cardiac rehabilitation. *Can J Cardiovasc Nurs*. 2011; 21: 15-20.

14. Lemstra ME, Alsabbagh W, Rajakumar RJ, Rogers MR and Blackburn D. Neighbourhood income and cardiac rehabilitation access as determinants of nonattendance and noncompletion. *Can J Cardiol*. 2013; 29: 1599-603.

15. Conraads VM and Beckers PJ. Exercise training in heart failure: practical guidance. *Heart*. 2010; 96: 2025-31.

16. Dolan P. Modeling valuations for EuroQol health states. *Med Care*. 1997; 35: 1095-108.

17. Rabin R and de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med*. 2001; 33: 337-43.

18. Snaith RP. The Hospital Anxiety And Depression Scale. *Health and quality of life outcomes*. 2003; 1: 29.

19. Marzolini S, Brooks D and Oh PI. Sex differences in completion of a 12-month cardiac rehabilitation programme: an analysis of 5922 women and men. *Eur J Cardiovasc Prev Rehabil*. 2008; 15: 698-703.

20. Shanmugasegaram S, Oh P, Reid RD, McCumber T and Grace SL. Cardiac rehabilitation barriers by rurality and socioeconomic status: a cross-sectional study. *Int J Equity Health*. 2013; 12: 72.

21. Rusinaru D, Saaidi I, Godard S, Mahjoub H, Battle C and Tribouilloy C. Impact of chronic obstructive pulmonary disease on long-term outcome of patients hospitalized for heart failure. *Am J Cardiol*. 2008; 101: 353-8.

22. Kwon BJ, Kim DB, Jang SW, et al. Prognosis of heart failure patients with reduced and preserved ejection fraction and coexistent chronic obstructive pulmonary disease. *Eur J Heart Fail*. 2010; 12: 1339-44.

23. Mentz RJ, Fiuzat M, Wojdyla DM, et al. Clinical characteristics and outcomes of hospitalized heart failure patients with systolic dysfunction and chronic obstructive pulmonary disease: findings from OPTIMIZE-HF. *Eur J Heart Fail*. 2012; 14: 395-403.

24. Yoshihisa A, Takiguchi M, Shimizu T, et al. Cardiovascular function and prognosis of patients with heart failure coexistent with chronic obstructive pulmonary disease. *J Cardiol*. 2014.

25. Brammas A, Jakobsson S, Ulvenstam A and Mooe T. Mortality after ischemic stroke in patients with acute myocardial infarction: predictors and trends over time in Sweden. *Stroke*. 2013; 44: 3050-5.

26. Le Jemtel TH, Padeletti M and Jelic S. Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. *J Am Coll Cardiol*. 2007; 49: 171-80.

27. De Angelis C, Bunker S and Schoo A. Exploring the barriers and enablers to attendance at rural cardiac rehabilitation programs. *Aust J Rural Health*. 2008; 16: 137-42.

28. De Smedt D, Clays E, Annemans L, Pardaens S, Kotseva K and De Bacquer D. Self-reported health status in coronary heart disease patients: A comparison with the general population. *Eur J Cardiovasc Nurs*. 2014.

29. De Smedt D, Clays E, Annemans L, et al. Health related quality of life in coronary patients and its association with their cardiovascular risk profile: results from the EUROASPIRE III survey. *Int J Cardiol*. 2013; 168: 898-903.

30. Smedt DD, Clays E, Annemans L, et al. The association between self-reported lifestyle changes and health-related quality of life in coronary patients: the EUROASPIRE III survey. *Eur J Prev Cardiol*. 2013.

31. Piper ME, Kenford S, Fiore MC and Baker TB. Smoking cessation and quality of life: changes in life satisfaction over 3 years following a quit attempt. *Ann Behav Med*. 2012; 43: 262-70.

32. Martin CK, Church TS, Thompson AM, Earnest CP and Blair SN. Exercise dose and quality of life: a randomized controlled trial. *Arch Intern Med.* 2009; 169: 269-78.

33. Pajak A, Jankowski P, Kotseva K, Heidrich J, de Smedt D and De Bacquer D. Depression, anxiety, and risk factor control in patients after hospitalization for coronary heart disease: the EUROASPIRE III Study. *Eur J Prev Cardiol*. 2013; 20: 331-40.

Supplement 1. Clinical characteristics according to frequency of the training program

	Total population N=489	2x/week N=183	3x/week N=304	P
Age (years)	60±11	62±12	59±10	<0.001
Men (%)	80	71	85	<0.001
BMI (kg/m²)	27±4	27±4	27±4	0.061
LVEF (%)	59±16	57±16	60±15	0.052
NT-proBNP (pg/ml)	475 (211-1073)	606 (246-1582)	413 (188-872)	0.006
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Exercise training after (%) ACS	42	39	43	0.609
Cardiac surgery	50	51	49	
Heart failure	8	10	8	
Risk factors & comorbidities (%)				
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Hyperlipidemia	71	72	71	0.839
Diabetes	18	18	18	0.938
Smoking	7	5	7	0.310
COPD	5	6	5	0.572
CVA	3	4	3	0.604
PAD	5	6	4	0.392
AF at start CR	1	2	1	0.771
Medication (%)				
Antiplatelets	89	88	90	0.611
Lipid lowering drugs	80	80	81	0.828
β blockers	88	89	88	0.903
ACE inhibitors/ ARB	51	53	49	0.393
Diuretics	20	25	17	0.041
Spironolacton	15	16	14	0.379
Exercise capacity				
Load (Watt)	114±38	103±36	121±38	<0.001
HR at anaerobic threshold (/min)	100±17	98±17	101±17	0.092
Peak VO$_2$ (ml.min^{-1}.kg^{-1})	19±6	18±5	20±6	<0.001
VE/VCO$_2$ slope	32±6	33±6	32±6	0.050
6MWD (m)	432±93	399±102	452±80	<0.001
Training sessions	42 (29-45)	33 (20-42)	44 (38-45)	<0.001
Drop-out (%)	20	32	12	<0.001

Categorical variables are presented as percentages, normally distributed continuous variables are presented as mean ± standard deviation, non normally continuous variables are presented as median (interquartile range).
BMI, body mass index; ACS, acute coronary syndrome; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro Brain Natriuretic Peptide; GFR, glomerular filtration rate; CR, cardiac rehabilitation; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; PAD, peripheral arterial disease; AF, atrial fibrillation; ACE inhibitors, Angiotensin Converting Enzym inhibitor, ARB, Angiotensin Receptor Blocker; HR, heart rate; peak VO$_2$, peak oxygen consumption; VE/VCO$_2$ slope, ventilatory slope; 6WMD, six-minute walking distance.

Supplement 2. Psychosocial and logistic factors according to frequency of the training program

		Total population N=489	2x/week N=183	3x/week N=304	P
Education level (%)	Primary education	32	38	28	0.042
	Secondary education	36	36	36	
	High education	32	27	36	
Partner (%)		83	78	86	0.033
Occupational status (%)	Employed	39	26	47	0.001
	Retired	47	57	41	
	Others	14	17	12	
Dependency for transport to CR (%)		27	32	24	0.060
Distance to CR (%)	≤10km	32	36	28	0.176
	>10 and ≤20km	48	45	51	
	>20km	20	19	21	
EQ-5D Mobility (%)	No problems	81	73	86	0.001
	Some problems	19	27	14	
	Severe problems	0	0	0	
EQ-5D Self-care (%)	No problems	95	90	98	<0.001
	Some problems	5	10	2	
	Severe problems	0	0	0	
EQ-5D Usual activities (%)	No problems	66	63	68	0.120
	Some problems	28	29	28	
	Severe problems	6	8	4	
EQ-5D Pain/ discomfort (%)	No problems	51	50	51	0.190
	Some problems	47	47	48	
	Severe problems	2	3	1	
EQ-5D Anxiety/ depression (%)	No problems	76	71	78	0.153
	Some problems	23	26	21	
	Severe problems	1	3	1	
EQ-5D$_{index}$		0.76 (0.66-1)	0.75 (0.66-1)	0.76 (0.71-1)	0.042
EQ-5D VAS		70 (60-75)	69 (60-75)	70 (60-77)	0.057
HADS – Anxiety		5 (3-8)	5 (3-8)	5 (2-8)	0.359
score between (%)	0-7	69	67	70	0.366
	8-10	19	19	20	
	≥11	11	14	10	0.156
HADS – Depression		4 (2-7)	4 (2-7)	4 (2-7)	0.538
score between (%)	0-7	77	77	77	0.226
	8-10	16	13	17	
	≥11	7	9	6	0.165

Categorical variables are presented as percentages, normally distributed continuous variables are presented as mean ± standard deviation, non normally continuous variables are presented as median (interquartile range). CR, cardiac rehabilitation; EQ-5D, EuroQOL-5D; VAS, visual analogue scale; HADS, hospital anxiety and depression scale.

Chapter 8.

Impact of the preoperative risk and the type of surgery on exercise capacity and training after valvular surgery

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Abstract

Information on exercise capacity and training in patients who underwent valvular surgery is scarce. The aim of this study is to evaluate postoperative exercise capacity and functional improvement after exercise training according to the preoperative risk and type of surgery. In this prospective study, 145 patients who underwent aortic valve surgery (AVS) or mitral valve surgery (MVS) and who were referred for cardiac rehabilitation, were stratified according to the preoperative risk (European System for Cardiac Operative Risk Evaluation [EuroSCORE]) and type of surgery (sternotomy vs ministernotomy or port access). Exercise capacity was evaluated at the start and end of cardiac rehabilitation. Postoperative exercise capacity and the benefit from exercise training were compared between the groups. Patients with a higher preoperative risk, had a worse postoperative exercise capacity, with a lower load, peak VO_2, anaerobic threshold and 6-minute walking distance (all $p<0.001$) and a higher VE/VCO_2 slope ($p=0.01$). In MVS, port access patients performed significantly better at baseline (all $p<0.05$) but in AVS, ministernotomy patients performed better than sternotomy patients with a concomitant coronary artery bypass graft ($p<0.05$). Training resulted in an improvement in exercise capacity in each risk group and each type of surgery (all $p<0.05$). This gain in exercise capacity was comparable for the EuroSCORE risk groups and for the types of surgery, for patients after AVS or MVS. In conclusion, exercise capacity after cardiac surgery is related to the preoperative risk and the type of surgery. Despite these differences in postoperative exercise capacity, a similar benefit from exercise training is obtained, regardless of their preoperative risk or type of surgery.

