Combining cardiopulmonary exercise testing and exercise echocardiography: Understanding the relationship between cardiac contractile function and exercise tolerance

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ABSTRACT

Most diseases of cardiac function are defined by a description of the heart at rest. However, at rest, symptoms are often less evident and are often exacerbated when patients are exerting themselves. Resting examination shows a high degree of overlap between normality and disease. Cardiopulmonary exercise testing (CPET) provides an overall assessment of a patient's well-being and can be combined with echocardiography. This thesis uses the highly quantifiable and validated measures from CPET to describe how anatomical and physiological augmentation measured during exercise echocardiography relates to exercise tolerance. In order to do this a distinct population of 69 patients with atrial fibrillation (AF) were examined in study one. The absence of any relationship between resting echocardiographic parameters and exercise parameters justified the subsequent range of studies to assess different disease states under stress conditions to try and establish a relationship between heart function and exercise tolerance. Study two, examined 80 patients with systolic heart failure and demonstrated that of all the measured parameters, systolic longitudinal velocity (S') measured on exercise was a powerful predictor for survival and cardiac hospitalisation. Study three was established to determine if this powerful relationship to prognosis translated into a greater response to cardiac resynchronisation therapy (CRT) in 38 patients with systolic heart failure clinically selected for CRT. However peak exercise S' was unable to predict a positive response to patients receiving CRT. Study four examined the relationship between exercise S' and other echocardiographic parameters to $\dot{V}O_{2\,peak}$ and clinical outcomes in 32 patients with severe aortic stenosis. Exercise tolerance was an important predictor of adverse events rather than valve severity and heavily dependent on the ability of the left ventricle to augment its longitudinal velocity during exercise. All of these studies highlight the powerful relationship between systolic myocardial velocity, $\dot{V}O_{2\,peak,}$ and prognosis. However focus has always been on peak values. The normal augmentation of heart function described using S' throughout exercise and its relation to increasing $\dot{V}O_2$ was still poorly described. Study five investigated this augmentation curve in 57 healthy first time marathon runners. The shape of the myocardial augmentation curve and its relation to $\dot{V}O_2$ is described as a linear function with good relationships between $\dot{V}O_2$

and S'. The slope between S' and $\dot{V}O_2$ showed a strong positive relationship with $\dot{V}O_{2\,peak}$ suggesting that submaximal slope values are able to predict $\dot{V}O_{2\,peak}$ values which is valuable in patients who are not able to exercise to maximal exertion. This is new way to describe heart function and critically appraised in more detail than ever before. Integrating CPET with exercise echocardiography provides unique and robust data that can provide new and valuable insights into disease processes. It provides greater insights into contracting of diseased myocardium and exercise tolerance. This thesis demonstrates that contractile reserve and $\dot{V}O_2$ are strongly related and examining them both simultaneously provides mechanistic and diagnostic insights.

DECLARATION

I declare that the research contained in this thesis, unless otherwise formally indicated within the text, is the original work of the author. The thesis has not been previously submitted to this or any other university for a degree, and does not incorporate any material already submitted for a degree.

Signed: 

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LIST OF ABBREVIATIONS

6-MWT	6-Minute Walk Test (m)
ACSM	American College of Sports Medicine
AF	Atrial Fibrillation
AS	Aortic stenosis
ATS	American Thoracic Society
A’	Atrial contraction
BMI	Body Mass Index ($kg \cdot m^{-2}$)
BSA	Body Surface Area (m^2)
$C(a\text{-}\bar{v})O_2$ diff	Arteriovenous oxygen difference
CO_2	Carbon Dioxide
COPD	Chronic Obstructive Pulmonary Disease
CHD	Coronary heart disease
CPET	Cardiopulmonary exercise test
CRT	Cardiac resynchronisation therapy
CW	Continuous wave
DGH	District General Hospital
DBP	Diastolic Blood Pressure (mmHg)
E’	Mitral annular early diastolic velocity
E/E’	Ratio between early mitral inflow velocity and mitral annular early diastolic velocity
ECG	Electrocardiogram
EF	Ejection Fraction (%)
EDV	End Diastolic Volume (mL)
ESV	End Systolic Volume (mL)
EVP	Exercise ventilatory power
GLS	Global longitudinal strain (%)
HF	Heart Failure

HFPEF	Heart failure with preserve ejection fraction
HFREF	Heart failure with reduced ejection fraction
HR	Heart Rate (beats · min^{-1})
INR	International Normalized Ratio
IQR	Median Interquartile Range
LA	Left Atrium
LV	Left Ventricle
LVOT	Left Ventricular Outflow Tract
LVEF	Left ventricular Ejection Fraction (%)
Lat	Lateral
Max V	Maximal velocity through the aortic valve ($cm \cdot s^{-1}$)
Mean PG	Mean pressure gradient through the aortic valve (mmHg)
MR	Mitral regurgitation
MS	Mitral stenosis
NYHA	New York Heart Association
NHS	National Health Service
NT-ProBNP	N-terminal pro-type natriuretic peptide ($pg \cdot mL^{-1}$)
M-mode	Motion mode
MI	Myocardial infarction
O_2	Oxygen
OUES	Oxygen uptake Efficiency Slope (($mL \cdot min^{-1}$)·($L \cdot min^{-1}$)$^{-1}$)
$P_{ET}O_2$	End-Tidal oxygen tension (mmHg)
$P_{ET}CO_2$	End-Tidal carbon dioxide tension (mmHg)
PW	Pulsed wave
$\dot{Q}$	Cardiac output ($L \cdot min^{-1}$)
$\dot{Q}CO_2$	Carbon dioxide production by the exercising muscles

$\dot{Q}O_2$	Oxygen uptake by the exercising muscles
QoL	Quality of Life
RER	Respiratory Exchange Ratio
R&D	Research & development
RPM	Revolutions per minute
RR	Respiratory rate
RWT	Relative wall thickness
S’	Systolic longitudinal velocity ($cm \cdot s^{-1}$)
SD	Standard Deviation
SBP	Systolic Blood Pressure (mmHg)
Sep	Septal
SV	Stroke volume (mL)
TVI	Tissue Velocity Imaging
V_D	Dead space
$\dot{V}_E$	Minute Ventilation volume ($L \cdot min^{-1}$)
$\dot{V}_E/\dot{V}O_2$	Ventilatory equivalent for O_2
$\dot{V}_E/\dot{V}CO_2$	Ventilatory equivalent for CO_2
$\dot{V}CO_2$	Carbon Dioxide elimination ($L \cdot min^{-1}$)
$\dot{V}O_2$	Oxygen uptake ($L \cdot min^{-1}$; $mL \cdot kg^{-1} \cdot min^{-1}$)
$\dot{V}O_2$peak	Highest $\dot{V}O_2$ measured during an CPET
$\dot{V}O_2$max	Highest $\dot{V}O_2$ achieved for a presumed maximal effort
VT	Ventilatory threshold
V_t	Tidal volume
WR	Work rate (W)

CHAPTER 1

INTRODUCTION

Most diseases of cardiac function and particularly heart failure (HF) are defined by a description of the heart at rest (Ponikowski *et al.*, 2016; Vahanian *et al.*, 2012). At rest, cardiac output ($\dot{Q}$) requirement is relatively low and symptoms may not be present. Symptoms at rest may not become apparent until cardiac dysfunction is far advanced. Consequently there is a relatively poor correlation between measures of resting heart function and symptomatic limitation (Witte *et al.*, 2004). Symptoms often appear when patients are exerting themselves. Evaluating patients during exercise provides a complete overall assessment of a patient. Cardiopulmonary exercise testing (CPET) is an objective measure to evaluate prognosis, risk stratification of disease progression, effect of treatments and it provides an objective assessment of a patient's exercise tolerance. Numerous studies and statements have acknowledged the potential CPET can have in daily practice but CPET is still an underused test in day-to-day cardiology (Cohen-Solal *et al.*, 1997; Domanski *et al.*, 2017; Mehra *et al.*, 2016; Older *et al.*, 1993; O'Neill *et al.*, 2005; Opasich *et al.*, 1998; Piepoli *et al.*, 2006a; Piepoli *et al.*, 2017; Smith *et al.*, 2009; van Le *et al.*, 2016). While CPET provides an overall assessment of cardiopulmonary wellbeing, it lacks the ability to provide a detailed anatomical and pathological assessment of facets; fortunately in can be combined with echocardiography. Echocardiography is the most extensively used diagnostic test performed in cardiology. It is a powerful, non-invasive, safe, and painless test and routinely used in the diagnosis, management and follow-up. Echocardiography is predominantly performed at rest, but during exercise it provides useful and valuable prognostic information (Lancellotti *et al.*, 2016; Sicari *et al.*, 2008). The combination of CPET and exercise echocardiography offers a unique, quick, complete and objective clinical assessment which may provide superior information regarding patient's prognosis and diagnosis compared to assessments solely done at rest. This exciting combination of two established tests may support the clinical decision making process which may improve patient's care. It is straightforward to combine a CPET with an exercise echocardiography protocol and an ideal opportunity for CPET to be incorporated more widely into daily clinical practice. The overall aim of this thesis is to describe and evaluate the complex relationship between exercise echocardiography and CPET in a variety of different cardiac patients and to determine the extent of any relationships between exercise parameters and myocardial function.

CHAPTER 2

REVIEW OF THE LITERATURE

2.1 Epidemiology of cardiovascular disease

Cardiovascular disease (CVD) is the second biggest cause of death in the United Kingdom (UK) (BHF, 2015), causing 27% of all deaths while cancer caused 29% of deaths. CVD includes all diseases of the heart and circulation including coronary heart disease and stroke. Morbidity of CVD is equal among male and females, and a total of 7 million people live with CVD in the UK (BHF, 2015). Ischaemic heart disease is the most common type and is the UK's single biggest killer. 1 in 6 men and 1 in 10 women die from coronary heart disease, most frequently due to a myocardial infarction (MI) (Bhatnagar *et al.*, 2015). In the UK, 188.000 hospital visits are due to MIs, which equates to one every three minutes. The estimated number of people in the UK living with HF is around half a million, the estimated number of people with AF, which is the most common sustained cardiac arrhythmia and a major cause of stroke, is an estimated 1.1 million people (Bhatnagar *et al.*, 2015). Valvular heart disease prevalence is as common as HF, with 2.5% of people in the UK suffering from the disease. In people over 75 years of age this number increase to more than 10% (Nkomo *et al.*, 2006). The total cost of CVD to the UK economy is estimated to be around £15 billion each year (BHF, 2015). The majority of people in the UK have at least one CVD-related risk factor such as smoking, hypertension, abnormal blood lipids, obesity, or physical inactivity (Macera *et al.*, 2003; Warburton *et al.*, 2006). It is therefore vital to continue to improve diagnosis and management of CVD.

2.2 Exercise and cardiovascular health

The importance of exercise and cardiovascular health has been broadly recognised (Morris and Heady, 1953; Press *et al.*, 2003; Warburton *et al.*, 2006). Early research discovered a relationship between habitual exercise and the occurrences of early symptoms of cardiovascular disease and subsequently, there have been extensive follow-up reports published about the importance of physical activity (Macera *et al.*, 2003; Morris and Heady, 1953; Press *et al.*, 2003; Schuler *et al.*, 2013; Warburton *et al.*, 2006). Exercise plays a vital role in people's well-being and regular physical activity has a favourable effect on the five major modifiable cardiac risk factors (hypertension, abnormal blood lipids, smoking, obesity, and physical inactivity)(Macera *et al.*, 2003;

Warburton *et al.*, 2006). CVD and the relative risk of death has been reported to be reduced by 20-35% when people engage in regular physical activity (Barlow *et al.*, 2012; Macera *et al.*, 2003).

2.2.1 Physiological response to exercise

The ability to undertake physical exercise is heavily related to the cardiovascular system's ability to supply oxygen (O_2) to the muscles, and the pulmonary system's capability to remove carbon dioxide (CO_2) from the blood via the lungs. Exercise increases the amount of oxygen consumption and carbon dioxide production in the muscle, $\dot{Q}O_2$ and $\dot{Q}CO_2$ respectively. Cardiopulmonary exercise is the interaction between the heart, circulatory system, and pulmonary system, which exchanges O_2 and CO_2, provides energy, and permits an individual to perform work. It delivers fully oxygenated blood to the peripheral tissues, it allows for cellular uptake of oxygen, the use of oxygen within the tissue, and the return of partially desaturated blood to the lungs. The Wasserman model provides an excellent integrative overview of the systems (Figure 2.1).