Key words: valvular heart disease, minimal invasive surgery, exercise capacity, EuroSCORE

1   Introduction

Information on exercise capacity and exercise training in patients who underwent valvular surgery is scarce. Current literature suggests that exercise capacity does not recover spontaneously after aortic valve surgery (AVS) or mitral valve surgery (MVS).[1-3] This argues in favor of the need for cardiac rehabilitation. The primary aim of this study was to evaluate the difference in exercise capacity early after valvular surgery between patients with a low or high preoperative risk profile, assessed using the European System for Cardiac Operative Risk Evaluation (EuroSCORE). Similarly, the difference in postoperative exercise capacity was evaluated between patients after invasive versus minimal invasive surgery. The secondary aim was to assess whether the functional improvement after exercise training was affected by this preoperative risk profile or type of surgery.

2   Methods

One hundred and forty-five patients who underwent AVS (n=72) or MVS (n=73) for valvular regurgitation or stenosis and who were referred for cardiac rehabilitation between October 2007 and March 2012 were prospectively included. Patients with multivalvular disease were not eligible for inclusion and neither were patients with transcatheter aortic valve implantation or mitraclip because of the fewer number of these procedures. Only patients with classic sternotomy, ministernotomy or port access were considered for analysis. Combined coronary artery bypass graft (CABG) and valvular surgery was performed in 52 patients (36%). This study protocol was approved by the ethical committee of the two participating hospitals (AZ Maria Middelares Ghent and Onze-Lieve-Vrouw Hospital Aalst) and all patients gave informed consent. The clinical investigations were conducted according to the principles of the declaration of Helsinki.

The EuroSCORE was used to assess the mortality risk in cardiac surgery. EuroSCORE I calculation consists of patient, cardiac and operation-related factors and results in an additive and a logistic risk score.[4] According to the additive EuroSCORE, patients were divided into 3 risk groups.[5] A score ranging from 0 to 2 was classified as a low risk (n= 20), 3 to 5 as a medium risk (n=64) and > 5 as a high risk profile (n=60). EuroSCORE was not calculated for 1 patient because of missing data on left ventricular function. The decision regarding the type of surgery (classic sternotomy vs ministernotomy or port access) was made by the cardiac surgeon on the basis of preoperative clinical data and anatomic status.

Cardiopulmonary exercise testing was performed 1 month (31±16 days) after surgery on a cyclo-ergometer using a ramp protocol adapted to the patient's physical status. Ventilatory and respiratory gas measurements were obtained on a breath-by-breath basis using an Oxycon Pro spirometer (Jaeger – Viasys Healthcare, Germany). Heart rate was continuously registered by a 12-lead electrocardiogram and blood pressure was non-invasively measured, using a manual sphygmanometer every 2 minutes during the exercise test. Patients exercised to the limits of their functional capacities established by a respiratory exchange ratio >1.15 or until the physician stopped the test because of adverse signs and/or symptoms, such as chest pain, dizziness, potentially life-threatening arrhythmias, significant ST segment displacement (≥1mm), and marked systolic hypotension or hypertension. The maximal achieved load during incremental exercise was recorded. Peak oxygen consumption (peak VO_2) was defined as the mean of the last 30 seconds of peak exercise and was expressed as millilitre per minute per kilogram. The slope of the linear relation between VE (y axis) and VCO_2 (x axis), the VE/VCO_2 slope, was calculated by including all data points to the end of the exercise. The anaerobic threshold (AT) was defined as the exercise level at which ventilation starts to increase exponentially, relative to the increase in VO_2.[6] At the beginning of the exercise training program, a 6-minute walk test was performed in a 30-m hallway. The distance a patient could quickly walk in a period of 6 minutes (i.e. 6-minute walking distance [6MWD]) was measured. This protocol was repeated at the end of the rehabilitation program. The gain in exercise capacity was expressed as a percentage of improvement and calculated for the previously mentioned exercise parameters: (exercise parameter$_{end}$ – exercise parameter$_{start}$)/ (exercise parameter$_{start}$) *100.

Rehabilitation was initiated at the hospital on the first day after surgery and focused on respiration in combination with low-intensity aerobic exercises. After discharge, patients were encouraged to continue low-intensity aerobic exercises at home until they were referred for outpatient cardiac rehabilitation (43 ± 22 days after surgery). Outpatient rehabilitation was started not earlier than 4 weeks after surgery to ensure optimal healing. Patients trained 2 or 3 times a week for 60 minutes during a period of 3 to 5 months with a maximum of 45 sessions. The exercise training program consisted of a combination of aerobic and strengthening exercises. Aerobic training mainly included cycling (15 minutes), treadmill walking (15 minutes) and stepping (5 minutes) and was performed at an intensity of the heart rate at AT combined with an evaluation of the rating of perceived exertion. Strengthening exercises (15 minutes) primarily targeted lower body muscles with leg press and leg curl exercises at 60% of 1 repetition maximum for 2 sets of 15 to 20 repetitions. In a later phase, after the sternum had healed, upper body strength training for biceps, triceps and trunk was added. Every training session was initiated and terminated with 5 minutes warm-up and cool-down period.

Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 21.0 (Armonk, New York, USA: IBM Corp). Differences in clinical characteristics between patients who had AVS or MVS were assessed with chi square and Independent Samples *t* test or Mann Whitney *U* test, as appropriate. Because of an unequal number of patients and an unequal spread in variances, nonparametric tests were chosen for analyzing exercise capacity according to the preoperative risk profile. Differences in baseline exercise capacity and differences in functional improvement after the exercise training program were evaluated with Kruskal Wallis-test or Mann-Whitney *U* test, depending on the number of groups. A Wilcoxon matched- pairs signed-ranks test was used to evaluate the improvement after the exercise training program within each group separately. Same statistical tests were used to evaluate the differences between invasive versus minimal invasive surgery. A p value <0.05 was considered to be statistically significant.

3   Results

Clinical characteristics of the 145 study patients are listed in Table 1. Age, gender and body mass index were comparable between AVS and MVS. MVS patients had a slightly lower preoperative left ventricular function as compared with AVS patients (60% vs 67%, p<0.01). MVS was mainly performed for mitral regurgitation (97%) whereas AVS patients were mainly referred for aortic stenosis (75%). Mitral valve repair was performed in 85% of those who were referred for MVS. The large majority of patients who were referred for AVS underwent aortic valve replacement. In mitral valve disease, sternotomy was performed in 40 patients (55%), of whom 28 patients underwent also CABG and 33 patients (45%) underwent minimal invasive surgery through port access. Sternotomy was performed in 45 patients with aortic valve disease (63%) of whom 23 patients had a concomitant CABG and 27 patients (37%) underwent a ministernotomy. Patients attended 38 training sessions on an average; this number was comparable for AVS and MVS. At the end of the exercise training program, an overall increase in exercise capacity was seen in the total patient group with an increase of 31% in load, 23% in peak VO_2, 10% in AT and 26% in 6MWD. A decrease of 5% was recorded for the VE/VCO_2 slope.

Exercise capacity early after surgery and functional improvement after attending cardiac rehabilitation, was assessed for all patients according to the EuroSCORE risk profile (Figure 1). Patients with a higher preoperative risk, had a worse postoperative exercise capacity as expressed by a lower load, peak VO_2, AT and 6MWD (all p<0.001) and a higher VE/VCO_2 slope (p=0.01). Load, peak VO_2, and 6MWD at baseline were significantly different between the 3 risk groups (all p<0.01). AT

Table 1. Clinical characteristcs of the total patient group and patients who underwent AVS or MVS

Variable	Total group n=145	Mitral valve surgery n=73	Aortic valve surgery n=72	P value
Age (years)	64 ± 10	64 ± 9	65 ± 12	0.696
Men	74%	71%	76%	0.480
BMI (kg/m²)	26±4	25±3	26±4	0.128
LVEF (%)	64 ± 13	60 ± 15	67 ± 11	0.004
EuroSCORE risk profile				0.296
low risk	14%	18%	10%	
medium risk	44%	45%	43%	
high risk	42%	37%	47%	
Aetiology valve disease				<0.001
regurgitation	61%	97%	25%	
stenosis	39%	3%	75%	
AVS/MVS				<0.001
mechanical prosthetic valve	17%	4%	30%	
bioprosthetic valve	40%	11%	69%	
repair	43%	85%	1%	
CABG	36%	38%	33%	0.528
Type of surgery				<0.001
sternotomy	58%	55%	63%	
ministernotomy	19%	-	37%	
port access	23%	45%	-	
NYHA classification				0.990
I	69%	70%	68%	
II	26%	25%	27%	
III	5%	5%	5%	
NT-proBNP (pg/ml)	565 (309-1149)	686 (357-1508)	476 (297-919)	0.225
Hypertension	50%	45%	54%	0.281
Hyperlipidemia	40%	44%	36%	0.342
Diabetes	12%	4%	19%	0.004
Smoking	9%	6%	12%	0.271
COPD	1%	2%	0%	0.489
PAD	3%	3%	4%	0.681
AF at start cardiac rehabilitation	13%	12%	14%	0.781
Pacemaker	6%	4%	7%	0.494
Medication				
B-blocker	88%	82%	94%	0.022
ACE-I/ARB	37%	34%	39%	0.562
diuretics	26%	29%	22%	0.366
statins	49%	44%	54%	0.213

Categorical variables are presented as percentages, normally distributed continuous variables are presented as mean ± SD, non normally continuous variables are presented as median (interquartile range).
ACE-I, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NT-proBNP, N-Terminal pro brain natriuretic peptide; NYHA, New York Heart Association; PAD, peripheral arterial disease.

was significantly decreased, and VE/VCO$_2$ slope was significantly increased in the high-risk group as compared with the low- and medium-risk group (all $p<0.05$). Exercise training resulted in a significant improvement in load, peak VO$_2$, AT and 6MWD in each risk group separately (all $p<0.01$). A small but significant decrease in the VE/VCO$_2$ slope was only present in the medium- and high-risk patient groups ($p<0.05$). The percentage of improvement in exercise capacity was comparable in low-, medium- and high-risk groups. Table 2 lists the training effects according to the preoperative risk

profile, stratified by aortic and mitral valve disease. In patients with MVS, postoperative exercise capacity was significantly worse in high-risk as compared with low-/medium-risk patients (all p<0.01). In contrast, load, peak VO_2, AT and 6MWD were lower but not significantly different in high-risk as compared with low-/medium-risk AVS patients. Only in AVS, VE/VCO_2 slope was significantly higher in high-risk patients (p<0.05). After exercise training, distinct improvements in load, peak VO_2 and 6MWD were seen in all groups (all p<0.01). An increase in the AT was present in MVS (all p<0.05). The VE/VCO_2 slope was significantly decreased in the high-risk group of AVS (p<0.05). The functional improvement in exercise capacity was generally comparable in low-/medium-risk and high-risk patients, for AVS and MVS.

Load (Watt)	Low risk	Medium risk	High risk
Start CR	148±37	100±29	79±24
End CR	201±52	127±39	103±32

Peak VO_2 (ml.min^{-1}.kg^{-1})	Low risk	Medium risk	High risk
Start CR	27±7	18±4	16±4
End CR	33±6	23±6	19±5

VE/VCO_2 slope	Low risk	Medium risk	High risk
Start CR	28±5	31±5	36±6
End CR	26±5	30±6	34±7

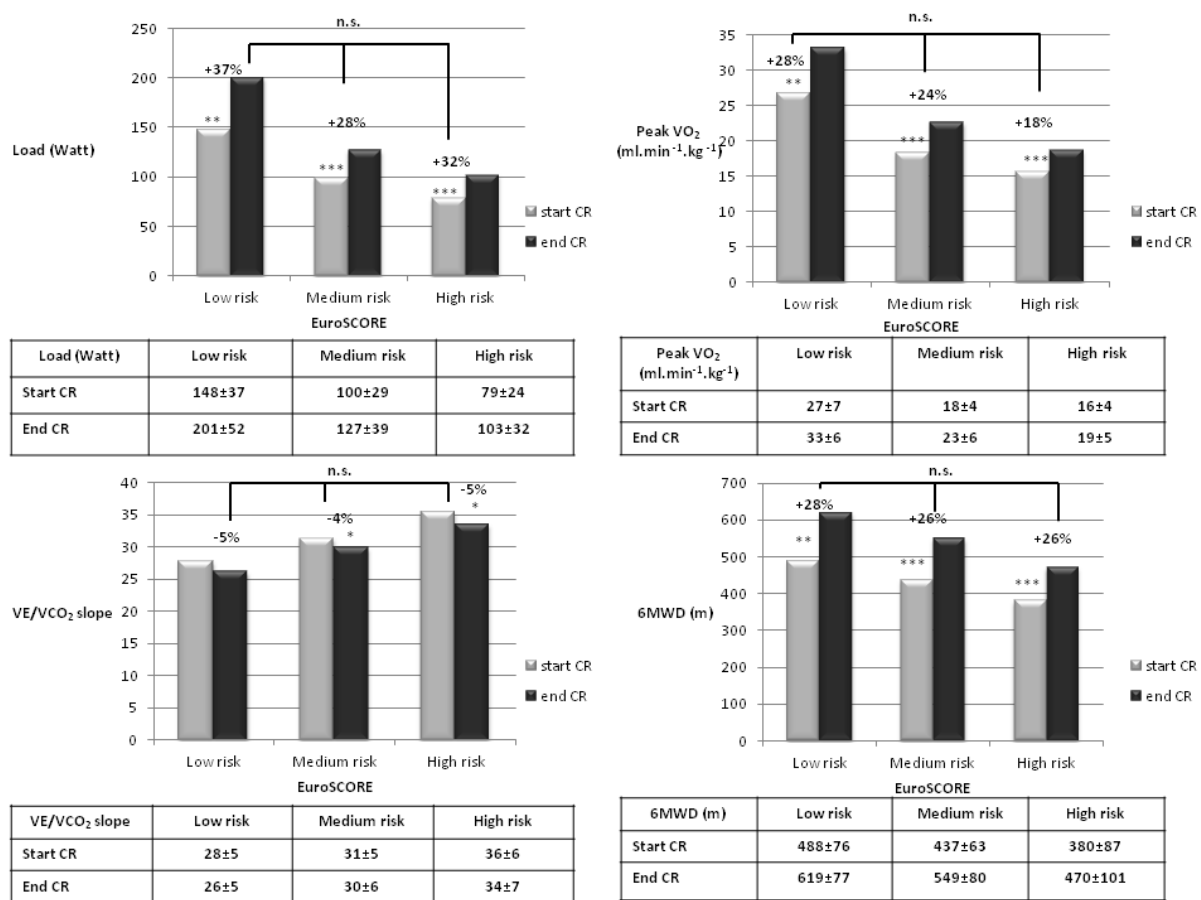| 6MWD (m)	Low risk	Medium risk	High risk
Start CR	488±76	437±63	380±87
End CR	619±77	549±80	470±101

Figure 1. Exercise capacity and training benefits according to the preoperative risk profile

Exercise capacity after valvular surgery - expressed as the load, peak VO_2, VE/VCO_2 slope and 6MWD- is shown at the start and end of the cardiac rehabilitation program, according to the EuroSCORE risk profile. Variables are presented as the mean ± SD in the table. The improvement in exercise capacity is presented in percentage (%) above the bars in each group separately, significance levels are indicated with an asterisk (*p<0.05 **p<0.01 and ***p<0.001). Differences in training benefits between the EuroSCORE risk groups are shown on top of the figure. CR, cardiac rehabilitation.

Table 2. Training effect according to the preoperative risk profile, stratified by valve disease

Variable	MVS (n=73)					AVS (n=71)				
	low/medium risk (n=46)		high risk (n=27)		diff in training effects between risk groups	low/medium risk (n=38)		high risk (n=33)		diff in training effects between risk groups
	mean ± SD	p value	mean ± SD	p value	p value	mean ± SD	p value	mean ± SD	p value	p value
Load (Watt)										
start CR	122 ± 36	] <0.001	78 ± 22***	] 0.001		102 ± 39	] <0.001	80 ± 26	] 0.004	
end CR	157 ± 49		98 ± 30			136 ± 60		108 ± 35		
Δ Load (%)	29 ± 16		26 ± 22		0.452	33 ± 20		39 ± 36		0.918
Peak VO$_2$ (ml.min^{-1}.kg^{-1})										
start CR	21 ± 6	] <0.001	15 ± 4***	] 0.006		19 ± 6	] 0.001	17 ± 3	] 0.003	
end CR	26 ± 8		17 ± 5			25 ± 6		21 ± 5		
Δ Peak VO$_2$ (%)	23 ± 18		15 ± 17		0.135	29 ± 27		23 ± 21		0.603
HR at AT (/min)										
start CR	99 ± 17	] 0.004	86 ± 12**	] 0.028		102±12	] 0.134	99±24	] 0.209	
end CR	110 ± 18		92 ± 11			109±17		107±21		
Δ HR at AT (%)	12 ± 20		8 ± 11		0.577	8±17		9±20		0.930
VE/VCO$_2$ slope										
start CR	31 ± 5	] 0.092	35 ± 7	] 0.422		30 ± 7	] 0.101	36 ± 5*	] 0.012	
end CR	30 ± 6		35 ± 8			28 ± 5		32 ± 4		
Δ VE/VCO$_2$ slope (%)	-4 ± 12		-2 ± 12		0.553	-5 ± 13		-9 ± 8		0.186
6MWD (m)										
start CR	472 ± 62	] <0.001	359 ± 76***	] <0.001		430 ± 69	] <0.001	394 ± 92	] <0.001	
end CR	582 ± 73		460 ± 93			551 ± 90		478 ± 108		
Δ 6MWD (%)	24 ± 13		30 ± 24		0.501	29 ± 13		22 ± 13		0.021

Data are presented as mean ± SD. Differences in baseline exercise capacity between low-/medium-risk and high-risk groups are presented with an asterisk *p<0.05**p<0.01 ***p<0.001.
CR, cardiac rehabilitation; Diff, difference; HR at AT, heart rate at the anaerobic threshold; Δ HR at AT (%), percentage of improvement in the HR at AT after exercise training; Δ load (%), percentage of improvement in load after exercise training; Δ peak VO$_2$ (%), percentage of improvement in peak VO$_2$ after exercise training; Δ VE/VCO$_2$ slope (%), percentage of improvement in VE/VCO$_2$ slope after exercise training.Δ6MWD (%), percentage of improvement in 6MWD after exercise training.
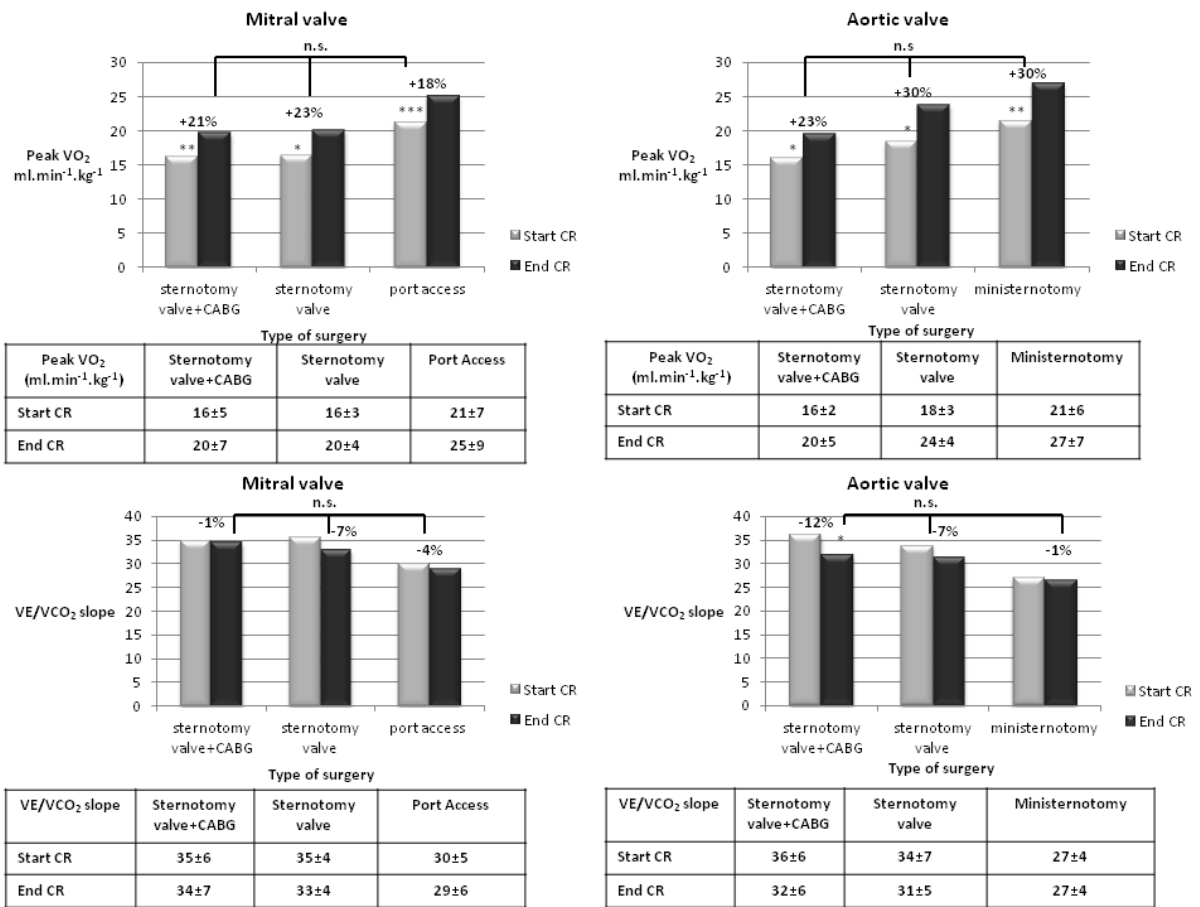
Peak VO$_2$ (ml.min^{-1}.kg^{-1})	Sternotomy valve+CABG	Sternotomy valve	Port Access
Start CR	16±5	16±3	21±7
End CR	20±7	20±4	25±9

Peak VO$_2$ (ml.min^{-1}.kg^{-1})	Sternotomy valve+CABG	Sternotomy valve	Ministernotomy
Start CR	16±2	18±3	21±6
End CR	20±5	24±4	27±7

VE/VCO$_2$ slope	Sternotomy valve+CABG	Sternotomy valve	Port Access
Start CR	35±6	35±4	30±5
End CR	34±7	33±4	29±6

VE/VCO$_2$ slope	Sternotomy valve+CABG	Sternotomy valve	Ministernotomy
Start CR	36±6	34±7	27±4
End CR	32±6	31±5	27±4

Figure 2. Exercise capacity and training benefits according to the type of surgery

Exercise capacity after valvular surgery - expressed as the peak VO$_2$ and VE/VCO$_2$ slope- is shown at the start and end of the cardiac rehabilitation program, according to the type of surgery. Variables are presented as the mean ± SD in the table. The improvement in exercise capacity is presented in percentage (%) above the bars in each group separately, significance levels are indicated with an asterisk (*p<0.05 **p<0.01 and ***p<0.001). Differences in training benefits between the types of surgery are shown on top of the figure.