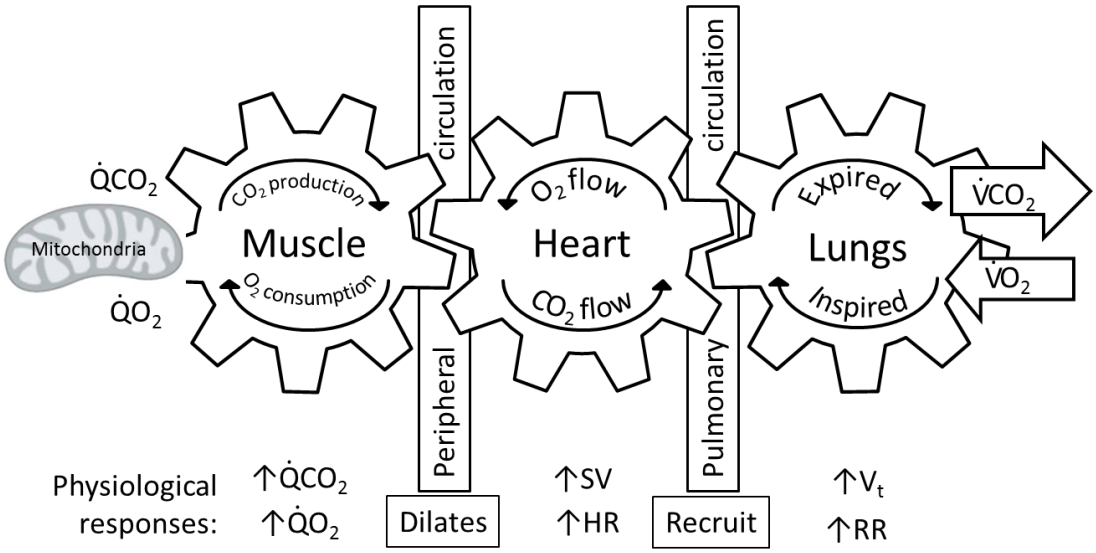


Figure 2.1: The integrative physiological response of the different organ systems to exercise. CO_2 - carbon dioxide, HR - heart rate, O_2 - oxygen; $\dot{Q}CO_2$ - carbon dioxide production by the exercising muscles; $\dot{Q}O_2$ - oxygen uptake by the exercising muscles; SV - stroke volume; V_t - tidal volume; RR – respiratory rate, $\dot{V}CO_2$ - carbon dioxide production; $\dot{V}O_2$ - oxygen uptake. Adapted from Wasserman (Wasserman *et al.*, 2005)

During exercise the primary function of the heart is to sustain $\dot{Q}$. The four determinants of $\dot{Q}$ are heart rate (HR), contractibility, preload and afterload (Vincent, 2008). Preload is the degree of myocardial stretch put on the ventricles by the amount of entering blood volume, which can be substituted with end diastolic volume (EDV). In the early stages of an exercise bout $\dot{Q}$ increases and consequently there is a significant increase in preload through the use of the Frank-Starling mechanism, which is the ability of the heart to change the contraction force and to control stroke volume (SV) in response to changes in venous return (Fletcher *et al.*, 2001). Afterload is the resistance the ventricle must pump against in order to eject blood and is mostly reliant on aortic pressure. Elevated blood pressure and aortic valve disease both increase left ventricular afterload. Reducing afterload can increase $\dot{Q}$, this is important in conditions where contractibility is impaired.

The main physiological response to exercise is an increase in the body's oxygen consumption ($\dot{V}O_2$). The cardiopulmonary system response can be explained by the Fick equation (Figure 2.2), where $\dot{Q}$ is the cardiac output and $C(a\text{-}\bar{v})O_2$diff is the arteriovenous oxygen difference.

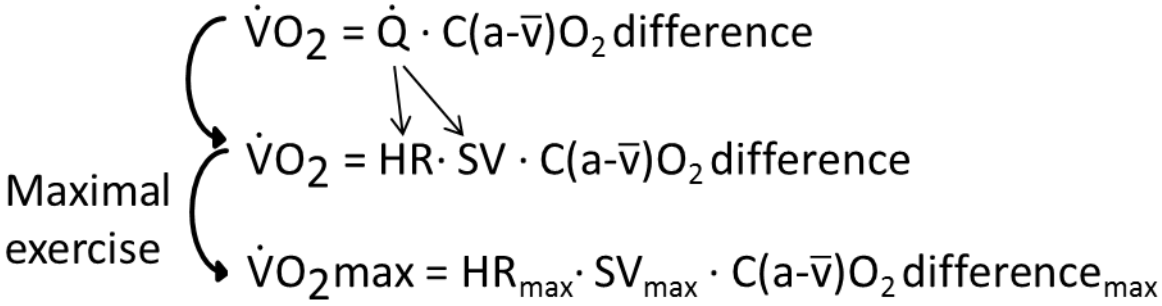


Figure 2.2: the Fick equation. $\dot{V}O_2$ – oxygen consumption, $\dot{Q}$ – cardiac output; $C(a\text{-}\bar{v})O_2$difference – arteriovenous oxygen difference, HR – heart rate; SV – stroke volume

$\dot{Q}$ is the volume of blood pumped by the heart and is determined by the product of HR and SV, whereas $C(a\text{-}\bar{v})O_2$diff is a peripheral factor, which describes the ability of the muscles to extract oxygen from the blood. During exercise the $C(a\text{-}\bar{v})O_2$diff remains relatively constant and during peak exercise stops increasing both in normal individuals and patients with cardiac disease (Luks *et al.*, 2013). In healthy individuals, at the

initiation of exercise, HR and SV rise incrementally, accompanied by an increase in mean arterial pressure and an increased $\dot{Q}$. Simultaneously, vascular resistance in skeletal muscle declines in response to increasing metabolic demands, particularly oxygen extraction. At around 40-60% of maximal exercise the rise in SV plateaus, $\dot{Q}$ becomes HR dependent and the blood pressure rise becomes steeper (Haykowsky *et al.*, 2011) (Figure 2.3). Any further enhancement of $\dot{Q}$ in the latter stages of exercise is primarily due to increases in HR. $\dot{V}O_2$ will rise steadily with incremental exercise till an individual's maximum is reached where $\dot{V}O_2$ will plateau. This plateau is defined as a person's true physiological maximum exercise oxygen consumption and can be determined in the final stages of exercise when work rate increases but $\dot{V}O_2$ plateaus. In healthy individuals, high intensity exercise can result in an increase of $\dot{Q}$ of 4 to 6-fold, a 2 to 4-fold increase in HR and a rise in SV of 20-50% (Figure 2.3).