CR, cardiac rehabilitation.

Differences in exercise capacity early after surgery and in functional improvement after cardiac rehabilitation according to the type of surgery are shown in Figure 2. As the results for load, AT and 6MWD were comparable with peak VO$_2$, only the results of peak VO$_2$ and VE/VCO$_2$ slope are shown in Figure 2. In MVS, patients who had port access performed significantly better at baseline regarding peak VO$_2$ and VE/VCO$_2$ slope (overall p <0.05) as compared with patients who had sternotomy with or without CABG (p<0.05). In AVS, baseline exercise capacity was also different (overall p<0.05) but only between ministernotomy patients and patients who had a sternotomy with CABG (p<0.05). No significant difference in baseline exercise capacity was found between the groups who had a ministernotomy or a sternotomy for valve surgery, except for the VE/VCO$_2$ slope (p<0.01). Exercise

training resulted in an improvement in load, peak VO_2, AT and 6MWD for each type of surgery, in AVS or MVS (all $p<0.05$). However, only in patients who had sternotomy for AVS in combination with CABG, a small but significant decrease in the VE/VCO_2 slope was seen ($p<0.05$). The gain in exercise capacity was comparable for the 3 types of surgery, both for patients after AVS or MVS.

4   Discussion

The main novel finding of this study is that exercise capacity after valvular surgery is related to the preoperative risk and to the type of surgery. However, a similar benefit from exercise training can be obtained, independent of the preoperative risk class or the type of surgery. Therefore, exercise training should be offered to all patients after valvular surgery, regardless their EuroSCORE risk (low or high risk) or type of surgery (classic sternotomy or minimal invasive surgery).

Our study results revealed that patients who had a high preoperative risk, had also the worst exercise capacity early after surgery. As exercise performance does not recover spontaneously after valvular surgery,[1-3] exercise training is recommended, in particular in this high-risk group. In this study, all patients were included in a cardiac rehabilitation program irrespective of their risk profile. Although exercise capacity at the end of the training program remained the lowest in patients at high risk, their benefit from exercise training was similar to that obtained in other risk groups. In literature, peak VO_2 is the most frequently used parameter to evaluate functional improvements after an intervention. In this study, the improvement in peak VO_2 ranged from 18% to 28% according to their preoperative risk profile, respectively, which is in accordance with previous studies in heart valve patients and other cardiac patient groups.[7-10] Besides peak VO_2, also other exercise variables were evaluated, more specifically the load, AT, 6MWD and VE/VCO_2 slope. In contrast to the other 4 variables, modest changes were observed in the VE/VCO_2 slope. This may be due to the different physiologic properties of this parameter as compared with the peak VO_2,[11] but also to the applied exercise training program. Studies regarding the influence of the intensity and the type of exercise training on the VE/VCO_2 slope after heart valve surgery are currently lacking. An alternative explanation may be the intrinsic characteristics of this study population. In this study, no patients with severe signs of decompensation were included, as expressed by the relatively low levels of N-Terminal pro-brain natriuretic peptide, and the VE/VCO_2 slope has been shown to be increased specifically in heart failure patients. Previous research has indicated that patients after AVS have a better exercise performance as compared with patients after MVS, even 6 months after surgery.[12] To exclude potential differences due to the type of valve disease, the effects of the preoperative risk on exercise performance were also assessed for aortic and mitral valve disease separately. Although in

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both types of valve disease the high-risk group appeared to have a lower level of baseline exercise performance, there was only a distinct difference between the risk groups in mitral valve disease. Training benefits however, were similar between the risk groups in both types of valve disease.

This study shows that patients after minimal invasive surgery have a better exercise performance early after surgery than patients who had a sternotomy, but these findings should be interpreted with caution. In mitral valve patients, a better exercise capacity is seen in patients who had a port access as compared with a sternotomy, despite whether it was combined with CABG or not. In aortic valve patients, patients after ministernotomy performed better than those who had sternotomy with a concomitant CABG. This could implicate that a ministernotomy, in contrast to a port access, is not always a less invasive procedure than a sternotomy. However, age could be an additional factor to explain these results. In the mitral valve group, patients who had a port access were considerably younger than their counterparts. In the aortic valve group, patients who underwent a ministernotomy differed in age from those who had a sternotomy with concomitant CABG. As patients who had minimal invasive surgery performed relatively well early after surgery with a peak VO_2 of 21 ml.min^{-1}.kg^{-1} on average, one could suggest there is no need for exercise training in this particular group. In contrast, this is not an excellent result for a young, otherwise healthy population with a preserved systolic function and may thus indicate an impaired exercise capacity. In addition, these patients also had a benefit of exercise training that was comparable with the training effects in patients after invasive surgery. These findings indicate that all patients should be advised to attend cardiac rehabilitation, regardless of their type of surgery.

This study has several limitations. No data on the preoperative exercise capacity were available. However, maximal exercise testing is often contraindicated in high-risk patients before surgery (e.g. patients with severe aortic valve stenosis). The inclusion of patients with valvular regurgitation and stenosis may have affected postoperative remodeling and exercise capacity. The lack of a comparison with a control group to evaluate spontaneous recovery after surgery is another shortcoming. Nevertheless, other studies have already demonstrated that there is no or little spontaneous improvement in exercise capacity after valvular surgery.[1-3] Since the study was performed between 2007 and 2012, EuroSCORE I instead of EuroSCORE II has been used with a potential overestimation of the risk as a result.[13] As fewer than 1/2 of eligible cardiovascular patients actually benefit from cardiac rehabilitation in most European countries,[14] a potential selection bias toward healthier patients could not be excluded. Frequency and length of the training period were varying between patients, which may be a barrier for standardisation of the training protocol. Despite this variation between patients, no significant difference was found between the patient groups, thereby excluding

a potential confounding effect on the results. A small number of patients in some subgroups may have led to underpowered results, in particular in the risk analyses, stratified by valve disease. Therefore, these results should be interpreted with caution. This study was only focused on the ventilatory gains after exercise training, future research should also evaluate the potential benefits on body weight, lipid profile and quality of life.

5   References

1. Le Tourneau T, de Groote P, Millaire A, et al. Effect of mitral valve surgery on exercise capacity, ventricular ejection fraction and neurohormonal activation in patients with severe mitral regurgitation. *J Am Coll Cardiol*. 2000; 36: 2263-9.

2. Tamas E, Nielsen NE, Vanhanen I and Nylander E. Measurement of physical work capacity in patients with chronic aortic regurgitation: a potential improvement in patient management. *Clin Physiol Funct Imaging.* 2009; 29: 453-7.

3. Hedman K, Tamas E and Nylander E. Decreased aerobic capacity 4 years after aortic valve replacement in male patients operated upon for chronic aortic regurgitation. *Clin Physiol Funct Imaging*. 2012; 32: 167-71.

4. Roques F, Nashef SA, Michel P, et al. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. *Eur J Cardiothorac Surg.* 1999; 15: 816-22; discussion 22-3.

5. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S and Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg*. 1999; 16: 9-13.

6. Conraads VM and Beckers PJ. Exercise training in heart failure: practical guidance. *Heart*. 2010; 96: 2025-31.

7. Temfemo A, Chlif M, Mandengue SH, Lelard T, Choquet D and Ahmaidi S. Is there a beneficial effect difference between age, gender, and different cardiac pathology groups of exercise training at ventilatory threshold in cardiac patients? *Cardiol J*. 2011; 18: 632-8.

8. Belardinelli R, Georgiou D, Cianci G and Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. *Circulation*. 1999; 99: 1173-82.

9. Belardinelli R, Paolini I, Cianci G, Piva R, Georgiou D and Purcaro A. Exercise training intervention after coronary angioplasty: the ETICA trial. *J Am Coll Cardiol*. 2001; 37: 1891-900.

10. Meurin P, Iliou MC, Ben Driss A, et al. Early exercise training after mitral valve repair: a multicentric prospective French study. *Chest*. 2005; 128: 1638-44.

11. Tumminello G, Guazzi M, Lancellotti P and Pierard LA. Exercise ventilation inefficiency in heart failure: pathophysiological and clinical significance. *Eur Heart J*. 2007; 28: 673-8.

12. Gohlke-Barwolf C, Gohlke H, Samek L, et al. Exercise tolerance and working capacity after valve replacement. *J Heart Valve Dis*. 1992; 1: 189-95.

13. Nashef SA, Roques F, Sharples LD, et al. EuroSCORE II. *Eur J Cardiothorac Surg*. 2012; 41: 734-44; discussion 44-5.

14. Bjarnason-Wehrens B, McGee H, Zwisler AD, et al. Cardiac rehabilitation in Europe: results from the European Cardiac Rehabilitation Inventory Survey. *Eur J Cardiovasc Prev Rehabil*. 2010; 17: 410-8.

5 Discussion

1 Introduction

Exercise intolerance, characterized by fatigue and dyspnoea, is a key phenomenon in HF but is also present in other cardiac diseases. It is an ominous sign for a poor prognosis, whose mechanisms are not completely understood thus far. Cardiac rehabilitation has been proven to affect exercise intolerance by acting on its determinants, however, it is not clear whether its effectiveness is determined by left ventricular function or neurohormonal activation. Despite the clear benefits of CR, figures on participation and drop-out in CR are disappointing. Although exercise intolerance is seen also in VHD patients, exercise training has received little attention in this patient group at present.

This work is composed of three parts, each focusing on a different aspect of exercise intolerance and its treatment. The first part aims to gain insight in the pathophysiological mechanisms underlying exercise intolerance, in particular in the reflex mechanism arising from the muscle, i.e. the ergoreflex. The second part describes the clinical characteristics and short-term outcome of hospitalized HF patients together with the effects of an exercise training program in patients with a wide range of left ventricular function and neurohormonal activation. Barriers in the implementation of CR including attendance and adherence to CR are discussed in the last part, together with a chapter focused on exercise capacity and the value of exercise training in VHD.

2 Exercise intolerance in heart failure: mechanisms and relevance of the ergoreflex

2.1 Main findings

The primary aim of this study was to evaluate the presence of ergoreflex activity and its current relationship to exercise intolerance and subsequent prognosis in a broad spectrum of subjects. We evaluated healthy subjects (n=29), patients with CAD (n=25) and HF patients (n=51). Ergoreflex activity turned out to contribute to hyperventilation only in those HF patients with persistent symptoms despite optimal medical treatment. In addition, ergoreflex activity was closely associated with the MAGGIC mortality risk score, thereby emphasizing the link with the severity of HF. In contrast, ergoreflex activity was not present in healthy subjects and neither in patients with CAD or stable HF.

2.2   Clinical implications

The introduction of ACE-inhibitors and β blockers as a standard of care in HF may have influenced the results presented in this work. Both drugs are known to influence neurohormonal activation and a decrease in the ventilatory slope has already been described in literature.[1-4] It may therefore be possible that ergoreflex activation in HF patients was lower in this study compared with earlier studies owing to the prescribed medication. Nevertheless, a substantial part of HF patients did have ergoreflex activation in spite of the use of aforementioned medication, suggesting that this mechanism becomes upregulated late in the disease process. This late presentation is also related to a poor prognosis, with ergoreflex activation being present in those patients who have an intermediate or high mortality risk according to the MAGGIC score and in those patients who have a peak $VO_2 < 14$ ml.min^{-1}.kg^{-1} and a VE/VCO_2 slope > 45.[5] The presence of ergoreflex activity may be a signal to reconsider the patient's condition and his treatment.

Despite its link with prognosis in patients with increasing disease severity, this parameter is not appropriate to evaluate outcome in the early onset of this disease and for this reason cannot be used among a broad spectrum of cardiac patients. The presence of a slightly increased VE/VCO_2 slope in patients who did not present with ergoreceptor activation, i.e. patients with CAD and a subgroup of stable HF patients, may suggest that other mechanisms are responsible for the early onset of this increased ventilatory drive.

2.3   Strengths and limitations

The main strength of our study was that we did not focus on a particular subgroup of cardiac patients, but tried to evaluate the ergoreflex activation among a broad spectrum of subjects. This approach has led us to suggest that under current medical treatment, the activation of the ergoceptors becomes present only late in the disease process. Nevertheless, longitudinal studies should investigate the precise onset of ergoreflex activation during the disease process.

As already previously mentioned, it is possible that the use of some pharmacological agents has influenced our results. In our opinion, however, it was more clinically relevant to assess patients who were treated according to the current medical guidelines than to interrupt their treatment. In clinical practice, a patient's state is also interpreted taking into account his treatment, e.g. in the interpretation of cardiopulmonary exercise testing.

Due to the relatively small sample size, it was not possible to assess outcome. Therefore, the MAGGIC mortality risk score was used, but this cannot replace outcome analyses regarding short or long-term prognosis, which should be subject of further studies.

2.4 Future prospects

Because ergoreflex activity represents a poor prognosis, longitudinal studies in patients with asymptomatic left ventricular dysfunction are necessary to investigate the precise onset of ergoreflex activation during the course of the disease. This onset may also indicate when the current treatment is failing and perhaps more intensive treatment is warranted. Given the changes in pharmacological treatment, larger longitudinal studies are also needed to evaluate its influence on outcome properly.

In addition, since research has focused solely on HFREF patients thus far, a thorough investigation on the underlying mechanisms of exercise intolerance including ergoreflex activation is necessary in HFPEF patients. Since ergoreflex activity also contributes to the blood pressure response, a second point of interest may be to explore the role of ergoreflex activation in hypertensive patients and moreover, how renal denervation may have an influence on this mechanism.

Furthermore, the current pharmacological agents that are thought to influence ergoreflex activity, such as β blocker therapy, need to be further analyzed on how they could possibly affect this mechanism. In addition, the effects of more advanced therapeutic modalities such as CRT, should be considered. The improvement in exercise capacity which is seen after CRT implantation is thought to be partially driven by peripheral changes[6] and a small non-randomized study revealed already a decrease in ergoreflex activation after CRT implantation.[7] Similar results were obtained in a subgroup of our patient population who received CRT implantation (n=8), with a decrease in ergoreflex activity six months after implantation. However, further studies are necessary to entirely investigate the underlying mechanisms in both responders and non-responders to CRT.

Another interesting topic remains which mechanisms are responsible for the increased ventilatory response in patients not having an increased ergoreflex activation. These may include chemoreceptor activation,[8] but also disturbances occurring at the lung level.[3, 9, 10] and should be the focus of further research.

3 Outcome and the key role of exercise training in heart failure

3.1 Main findings

In order to investigate the characteristics and outcome of patients admitted with HF in Belgium, the BIO-HF registry was used (n=904). Our registry consisted mainly of elderly patients, of whom 60% presented with a preserved LVEF or only a moderately reduced LVEF. LVEF did not predict outcome with a similar event rate for mortality and rehospitalisation in both patients with reduced and preserved LVEF. Short-term outcome was rather driven by the absence of β blocker prescription at discharge and the presence of different comorbidities.

In the second chapter of this part, the role of left ventricular function and neurohormonal activation in exercise intolerance and the effect of an exercise training program among a broad spectrum of CAD patients were analyzed, based on data from the Cardiac Rehabilitation Database (n=581). Exercise capacity was slightly worse in patients with a reduced ejection fraction compared with those with a preserved ejection fraction which is in line with previous observations.[11] More importantly, a similar decrease in exercise capacity was seen in both groups with increasing neurohormonal activation. Exercise training improved exercise capacity regardless of this initial left ventricular function or neurohormonal activation .

3.2 Clinical implications

The BIO-HF registry is the first registry to report on clinical characteristics and outcome in hospitalized HF patients for Belgium. Our findings indicate a comparable trend as in larger international registries with a growing number of elderly patients with HFPEF, a population for who scientific evidence regarding optimal treatment is limited at present. A similar unfavorable outcome was seen in both groups of LVEF, which was mainly driven by the absence of β blocker prescription and the presence of different comorbidities. Therefore, more attention is needed for a systematic screening of comorbidities such as COPD when evaluating a patient's clinical state. In addition, since β blockers had a positive effect on outcome irrespective of the presence of COPD, this should not be a reason for not giving β blocker therapy.

The observation concerning the increasing prevalence of HFPEF with a similar detrimental outcome as HFREF, led us to the second chapter of this part. The predominant role of neurohormonal

activation in exercise capacity, may further confirm the findings of Van Veldhuisen et al.,[12] who stated that neurohormonal activation may be the primary driver of outcome instead of LVEF. As a result, patients in the highest level of neurohormonal activation, which may suggest the presence of HF, had a similar level of exercise intolerance regardless of their left ventricular function. Thus, patients with HFPEF may have a similar impaired exercise capacity as those with HFREF. However, they are currently not included in the Belgian reimbursement guidelines for cardiac rehabilitation. Our results have shown that an improvement in exercise capacity is possible after following an exercise training program, irrespective of left ventricular function or neurohormonal activation. Therefore, exercise training may be an effective treatment modality also in HF patients with preserved ejection fraction.

3.3 Strengths and limitations

The lack of nationwide registers makes it difficult to generalize our results, but we think that our data reflect the real-life situation in Belgium due to the fairly large sample size in both datasets and the consecutive inclusion over a longer time period.

Since patients with HFPEF are not eligible for inclusion in cardiac rehabilitation, it is difficult to evaluate the effect of exercise training in this group. Our work tries to provide an alternative by evaluating both patients with reduced and preserved LVEF according to the level of neurohormonal activation. This approach is similar to Van Veldhuisen et al.[12], who studied prognosis in HF according to natriuretic peptides across a wide range of LVEF. They stated that the use of natriuretic peptides to define HF may be an alternative to the strict echocardiographic criteria which are often difficult to measure and therefore not always useful for daily practice. However, these echocardiographic criteria remain the golden standard and should be included in further studies regarding exercise training in HFPEF. Another weakness is that our study population was restricted to CAD patients and is thus not representative for all HF patients.

3.4 Future prospects

Our findings regarding outcome should be interpreted with caution since only short-term outcome was considered and therefore, future studies are planned within the BIO-HF framework to assess one-year outcome and to see whether different characteristics or comorbidities may play a role in the long term. In addition, the role of neurohormonal activation in outcome will be investigated in

the entire study population as well as among subgroups including HF patients with reduced and preserved ejection fraction, and patients with different etiologies of HF.

Furthermore, since the objective of the BIO-HF registry is to collect data over a period of ten years, time trends will be assessed regarding in-hospital mortality, one-year outcome and treatment modalities (e.g. medication prescription) .

Because of the prognostic importance, a systematic screening for comorbidities should be performed on admission to the hospital. Currently, knowledge on comorbidities is based on self-recorded information or extracted from chart review, which makes it difficult to evaluate adequately the prevalence of these comorbidities and their impact on prognosis. Future therapeutic guidelines should also pay attention on how to deal with these comorbidities in HF patients to improve outcome. A closer cooperation with other disciplines within medicine is essential to provide an optimal treatment of comorbidities such as COPD and diabetes among the HF population. A detailed registration of the reasons for non-prescription of evidence-based medication is also planned to further improve the quality of care in HF patients.

The increasing prevalence and poor prognosis of HFPEF patients indicates the urgent need for novel treatment strategies. The results of our study indicate that exercise training may be a valuable part of this treatment, however, this should be further confirmed in larger randomized controlled trials. A new approach in the government guidelines concerning the reimbursement criteria for cardiac rehabilitation is necessary, so that patients with HFPEF may have equal access to CR as patients with HFREF.

4 Barriers in the implementation of cardiac rehabilitation

4.1 Main findings

Participation in CR is estimated to be low, in particular in HF patients but concrete figures are lacking for Belgium. Therefore, we evaluated participation in CR among HF patients, by evaluating both the BIO-HF registry and the Cardiac Rehabilitation Database for a similar period. Overall one third of eligible patients attended CR, but only 9% of patients admitted with HF did participate in a CR program. This is far below the achieved participation rates in patients with ACS (29%) or cardiac surgery (56%). HF patients not participating in CR, were mainly elderly and female patients and those with a preserved LVEF. HF patients who actually did participate in CR, had an equal training benefit as

patients participating after ACS or cardiac surgery, despite their worse clinical status and lower exercise capacity at the start of the program.