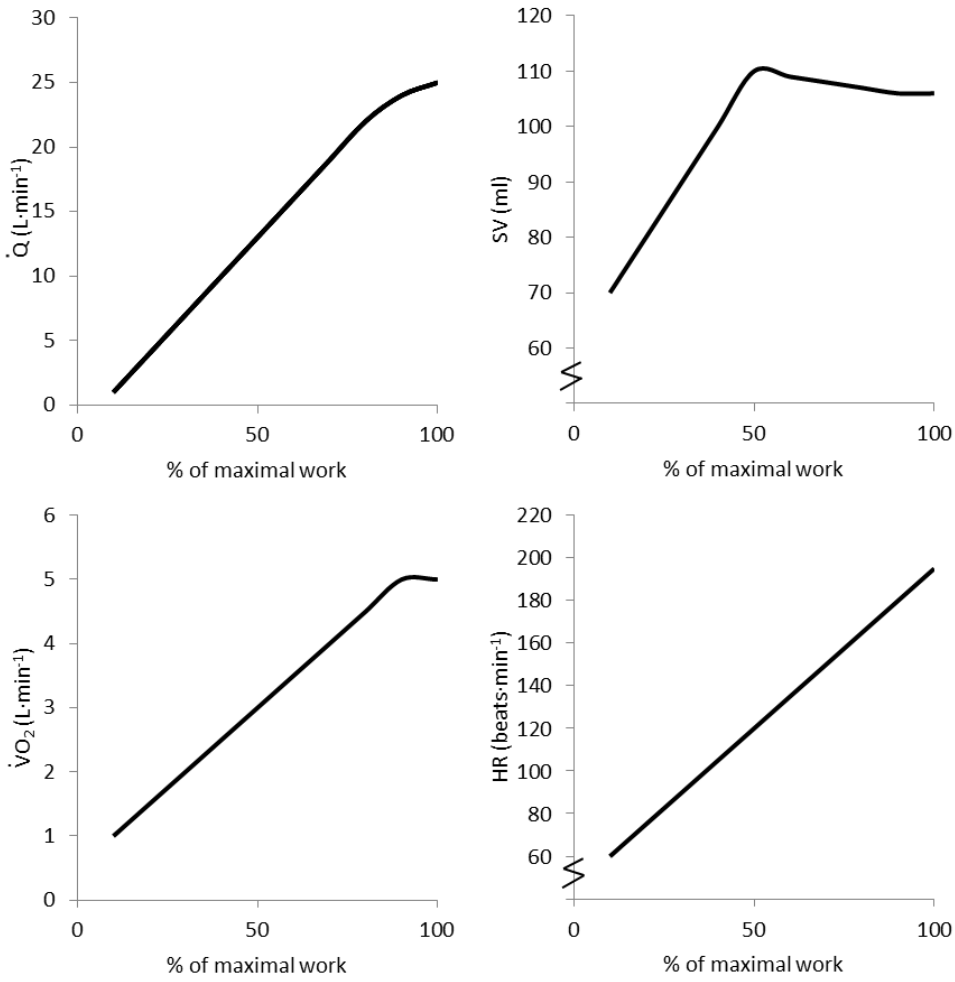


Figure 2.3: Circulatory responses to exercise in healthy individuals. $\dot{Q}$ – cardiac output, SV – stroke volume; $\dot{V}O_2$ - oxygen consumption; HR – heart rate

2.2.2 Physiological response to exercise in patients with a cardiac limitation

Heart function is the limiting factor in patients with valvular or ischaemic heart disease. Exercise tolerance will be lower than expected as cardiac function is unable to augment to sufficiently supply the exercising muscles. SV and $\dot{Q}$ are usually decreased throughout exercise compared to healthy individuals. In the early stages of cardiac dysfunction, the body will try to increase SV utilising the Frank-Starling mechanism which results in an increased EDV, increased HR and increased afterload. This will result in a lower than predicted $\dot{V}O_{2max}$ compared to healthy individuals (Luks *et al.*, 2013). Patients with a cardiac limitation often fail to increase $\dot{V}O_2$ normally relative to energy demands as work rate increases (Arena and Sietsema, 2011). Chronotropic incompetence is not uncommon which results in a maximal HR well below age predicted maximum and often a reduced rate in recovery is also observed (Luks *et al.*, 2013). Ventilation ($\dot{V}_E$) during exercise is typically higher at any given work rate for the most impaired individuals compared to normal individuals, however $\dot{V}_E$ is not the limiting factor for these patients. Augmentation in ventilatory drive during exercise occurs due to ventilation-perfusion mismatching demanding an increased level of ventilation relative to metabolic rate (see section 2.3.3.4 on ventilatory efficiency for more detail).

2.3 Cardiopulmonary exercise testing

CPET measures $\dot{V}O_2$, carbon dioxide production ($\dot{V}CO_2$) and $\dot{V}_E$ during exercise. It provides an overall assessment of the interaction between cardiac, musculoskeletal and the pulmonary systems. It provides information regarding maximal and submaximal responses to exercise. During a test, typical measurements such as blood pressure, oxygen saturation, electrocardiograms (ECGs), and subjective symptoms are monitored, in addition to ventilatory gas exchange. In order to measure ventilatory gas exchange calorimetry is used, which can be measured either directly or indirectly.

2.3.1 Measuring energy expenditure

Energy expenditure can be measured by several different techniques. The direct measure of a change in heat is termed direct calorimetry. This method uses an enclosed room (bomb calorimeter) and measures the amount of heat produced when food is burned in a sealed contained. This principle also applies to human metabolism when the amount of heat produced is measured in a sealed room (Figure 2.4). Heat generated within a person's body is transferred to the air and walls of the chamber. A person's metabolic rate is the temperature change in the air and water flowing through the chamber. The rise in temperature of the water can be converted to calories burned. An increase of 1° Celsius is equivalent to an input of heat (energy) of 1 kilocalorie (Brown *et al.*, 2005). Some disadvantages arise from direct calorimetry which include additional heat generated by exercise equipment, space needed and expenses (Battley, 1995).