A second barrier which is often mentioned together with the low participation rate, is drop-out in CR. We evaluated drop-out, defined as attending ≤50% of the training sessions, and tried to identify potential predisposing factors. Patients who attended CR after ACS, cardiac surgery or HF were prospectively included (n=489). One fifth of this population quit in the first half of the program. Demographic nor clinical characteristics could independently identify patients who were at risk for drop-out. The presence of comorbidities such as COPD and CVA involved a higher risk for drop-out as well as the absence of β blocker use. In addition, a vulnerable psychosocial background seemed to play a key role with singles, patients who were dependent for transport and those reporting problems regarding anxiety and depression being more likely to withdraw prematurely.

A different type of barrier than participation and drop-out, is the low number of studies that have been performed regarding exercise intolerance and the importance of exercise training among VHD patients. Current literature suggests that exercise capacity does not recover spontaneously after aortic valve surgery or mitral valve surgery.[13-15] Together with the expected increase in degenerative VHD, this argues in favour of the need for more research regarding exercise training in this population. For that reason, the final study assessed exercise intolerance and the effects of exercise training after valvular surgery (AVS n=72 and MVS n=73), according to the preoperative risk profile as assessed by the EuroSCORE and to the type of surgery. Patients with a higher preoperative risk and those who had invasive surgery, had a worse postoperative exercise capacity. Despite these differences in postoperative exercise capacity, training resulted in a similar improvement regardless of this preoperative risk or type of surgery.

4.2   Clinical implications

Participation in CR among HF patients is poor and may be partly due to the national government guidelines restricting reimbursement for HFPEF. However, we think that also in HFREF attendance is suboptimal and should gain more attention, given the clear training benefits which have been demonstrated. Increasing awareness of the benefit of exercise training may optimize referral to CR but also adaptation of training schemes and modalities to the patient's condition and preferences may be necessary to improve this low participation rate.[16]

The poor participation rate among elderly patients and women may be related to HFPEF, but also to the presence of comorbidities and differences in social status respectively. This could not be verified from our results but has been described in earlier studies.[17] Though, we have demonstrated the impact of comorbidities and psychosocial factors on drop-out, which emphasizes the importance of a multidisciplinary approach in CR, taking into account all different aspects of the physical and mental well-being of a patient.

Our results regarding VHD patients seem to indicate that patients after minimal invasive surgery perform better early after surgery. These findings should, however, be interpreted with caution because patients who had minimal invasive surgery were generally younger and the difference in exercise capacity did not apply to all subgroups of patients i.e. after aortic valve surgery. Despite their relatively worse exercise capacity, patients after invasive surgery had a similar training effect as those after minimal invasive surgery. The aforementioned findings suggest to further investigate the advantages of minimal invasive surgery compared with invasive surgery regarding exercise intolerance.

4.3   Strengths and limitations

The use of two parallel datasets in a single hospital gives us a unique opportunity to evaluate the attendance of HF patients to outpatient CR. As a result, we have an accurate figure concerning the participation rate instead of raw estimates. Another strength of our study was that we did not rely on reasons for drop-out given by patients, but rather prospectively collected potential predisposing factors. This approach has made it possible to identify those patients who were most vulnerable for drop-out, with a key role for comorbidities and psychosocial characteristics. Unfortunately, we did not have similar parameters concerning psychosocial characteristics at discharge from the hospital and we were thus not able to investigate their impact on the decision to attend CR.

In our study in VHD patients, we performed our analyses separately for AV and MV patients in order to exclude potential differences due to the type of valve disease. However, we did not consider the impact of the underlying aetiology i.e. stenosis or regurgitation, which may have influenced our results. In addition, not all types of surgery were included (e.g. transcatheter aortic valve implantation, mitraclip) because of the small number of these procedures but these should be subject of further investigation.

4.4   Future prospects

The current patient population that is candidate for attending CR is changing, with a growing part of elderly patients with comorbidities, suffering from complex pathologies and surgery, which makes cardiac rehabilitation more challenging. To date, cardiac rehabilitation programs are mostly based on an outpatient structure with little personal input of the patient. Future rehabilitation programs will have to deal with these novel patient characteristics and try to convene the patient's needs and his preferences. Therefore, a more individual approach in CR which is not only focused on the heart disease but also takes comorbidities into consideration, may be necessary. The possibilities and safety of home-based cardiac rehabilitation with the use of telemedicine should also be further investigated.

Since comorbidities are not only predictors of drop-out but also of a poor outcome, drop-out may indirectly represent an ominous sign for prognosis. Development of a risk stratification model, based on predictors for drop-out, would be helpful to screen patients from the early onset of CR and to provide an individual-tailored approach for those who are at risk for drop-out. In addition, the impact of drop-out on outcome parameters including recurrent events and mortality, may be another point of investigation. Psychosocial characteristics seem to influence drop-out similar to comorbidities, therefore, it would be interesting to register these characteristics already during the hospital stay to evaluate their influence on the decision to attend CR.

Since the prevalence of VHD continues to increase with increasing life expectancy, more studies are needed to gain knowledge on the underlying mechanisms of exercise intolerance in VHD. Furthermore, the impact of surgical interventions with inclusion of novel treatment modalities such as mitraclip and transcatheter aortic valve implantation has to be further explored as well as the role of exercise training. Currently, most rehabilitation programs in VHD are routinely based on prescriptions which were originally intended for HF or CAD patients. Therefore, future guidelines for VHD should include recommendations on the role of CR, specifically adapted to the characteristics of VHD patients.

5   Conclusion

The studies presented in this thesis have contributed to the knowledge on three different but related domains of exercise intolerance and its treatment.

The work presented in the first part has provided new information on the underlying mechanisms of exercise intolerance. We have demonstrated that ergoreflex activity contributes to hyperventilation only in those HF patients with persistent symptoms. Despite its link with the MAGGIC mortality risk score in patients with increasing disease severity, this parameter is not appropriate to evaluate outcome among a broad spectrum of cardiac patients. Mechanisms other than ergoreflex activity may be responsible for the early onset of the increased ventilatory drive.

Analysis of the BIO-HF registry has demonstrated an increasing prevalence of HFPEF patients with a similar outcome as patients with HFREF, indicating an urgent need for novel treatment strategies. Similar to outcome, a comparable trend towards a decrease in exercise capacity was seen in both groups of left ventricular function with increasing neurohormonal activation. Exercise training has been shown to improve exercise capacity regardless of this initial left ventricular function or neurohormonal activation and may therefore be an effective treatment modality also in HFPEF patients, a group which is currently not included for reimbursement in the Belgian legislation. Our study has also emphasized the link between comorbidities and outcome, which should be taken into consideration for future efforts to improve outcome.

The studies regarding the implementation of cardiac rehabilitation in clinical practice, have revealed that participation is poor, in particular among HF patients. In addition, one fifth of those patients actually attending CR, quit in the first half of the program with a predisposing role for comorbidities and psychosocial factors. These findings emphasize the importance of a multidisciplinary approach in CR, but also that adaptations in the current training modalities may be necessary to improve this sobering numbers. Finally, our study in VHD patients has drawn attention to exercise intolerance and the benefit of exercise training in patients after valvular surgery, which is necessary given the increasing prevalence that is expected with increasing life expectancy.

6 References

1. Arena R, Myers J and Guazzi M. The clinical and research applications of aerobic capacity and ventilatory efficiency in heart failure: an evidence-based review. *Heart Fail Rev*. 2008; 13: 245-69.

2. Sue DY. Excess ventilation during exercise and prognosis in chronic heart failure. *Am J Respir Crit Care Med*. 2011; 183: 1302-10.

3. Guazzi M, Marenzi G, Alimento M, Contini M and Agostoni P. Improvement of alveolar-capillary membrane diffusing capacity with enalapril in chronic heart failure and counteracting effect of aspirin. *Circulation*. 1997; 95: 1930-6.

4. Kitaoka H, Takata J, Hitomi N, et al. Effect of angiotensin-converting enzyme inhibitor (enalapril or imidapril) on ventilation during exercise in patients with chronic heart failure secondary to idiopathic dilated cardiomyopathy. *Am J Cardiol*. 2000; 85: 658-60, A10.

5. Arena R, Myers J, Abella J, et al. Development of a ventilatory classification system in patients with heart failure. *Circulation*. 2007; 115: 2410-7.

6. Piepoli MF, Villani GQ, Corra U, Aschieri D and Rusticali G. Time course of effects of cardiac resynchronization therapy in chronic heart failure: benefits in patients with preserved exercise capacity. *Pacing Clin Electrophysiol*. 2008; 31: 701-8.

7. Jaussaud J, Aimable L, Bordachar P, et al. Cardiac resynchronization therapy reduces metaboreflex contribution to the ventilatory response in heart failure population. *Cardiol Res Pract*. 2012; 2012: 914071.

8. Chua TP, Clark AL, Amadi AA and Coats AJ. Relation between chemosensitivity and the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol*. 1996; 27: 650-7.

9. Wada O, Asanoi H, Miyagi K, et al. Importance of abnormal lung perfusion in excessive exercise ventilation in chronic heart failure. *Am Heart J*. 1993; 125: 790-8.

10. Guazzi M, Reina G, Tumminello G and Guazzi MD. Alveolar-capillary membrane conductance is the best pulmonary function correlate of exercise ventilation efficiency in heart failure patients. *Eur J Heart Fail*. 2005; 7: 1017-22.

11. Moore B, Brubaker PH, Stewart KP and Kitzman DW. VE/VCO2 slope in older heart failure patients with normal versus reduced ejection fraction compared with age-matched healthy controls. *J Card Fail*. 2007; 13: 259-62.

12. 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. *J Am Coll Cardiol*. 2013; 61: 1498-506.

13. Le Tourneau T, de Groote P, Millaire A, et al. Effect of mitral valve surgery on exercise capacity, ventricular ejection fraction and neurohormonal activation in patients with severe mitral regurgitation. *J Am Coll Cardiol*. 2000; 36: 2263-9.

14. Tamas E, Nielsen NE, Vanhanen I and Nylander E. Measurement of physical work capacity in patients with chronic aortic regurgitation: a potential improvement in patient management. *Clin Physiol Function Imaging*. 2009; 29: 453-7.

15. Hedman K, Tamas E and Nylander E. Decreased aerobic capacity 4 years after aortic valve replacement in male patients operated upon for chronic aortic regurgitation. *Clin Physiol Function Imaging*. 2012; 32: 167-71.