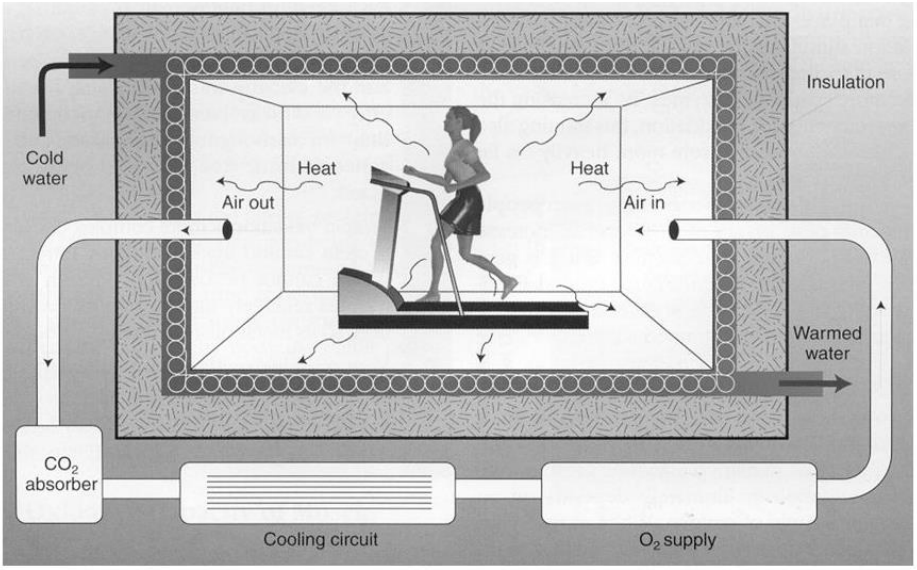


Figure 2.4: Direct calorimetry showing a calorimetric chamber (Wilmore and Costill, 2004)

Indirect calorimetry is a measure based on the principle that the amount of O_2 and CO_2 exchanged in the lungs is equal to the amount exchanged in the body tissues. This can be measured using respiratory gas exchange and converted to estimate energy expenditure (Frankenfield, 2010). The first human indirect calorimeter experiment was in 1790 by Antoine Lavoisier (Holmes, 1987) (Figure 2.5), however it took a further 110 years before the method of indirect calorimetry was fully accepted.

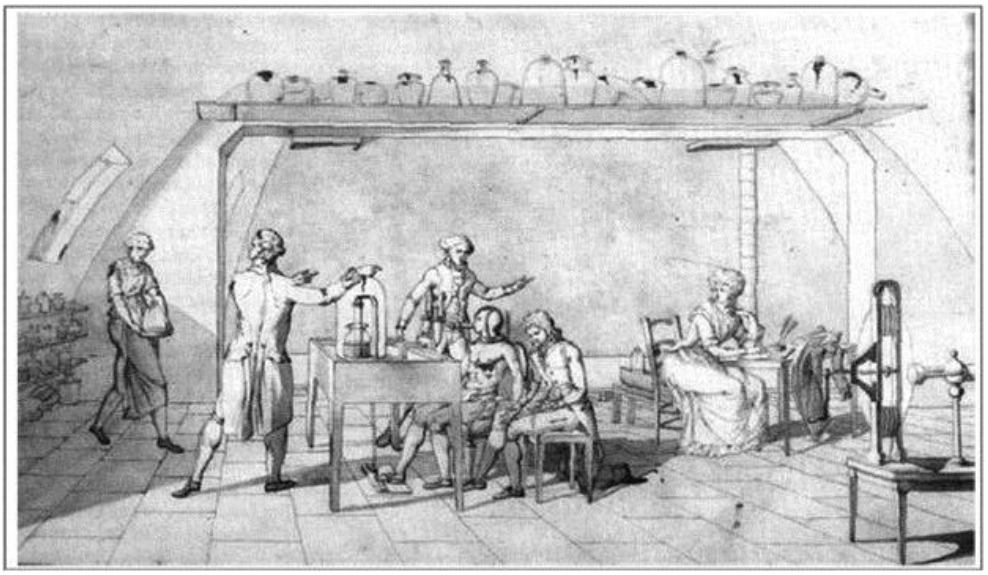


Figure 2.5: The first human indirect calorimetry by Lavoisier in 1790. A copper facemask wrapped with pine pitch and turpentine was used to collect the expired air. It is presumed that oxygen was breathed from a reservoir (closed circuit) and that the a pneumatic container was able to gather the residual air (Frankenfield, 2010)

Carl von Voit and his student Max Rubner were able to demonstrate agreement between gas exchange and heat production carrying on the work of Lavoisier (Lusk, 1919; Wilder, 1959). Indirect calorimetry technique is most often used in exercise physiology laboratories and produces comparable results to direct calorimetry (Seale *et al.*, 1990). In 1895, Adolf Magnus-Levy was the first researcher to apply indirect calorimetry directly to clinical medicine, which was followed by numerous studies looking at metabolism during disease, including HF, cancer and thyroid disease, and fever due to infection (Frankenfield, 2010; Lusk, 1919). Currently, the most frequent use for indirect calorimetry is for the assessment of exercise tolerance using CPET.

2.3.2 The cardiopulmonary exercise test

CPET is performed for a number of reasons and the most common objective is to evaluate cardiorespiratory fitness, it also describes the physiologic systems underlying exercise responses and determines the function-based prognostic stratification. The indications for CPET are diverse (Table 2.1).

Table 2.1: Indications for cardiopulmonary exercise testing

Evaluation of exercise tolerance
Evaluation of undiagnosed exercise intolerance / breathlessness of unknown cause
Evaluation of patients with cardiovascular diseases
Evaluation of patients with respiratory disease/symptoms
Preoperative risk evaluation prior to major surgery
Exercise evaluation and prescription for cardiac / pulmonary rehabilitation
Evaluation of impairment / disability
Evaluation for lung, heart, and heart-lung transplantation
Evaluation of the response to an intervention

Both treadmill and cycle ergometers are regularly used for CPET testing. The key is to involve large muscle groups such as during cycling or running. Cycle ergometers are less expensive, smaller, and less noisy compared to treadmills. However $\dot{V}O_{2\,peak}$ obtained on a cycle ergometer is 8-12% lower when compared to treadmill

exercise (Wasserman *et al.*, 2005). Using a cycle ergometer is often the modality of choice in patients who are elderly, obese, or use a cane or walker. These patients often have difficulty walking on the treadmill, and a cycle ergometer is weight bearing and therefore provides for a wider range of patients to be tested. There is less chance of falling, it is quieter, and there is a direct measurement of work performed. The test involves a period of rest, followed by a short warm-up, followed by an incremental increase in work rate until voluntarily exhaustion, and finished with a recovery phase.

2.3.3 Safety of a cardiopulmonary exercise test

CPET is a non-invasive, reproducible and safe test (American Thoracic Society, 2003; Skalski *et al.*, 2012). A review article by Myers *et al.*, (2014) summarising 19 different reports between 1971 and 2012 involving more than 2.1 million CPETs demonstrated total complication rates from 0 to 3.46 per 1000 tests (after exclusion of extremely high-risk patients with a history of life-threatening ventricular arrhythmias). Another review article by Skalski *et al.*, (2012) including 5060 CPET studies performed in a single centre, including patients with high-risk cardiovascular disease showed an event rate of 0.16% (most commonly sustained ventricular arrhythmias). No fatal events were observed, concluding that CPET is a safe procedure even in high-risk cardiac patients. The American Thoracic Society and the American College of Chest Physicians have reported a total risk of death for CPET performed is approximately 0.5 per 100,000 tests in healthy individuals and between 2 and 5 per 100,000 in patients with cardiovascular disease (American Thoracic Society, 2003). Absolute and relative contraindications to exercise testing are similar for both the American Heart Association (Fletcher *et al.*, 2001) and the British Cardiovascular Society (The Society for Cardiological Science and Technology, 2008) are displayed in table 2.2 (Fletcher *et al.*, 2001). Exercise testing should not be performed in the presence of absolute contraindications. Relative contraindications can be disregarded if benefits of conducting test outweigh risks of exercise.

Table 2.2: Contraindications to exercise testing (modified from (Fletcher *et al.*, 2001) and the British Cardiovascular Society (The Society for Cardiological Science and Technology, 2008)

Absolute indicators	Relative indicators
• Acute myocardial infarction	• Left main coronary artery stenosis
• High-risk unstable angina	• Moderate stenotic valvular heart disease
• Acute myocarditis or pericarditis	• Electrolyte abnormalities
• Uncontrolled symptomatic heart failure	• Tachyarrhythmias or bradyarrhythmias
• Acute aortic dissection	• Hyperthrophic cardiomyopathy and other forms of outflow tract obstruction
• Uncontrolled cardiac arrhythmias with haemodynamic compromise	• High-degree atrioventricular block
• Symptomatic severe aortic stenosis	• Mental or physical impairment leading to inability to exercise adequately
• Acute pulmonary embolism or pulmonary infarction	• Uncontrolled raised systolic blood pressure (SBP > 180 mmHg and/or DBP >100 mmHg)
	• Hypotension (SBP <90mmHg)
	• Recent stroke or transient ischaemic attack

SBP – systolic blood pressure; DBP – diastolic blood pressure

2.3.4 Key cardiopulmonary exercise parameters

2.3.4.1 Peak oxygen uptake

The maximal oxygen uptake is termed the $\dot{V}O_{2max}$. $\dot{V}O_{2max}$ is considered the gold standard for the measurement of cardiorespiratory fitness. $\dot{V}O_{2max}$ is defined as a person's true physiological maximum oxygen consumption and can be determined from a clear observed plateau in the final stages of exercise when work rate increase but $\dot{V}O_2$ plateaus. This plateau is often seen in an athletic population which is in contrast to clinical populations where a plateau is rarely observed and is poorly reproducible (Tavazzi *et al.*, 2001). Hence the term $\dot{V}O_{2peak}$, which is the more frequently used term in a clinical practice, and describes the highest $\dot{V}O_2$ during a test but criteria for maximal exertion are not fulfilled. Criteria for $\dot{V}O_{2max}$ include, besides a clear plateau, a respiratory exchange ratio (RER) above 1.10 and peak HR within 10 beats·min^{-1} of age predicted maximum (Piepoli *et al.*, 2006c). Available evidence has shown similar prognostic power for both variables (Day *et al.*, 2003). $\dot{V}O_{2peak}$ is superior to exercise duration or peak power when describing patients' exercise tolerance (Myers, 2005). $\dot{V}O_{2peak}$ is the primary physiological response to exercise training and is influenced by age, gender, exercise habits, heredity, and clinical status (Mezzani *et al.*, 2009). However $\dot{V}O_{2peak}$ tends to decrease with age, is usually lower in women, depends on lean muscle mass and can be affected by training (Piepoli *et al*., 2006b). Resting $\dot{V}O_2$ is around 3.5 mL·kg^{-1}·min^{-1} in healthy individuals and the highest ever recorded $\dot{V}O_{2max}$ was in a Norwegian cyclist in 2012 and measured 97.5 mL·kg ^{1}·min^{-1}. A reduction in $\dot{V}O_{2peak}$ is the initial parameter when investigating a decrease in exercise tolerance as it is affected by many cardiac and non-cardiac diseases and is a validated independent predictor for hospitalisation and death (Piepoli *et al*., 2006b; Weisman and Zeballos, 1994). Figure 2.6 shows $\dot{V}O_{2peak}$ measured in a 39 year old healthy recreational runner and a 76 year old patient with severe HF. $\dot{V}O_{2peak}$ was 36.6 mL·kg^{-1}·min^{-1} for the recreational runner which falls just below the normal range for his age, height and weight whereas the patient with severe HF demonstrated a significant reduced $\dot{V}O_{2peak}$ at 13.3 mL·kg^{-1}·min^{-1}.