16. Conraads VM and Beckers PJ. Exercise training in heart failure: practical guidance. *Heart*. 2010; 96: 2025-31.

17. Worcester MU, Murphy BM, Mee VK, Roberts SB and Goble AJ. Cardiac rehabilitation programmes: predictors of non-attendance and drop-out. *Eur J Cardiovasc Prev Rehabil*. 2004; 11: 328-35.

6 Summary

Cardiovascular disease remains the leading cause of death worldwide, but a better prevention and treatment policy has led to a decrease in mortality in coronary artery disease (CAD). Together with the ageing of the population, this success in secondary prevention and prolonging survival in patients suffering from coronary events, may contribute to the increasing overall prevalence of heart failure (HF). CAD is by far the most common cause of HF, but also other diseases including valvular heart disease (VHD) may eventually lead to HF. VHD is usually less regarded as a major public-health problem, however a substantial burden of this disease exists and will probably further increase, due to increasing life expectancy.

Exercise intolerance is a hallmark feature of HF and indicates a poor prognosis, but its origin is not completely understood thus far. Likewise, an impaired exercise capacity is also present in CAD and VHD patients with a similar prognostic value. Cardiac rehabilitation (CR) has been recommended in both CAD and HF but is currently not mentioned in the management guidelines on VHD. Despite its clear benefits, figures on participation in CR are disappointing.

This thesis is composed of three parts, each focusing on a different aspect of exercise intolerance and its treatment. The general aim was to obtain knowledge on the underlying mechanisms of exercise intolerance, both in patients with and without HF and to evaluate the outcome in HF and the effects of an exercise training program in a broader cardiac patient population. In addition, barriers in the implementation of cardiac rehabilitation were further explored in this work.

HF is marked by an interplay between the underlying myocardial dysfunction and the compensatory neurohormonal mechanisms, including the sympathetic nervous system. Neurohormonal activation, which is driven by peripheral reflex mechanisms, is thought to play a key role in exercise intolerance. It is remarkable that a reflex arising from the exercising muscle, i.e. the ergoreflex, may influence both fatigue and dyspnoea, being the major characteristics of exercise intolerance in HF. Therefore, the first part handles about exercise intolerance and its mechanisms with a focus on this muscle reflex. The role of the autonomic nervous system in the development of HF has been described in the first chapter of this work. The second chapter provides an overview on prognostically important cardiopulmonary exercise variables, such as the peak VO_2 and the VE/VCO_2 slope, and their determinants. The third chapter reports on the presence of ergoreflex activity and its current relation to exercise intolerance and subsequent prognosis in a broad spectrum of subjects, ranging from healthy subjects (n=29) and patients with CAD (n=25) to HF (n=51). Our findings have demonstrated that ergoreflex activation contributes to hyperventilation only in HF patients with persistent symptoms despite optimal medical treatment. In addition, the presence of ergoreflex activity was

closely associated with parameters of exercise intolerance and an increased mortality risk, thereby emphasizing the link with the severity of HF and prognosis. In contrast, ergoreflex activity was not present in healthy subjects and neither in patients with CAD or stable HF. This may suggest that this mechanism may become upregulated with increasing disease severity but is not responsible for the early onset of an increased ventilatory drive.

For the second and third part of this thesis, two datasets were used i.e. the Belgian BIO-HF registry, collecting data from hospitalized HF patients, and the Cardiac Rehabilitation database, a multidisciplinary registry collecting data from the diverse population that participates in CR.

The second part focuses on outcome in HF and exercise training as an effective treatment modality. Despite improvements in the treatment of HF, mortality and readmission rates remain high but figures for Belgium are lacking. In the fourth chapter, clinical characteristics and short-term outcome of hospitalized HF patients in Belgium (n=904) were assessed. Patients admitted with HF were mainly elderly patients with a relatively preserved left ventricular ejection fraction (LVEF), indicating the increasing prevalence of heart failure with preserved ejection fraction (HFPEF). In-hospital and short-term mortality after discharge were high, both 7% on an average, with short-term mortality being related to the absence of β blocker use and the presence of comorbidities rather than to LVEF. Comorbidities should therefore be the focus for further studies to improve outcome. The observation concerning the increasing prevalence of HFPEF with a similar outcome as HFREF, led us to the fifth chapter of this work which investigated the influence of LVEF and neurohormonal activation, as assessed by NT-proBNP, on exercise capacity and the effectiveness of exercise training among a broad spectrum of CAD patients (n=581). Our results have shown that exercise capacity shows a similar decrease with increasing neurohormonal activation, irrespective of left ventricular function. As a result, patients with the highest level of neurohormonal activation which may suggest the presence of HF, had a similar level of exercise intolerance in both groups of LVEF. Similar to outcome, this may indicate that neurohormonal activation is the primary driver of exercise capacity rather than LVEF. Moreover, exercise training resulted in an improvement in exercise capacity irrespective of neurohormonal activation or LVEF and may therefore be an effective treatment modality also in HFPEF, a group that is currently not included for reimbursement in the Belgian legislation.

CR has been recommended to improve exercise intolerance, health-related quality of life and prognosis but encounters several barriers in the implementation in the 'real life' setting, which are the focus of the third part of this work. Participation is poor in particular in HF, but concrete figures are lacking for Belgium. Therefore, we evaluated participation among HF patients in the sixth

chapter. Barely one out of ten patients admitted with HF did participate in CR which is far below the participation rates after acute coronary syndrome or cardiac surgery. Non-attendance to CR among HF patients was primarily related to age, female gender and a preserved LVEF. Nevertheless, HF patients who did actually participate in CR had an equal training benefit as patients after acute coronary syndrome or cardiac surgery. This low participation rate may be partly due to the restriction of reimbursement regarding HFPEF but also in HFREF attendance may be suboptimal. These findings emphasize the urgent need to increase awareness regarding the benefits of CR but also that adaptation of the current training modalities may be necessary to improve attendance to CR. In the seventh chapter, early withdrawal from CR was assessed among a population consisting of HF patients, patients after acute coronary syndrome and cardiac surgery (n=489). One fifth of this population quit in the first half of the program with a predisposing role for comorbidities and a vulnerable psychosocial background. Therefore, a multidisciplinary approach in CR is indispensable, taking into account all different aspects of the physical and mental well-being of a patient. Because of the expected increase in degenerative valvular heart disease (VHD) with increasing life expectancy, more attention is warranted concerning exercise intolerance and the effects of exercise training in this patient population. Our final study has provided additional information on this topic by evaluating the postoperative exercise capacity and the benefits of exercise training after valvular surgery (n=145), according to the preoperative risk profile and the type of surgery. Patients with a higher preoperative risk and those who had invasive surgery, had a worse postoperative exercise capacity. However, this should be interpreted with caution since this advantage regarding minimal invasive surgery was not applicable to all types of patients and a potential confounding effect of age was possible. Moreover, exercise training resulted in an improvement in exercise capacity, regardless of this preoperative risk profile or type of surgery. Our findings suggest to further investigate exercise intolerance, the impact of surgical interventions and the role of exercise training in this patient population.

7 Samenvatting

Cardiovasculaire aandoeningen blijven wereldwijd de belangrijkste doodsoorzaak, maar de vooruitgang in behandeling en het preventiebeleid voor coronair lijden hebben geleid tot een daling in sterfte. Samen met de vergrijzing van de bevolking, heeft dit succes in secundaire preventie en de verbeterde overlevingskansen voor patiënten die lijden aan coronaire aandoeningen er mede toe geleid dat er een toename is in de prevalentie van hartfalen (HF). Coronair lijden is veruit de belangrijkste oorzaak van HF, maar ook andere hartaandoeningen zoals kleplijden kunnen uiteindelijk leiden tot de ontwikkeling van HF. Kleplijden wordt doorgaans minder aanzien als een bedreiging voor de maatschappelijke gezondheid, hoewel er een aanzienlijk aantal patiënten lijdt aan deze aandoening en dit aantal naar de toekomst hoogstwaarschijnlijk nog verder zal toenemen door de stijgende levensverwachting.

Inspanningsintolerantie is een hoofdkenmerk van HF en wijst op een slechte prognose, maar de onderliggende mechanismen zijn tot op heden nog niet volledig gekend. Bij patiënten met coronair lijden en kleplijden is er eveneens sprake van een beperkte inspanningscapaciteit met een gelijkaardige prognostische waarde. Cardiale revalidatie (CR) wordt aanbevolen bij zowel patiënten met coronair lijden als patiënten met HF, maar wordt niet vermeld in de therapeutische richtlijnen voor patiënten met kleplijden. Ondanks de bewezen voordelen van CR, zijn de cijfers rond participatie teleurstellend.

Deze thesis is opgebouwd uit drie delen, die elk gericht zijn op een ander aspect van inspanningsintolerantie en de behandeling ervan. Het voornaamste doel was om kennis te verwerven over de onderliggende mechanismen van inspanningsintolerantie, zowel in patiënten met als zonder HF, alsook om de prognose bij HF patiënten te bestuderen en de effecten van een trainingsprogramma in een bredere cardiale patiëntenpopulatie. In het laatste deel van dit werk werden barrières bij de huidige toepassing van cardiale revalidatie besproken.

HF wordt gekenmerkt door een samenspel van de onderliggende cardiale dysfunctie en de compensatoire neurohormonale mechanismen, waaronder het sympathisch zenuwstelsel. Er wordt aangenomen dat neurohormonale activatie dat gemedieerd wordt door perifere reflexen, een belangrijke rol speelt in het ontstaan van inspanningsintolerantie. Het is opvallend dat een reflex die zijn oorsprong vindt in de werkende spieren, namelijk de ergoreflex, zowel vermoeidheid als kortademigheid zou kunnen beïnvloeden, wat de twee voornaamste karakteristieken zijn van inspanningsintolerantie bij HF. Daarom handelt het eerste deel van deze thesis over inspanningsintolerantie en de onderliggende mechanismen met de nadruk op de ergoreflex. De rol van het autonoom zenuwstelsel in de ontwikkeling van HF wordt beschreven in het eerste hoofdstuk

van dit werk. Het tweede hoofdstuk geeft een overzicht van de belangrijkste prognostische inspanningsparameters, zoals de peak VO_2 en de VE/VCO_2 slope, en hun determinanten. Het derde hoofdstuk evalueert de aanwezigheid van ergoreflexactiviteit en de huidige relatie met inspanningsintolerantie en prognose in een breed spectrum van proefpersonen, gaande van gezonde personen (n=29) en patiënten met coronair lijden (n=25) tot patiënten met HF (n=51). Onze resultaten hebben aangetoond dat ergoreflex activatie bijdraagt tot hyperventilatie, maar enkel in HF patiënten die symptomen blijven vertonen ondanks een optimaal medicamenteus beleid. Daarnaast was de aanwezigheid van ergoreflexactiviteit gerelateerd aan inspanningsintolerantie en een toegenomen kans op sterfte, waardoor het verband met de ernst van HF en de prognose benadrukt werd. In gezonde proefpersonen, patiënten met coronair lijden en patiënten met stabiel HF was er echter geen teken van ergoreflex activatie. Deze bevindingen zouden erop kunnen wijzen dat dit mechanisme pas actief wordt bij toenemende ziekte ernst maar niet verantwoordelijk is voor het allereerste begin van een toegenomen ventilatie.