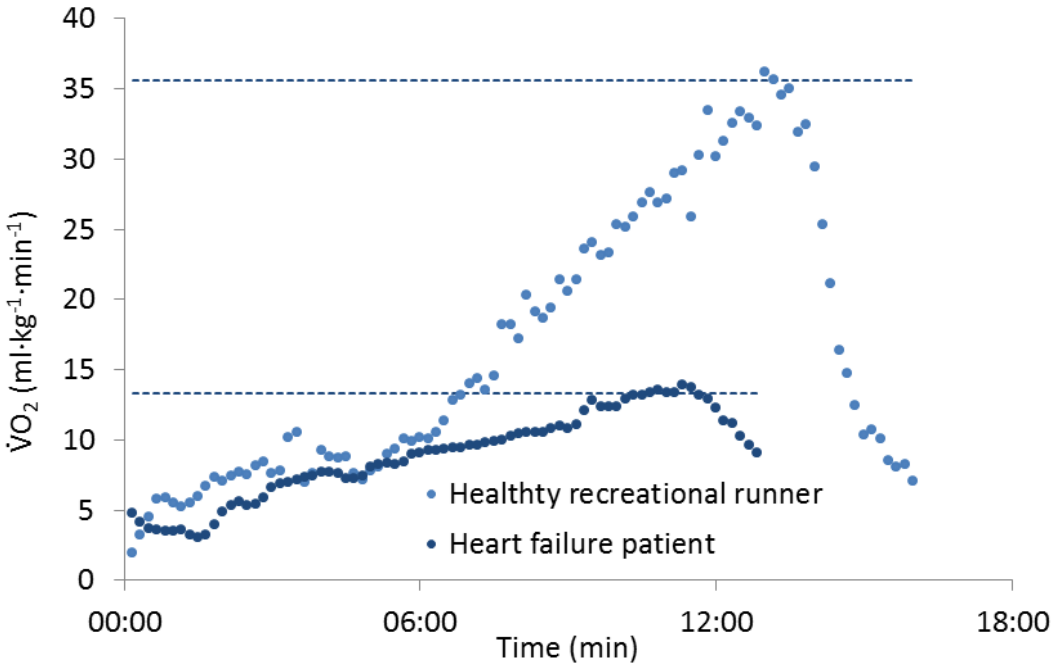


Figure 2.6: $\dot{V}O_{2peak}$ for a 39 year old healthy recreational runner, $\dot{V}O_{2peak}$ = 36.6 mL·kg^{-1}·min^{-1} vs. a 76 year old patient with HF, $\dot{V}O_{2peak}$ = 13.3 mL·kg^{-1}·min^{-1}. $\dot{V}O_{2peak}$ – peak oxygen uptake (data from patients seen clinically at Eastbourne DGH)

$\dot{V}O_{2peak}$ can be expressed as absolute (L·min^{-1}), relative values (mL·kg^{-1}·min^{-1}) or as percentage of predicted. Percentage predicted $\dot{V}O_2$ is often the preferred approach when reporting. There is no clear consensus on the normative values. The following statements state that a $\dot{V}O_{2peak}$ greater than 80% (Piepoli *et al.*, 2006a), greater than 84% (American Thoracic Society, 2003), or within 95% of the confidence interval (Balady *et al.*, 2010) or greater than 100% (Guazzi *et al.*, 2012) is considered normal. To add to this confusion there are several different formulae available to predict $\dot{V}O_{2peak}$ and these formulae give markedly different results (van Zalen *et al.*, 2017) - see section 3.5 for a detailed analysis of the most common used formulae predicting $\dot{V}O_{2peak}$. Using the relative value of $\dot{V}O_{2peak}$ provides a more honest analyses of patient's exercise tolerance. Weight and age need to be taken into account when analysing as a $\dot{V}O_{2peak}$ of 20 mL·kg^{-1}·min^{-1} is considered good for a 75 year old female, but this would be significantly reduced for a 30 year old male. Normal values per age group according to the American College of Sport Medicine (ACSM) can be found in table 2.3.

Table 2.3: Normative values for $\dot{V}O_{2\,max}$ (adapted from ACSM's guidelines (Thompson *et al.*, 2010)).

Age (years)	Superior	Excellent	Good	Fair	Poor	Very poor
Men	$\dot{V}O_{2\,max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)					
20-29	>56	51 – 55	46-50	42-45	38-41	<38
30-39	>54	48-53	44-47	41-43	37-40	<37
40-49	>53	46-52	42-45	38-41	35-37	<35
50-59	>50	43-49	38-42	35-37	31-34	<31
60-69	>46	39-45	35-38	31-34	27-30	<27
70-79	>42	36-41	31-35	28-30	24-27	<24
Women	$\dot{V}O_{2\,max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)					
20-29	>50	44-49	40-43	36-39	32-35	<32
30-39	>46	41-45	37-40	34-36	30-33	<30
40-49	>45	39-44	35-38	32-34	28-31	<28
50-59	>40	35-40	31-34	29-30	26-28	<26
60-69	>37	32-35	29-31	26-28	24-25	<24
70-79	>36	30-35	27-29	24-26	21-23	<21

$\dot{V}O_{2\,max}$ – maximal oxygen uptake

Vanhees *et al.*, (1994) investigated 527 patients with CVD and found that mortality decreased with increasing $\dot{V}O_{2peak}$ and concluded $\dot{V}O_{2peak}$ to be an independent predictor for mortality. A follow-up study in patients with known CVD revealed that an increase in $\dot{V}O_{2peak}$ of 1 $mL \cdot kg^{-1} \cdot min^{-1}$ resulted in a 9-10% reduction in cardiac mortality (Kavanagh *et al.*, 2002, 2003). Patients with HF with a $\dot{V}O_{2peak}$ above 18 $mL \cdot kg^{-1} \cdot min^{-1}$ are generally considered to have a good outcome at 1 year.

Current guidelines listing the criteria for heart transplantation state that patients who require a cardiac transplant qualify if $\dot{V}O_{2peak}$ is less than 14 $mL \cdot kg^{-1} \cdot min^{-1}$ (Mancini *et al.*, 1991; Mehra *et al.*, 2006, 2016). Beckles *et al.*, (2003) investigated the post-operative complications risk for patients undergoing tumour resection surgery and demonstrated that patients with a $\dot{V}O_{2peak}$ above 20 $mL \cdot kg^{-1} \cdot min^{-1}$ had no increased risk of complications or death, patients with a $\dot{V}O_{2peak}$ below 15 $mL \cdot kg^{-1} \cdot min^{-1}$ were

associated with an increased risk and patients below 10 $mL \cdot kg^{-1} \cdot min^{-1}$ had a very high risk for post-operative complications.