Voor het tweede en derde deel van deze thesis werd gebruik gemaakt van 2 datasets, namelijk de BIO-HF registry die data verzamelt van gehospitaliseerde HF patiënten, en de Cardiac Rehabilitation Database, dat een multidisciplinair register is waarin data worden verzameld van de patiëntenpopulatie die deelneemt aan CR.

Het tweede deel is gericht op de prognose van HF patiënten en training als een effectieve behandeling. Ondanks de verbeteringen in de behandeling van HF, blijven de sterfte – en hospitalisatiecijfers hoog, maar concrete gegevens voor België zijn momenteel niet beschikbaar. In het vierde hoofdstuk worden de klinische karakteristieken en korte termijn prognose geëvalueerd van gehospitaliseerde HF patiënten (n=904). Patiënten die opgenomen werden met HF, waren voornamelijk oudere patiënten met een relatief goed bewaarde linkerventrikel ejectiefractie (LVEF), wat wijst op een toename in hartfalen met bewaarde ejectiefractie (HFPEF). Zowel de sterfte tijdens hospitalisatie als op korte termijn na ontslag uit het ziekenhuis was hoog, beiden gemiddeld 7%, waarbij de korte termijn prognose gerelateerd was aan de afwezigheid van β blocker gebruik en de aanwezigheid van comorbiditeiten maar niet aan LVEF. De toename in prevalentie van HFPEF met een gelijkaardige prognose als patiënten met HFREF, heeft geleid tot het vijfde hoofdstuk waarin de invloed werd onderzocht van LVEF en neurohormonale activatie, gemeten d.m.v. NT-proBNP, op inspanningscapaciteit en de effectiviteit van training bij een brede patiëntenpopulatie met coronair lijden (n=581). Onze resultaten hebben aangetoond dat inspanningscapaciteit een daling kent met toenemende neurohormonale activatie, die gelijklopend is in zowel patiënten met gedaalde als bewaarde LVEF. Dit betekent dan ook dat bij patiënten met de grootste neurohormonale activatie,

wat kan wijzen op de aanwezigheid van HF, er een gelijkaardige mate van inspanningsintolerantie bestaat in beide groepen van LVEF. Dit zou er kunnen op wijzen dat inspanningscapaciteit net zoals prognose eerder bepaald wordt door neurohormonale activatie dan door LVEF. Daarenboven heeft het volgen van een trainingsprogramma geleid tot een verbetering in inspanningscapaciteit die losstaat van de initiële neurohormonale activatie of LVEF. Dit betekent dat training ook een effectieve behandeling kan zijn in HFPEF, een groep die momenteel nog niet in aanmerking komt voor terugbetaling volgens de Belgische wetgeving.

CR wordt aanbevolen om de inspanningscapaciteit te verbeteren alsook de gezondheidsgerelateerde levenskwaliteit en de prognose, maar er zijn verschillende barrières bij de toepassing ervan in de klinische praktijk, die dan ook het onderwerp vormen van het derde deel van dit werk. De participatiegraad in CR is laag, in het bijzonder bij HF patiënten maar concrete cijfers ontbreken in België. Om deze reden hebben we participatie bij HF patiënten onderzocht in het zesde hoofdstuk. Amper 9% van de patiënten die opgenomen werden met HF, participeerden in CR wat ver beneden de deelnamecijfers ligt bij patiënten met acuut coronair syndroom of cardiale chirurgie. Deze lage participatiegraad was voornamelijk gerelateerd aan een hoge leeftijd, het vrouwelijke geslacht en een bewaarde LVEF. Desalniettemin vertoonden de HF patiënten die toch deelnamen aan CR een gelijk trainingseffect als patiënten die deelnamen na acuut coronair syndroom of cardiale chirurgie. Deze lage participatiegraad kan deels te wijten zijn aan de beperking in terugbetaling voor patiënten met HFPEF maar ook de deelname bij HFREF is waarschijnlijk suboptimaal. Deze bevindingen benadrukken de nood aan een grotere bewustwording van de voordelen van CR maar ook dat een aanpassing van de huidige trainingsmodaliteiten misschien nodig is om de deelname in CR te verhogen. In het zevende hoofdstuk werd het vroegtijdig onderbreken van een revalidatieprogramma geëvalueerd in een patiëntenpopulatie bestaande uit HF patiënten, patiënten na acuut coronair syndroom en cardiale chirurgie (n=489). Een vijfde van deze populatie onderbrak het trainingsprogramma in de eerste helft, met een hoger risico voor patiënten met comorbiditeiten en een kwetsbare psychosociale achtergrond. Een multidisciplinaire aanpak in CR is dan ook noodzakelijk, waarbij rekening wordt gehouden met de verschillende aspecten van het fysieke en mentale welzijn van een patiënt. Omwille van de verwachte toename in degeneratief kleplijden met de stijgende levensverwachting, is er meer aandacht nodig voor inspanningsintolerantie en de effecten van training in deze patiëntenpopulatie. Onze laatste studie heeft hieromtrent nieuwe inzichten geleverd door postoperatieve inspanningscapaciteit en de effecten van training na klepchirurgie (n=145) te bestuderen volgens het preoperatief risicoprofiel en het type van toegepaste chirurgie. Patiënten met een hoger preoperatief risico en diegene die invasieve chirurgie hadden gehad, bleken een slechtere postoperatieve inspanningscapaciteit te hebben. Toch moeten

deze resultaten met voorzichtigheid geïnterpreteerd worden, aangezien het voordeel dat patiënten met minimaal invasieve chirurgie leken te hebben niet van toepassing was op alle onderzochte patiënten en er mogelijks ook een beïnvloedend effect van de leeftijd heeft meegespeeld. Training resulteerde in een verbetering in inspanningscapaciteit, ongeacht het preoperatief risicoprofiel of het type van chirurgie. Verder onderzoek is dan ook nodig naar inspanningsintolerantie, de impact van chirurgische interventies en de rol van training in deze patiëntenpopulatie.

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9 Publications

Papers in international peer-reviewed journals (A1)

Pardaens S, Willems AM, Vande Kerckhove B, De Sutter J. Participation in cardiac rehabilitation after hospitalization for heart failure: a report from the BIO-HF registry. Acta Cardiol. In press

Pardaens S, Vanderheyden M, Calders P, Willems AM, Bartunek J, De Sutter J. Activation of the ergoreceptors in cardiac patients with and without heart failure. J Cardiac Fail. 2014; 20:747-754.

Pardaens S, Moerman V, Willems AM, Calders P, Bartunek J, Vanderheyden M, De Sutter J. Impact of the preoperative risk and the type of surgery on exercise capacity and training after valvular surgery. Am J Cardiol. 2014; 113:1383-1389.

Pardaens S, Calders P, Derom E, De Sutter J. Exercise intolerance in heart failure: update on exercise parameters for diagnosis, prognosis and therapeutic interventions. Acta Cardiol. 2013; 68:495-504.

De Smedt D, Clays E, Annemans L, **Pardaens S**, Kotseva K, De Bacquer D. Risk factor awareness in a coronary population and the association with health-related quality of life outcomes. Int J Public Health. 2014; 59:475-483.

De Smedt D, Clays E, Annemans L, **Pardaens S**, Kotseva K, De Bacquer D. Self-reported health status in coronary heart disease patients: a comparison with the general population. Eur J Cardiovasc Nurs. 2014; Epub ahead of print

De Smedt D, Clays E, Annemans L, Boudrez H, De Sutter J, Doyle F, Jennings C, Kotseva K, Pajak A, **Pardaens S**, Prugger C, Wood D, De Bacquer D. The association between self-reported lifestyle changes and health-related quality of life in coronary patients: the EUROASPIRE III survey. Eur J Prev Cardiol. 2013; 21:796-805.

Vanhercke D, Claessens T, **Pardaens S**, Van Ransbeeck P, Vandekerckhove H, Verdonck P, De Sutter J. Assessment of variables affecting late left ventricular flow propagation velocity. Acta Cardiol. 2012; 67:391-397.

Chapters in books (B2)

Pardaens S and De Sutter J. Development of heart failure and the role of the autonomic nervous system of the heart in: RHJA Slart, RA Tio, PH Elsinga and M Schwaiger (eds) Autonomic Innervation of the Heart: Role of Molecular Imaging. Springer-Verlag (Heidelberg), 2015; in press.

Abstracts presented at international and national congresses (C2)

Pardaens S, Vanderheyden M, Willems AM, Bartunek J, De Sutter J. Ergoreflex activity is only present in CHF patients with persistent symptoms despite optimal medical treatment. Oral presentation for Young Investigator Award competition EuroPRevent Congress Rome 2013. Eur J Prev Cardiol. 2013; 20 (Suppl 1): S40.

Pardaens S, Vande Kerkchove B, Vanderheyden M, Willems AM, Bartunek J, Moerman V, De Sutter J. Exercise training results in a functional improvement after heart valve surgery, independent of the surgical technique. Oral presentation for Young Investigator Award competition EuroPRevent Congress Rome 2013. Eur J Prev Cardiol. 2013; 20 (Suppl 1): S38.

Pardaens S, Vanderheyden M, Willems AM Bartunek J, De Sutter J. Ergoreflex activity in healthy subjects: a reproducibility analysis. Poster presentation EuroPRevent Congress Rome 2013. Eur J Prev Cardiol. 2013; 20 (Suppl 1): S37.

Pardaens S, Vande Kerckhove B, Willems AM, Moerman V, De Sutter J. Exercise training in elderly heart failure patients. Poster presentation EuroPRevent Congress Rome 2013. Eur J Prev Cardiol. 2013; 20 (Suppl 1): S32.

Pardaens S, Vande Kerckhove B, Willems AM, Moerman V, De Sutter J. Exercise training after hospitalisation for heart failure: a highly underused but effective therapy for real life heart failure patients. Selected for best poster presentation BSC Brussels 2013. Acta Cardiol. 2013; 68 (1): 116. Poster presentation EuroPRevent Congress Rome 2013. Eur J Prev Cardiol. 2013; 20 (Suppl 1): S32.

Pardaens S, Willems AM, Tromp F, Van de Veire N, De Sutter J. Exercise training results in an improvement of chronotropic incompetence in patients with a preserved ejection fraction, independent of baseline NT-proBNP. Selected for best poster presentation EuroPRevent Congress Dublin 2012. Eur J Prev Cardiol. 2012; 19 (Suppl 1): S90.