2.3.4.2 Ventilatory threshold

The ventilatory threshold (VT) is a non-invasive, indirect measurement to determine submaximal exercise tolerance. It is observed as an increase in $\dot{V}_E$ disproportionate to the increase in $\dot{V}O_2$ during incremental exercise (Piepoli *et al.*, 2006c). The term VT is interchangeably used with anaerobic threshold. The VT is caused by an increased requirement to expire excess $\dot{V}CO_2$, as a consequence of increasing serum lactic acid concentrations secondary to anaerobic metabolism (Wasserman *et al.*, 1990). Changes in respiratory patterns, $\dot{V}O_2$ and $\dot{V}CO_2$ excretion are sensitive to shifts in metabolism because arterial pressures of O_2, CO_2, and pH are tightly controlled by homeostatic reflexes regardless of exercise intensity (Luks *et al.*, 2013). Below the VT, participants can theoretically exercise indefinitely without causing significant lactic acidosis. The VT (in contrast to $\dot{V}O_{2max}$) is particularly relevant to activities of daily living because these are usually low-intensity and of longer duration. Hence for the majority of those with chronic diseases, the VT provides key information about patient's functional ability as this often identifies the onset of breathlessness. Exercise training has previous demonstrated excellent improvements in VT (typically between 10 to 25% in sedentary individuals) (Balady *et al.*, 2010). The VT can be expressed in relative values or a percentage of predicted $\dot{V}O_{2peak}$. Normal values are between 50-60% of predicted $\dot{V}O_{2peak}$, between 40-50% is considered deconditioned or mild disease and less than 40% is an abnormally reduced VT (Kinnear and Blakey, 2014). Endurance trained individuals often obtain a higher VT. The VT has high test-retest reliability in healthy individuals (Amann *et al.*, 2004) and in patients with HF test-rest reliability was still high but the ability to detect the VT was slightly lower probably secondary to ventilatory abnormalities (Bensimhon *et al.*, 2008). Gitt *et al.*, (2002) showed that a low $\dot{V}O_2$ at the VT was a strong predictor of six-month survival in patients with HF. Older *et al.*, (1993) found significant lower post-operative deaths in elderly patients with mixed pathologies who had a VT above 11 $mL \cdot kg^{-1} \cdot min^{-1}$. A prospective study triaging patients' postoperative management based on the VT greater than

11 mL·kg-^{1}·min^{-1}, a $\dot{V}_E/\dot{V}CO_2$ ratio lower than 35 and no presence of ST changes on ECG resulted in a reduction in cardiovascular mortality from 18% to 4.6%, cardiovascular mortality was 0% for patients allocated for postoperative care bed on the ward (Older *et al.*, 1999).

The combination of $\dot{V}O_{2peak}$ and the VT can offer a more enhanced grading of the severity of a patient's impairment. Table 2.4 describes the grading of the severity of functional impairment in patients with chronic HF (Weber *et al.*, 1982). This grading allows an objective monitoring of the disease progression. Gitt *et al.*, (2002) looked at 223 CPET in HF patients and found that patients with a $\dot{V}O_{2peak}$ less than 14 mL·kg^{-1}·min^{-1} and a $\dot{V}O_2$ at the VT below 11 mL·kg^{-1}·min^{-1} had a 3.2 increased risk of death within 6 months. Figure 2.7 shows the VT measured in a 39 year old healthy recreational runner and a 76 year old patient with severe HF. $\dot{V}O_2$ at VT occurred at 23.1 mL·kg^{-1}·min^{-1} equivalent to 58% of peak predicted $\dot{V}O_2$ for the healthy recreational runner which falls well within the normal range for his age, height and weight whereas the patient with severe HF demonstrated a significant reduced $\dot{V}O_2$ at VT at 9.3 mL·kg^{-1}·min^{-1} equivalent to 46% of peak predicted $\dot{V}O_2$. How to determine the VT in detail is described in the methodology section (3.4.1).

Table 2.4 – Weber classification – functional capacity classification for HF patients (Weber *et al.*, 1982)

Functional class classification	$\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})	$\dot{V}O_2$ at VT (mL·kg^{-1}·min^{-1})	Deterioration of functional capacity
A	> 20	>14	Mild or absent
B	16-20	11-14	Mild – moderate
C	10-16	8-11	Moderate – severe
D	<10	<8	Severe

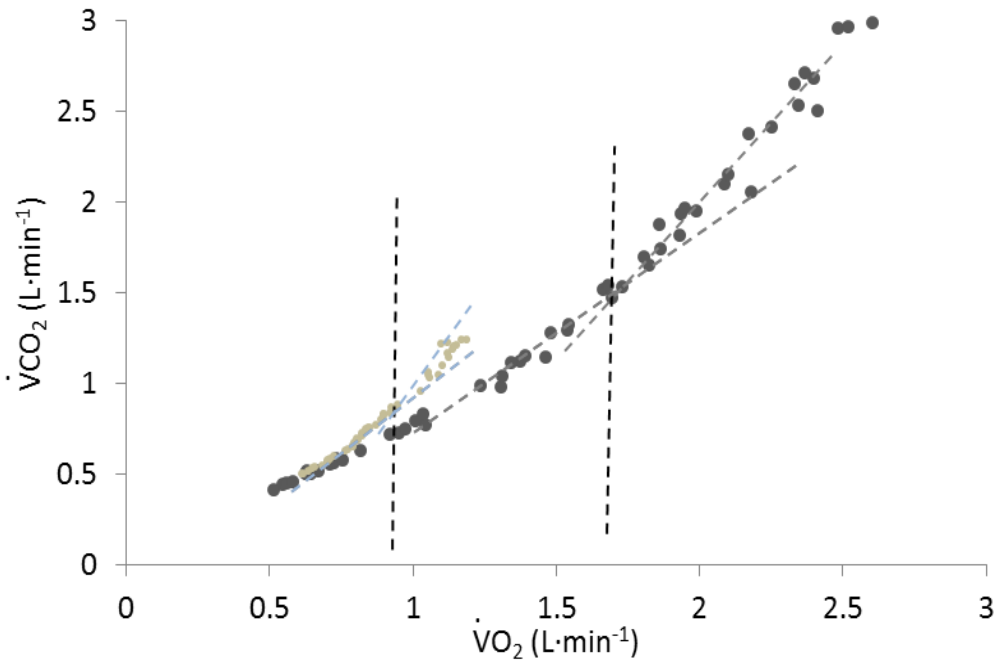


Figure 2.7: The VT for a 39 year old healthy recreational runner, VT = 1.6 L·min^{-1}= 23.1 mL·kg-^{1}·min^{-1} = 58% of peak predicted $\dot{V}O_2$ vs. a 76 year old patient with HF, VT = 0.7 L·min^{-1} = 9.3 mL·kg^{-1}·min^{-1} = 46% of predicted peak $\dot{V}O_2$. VT – ventilatory threshold; $\dot{V}O_2$ – oxygen uptake (data from patients seen clinically at Eastbourne DGH)

2.3.4.3 Oxygen uptake efficiency slope

The oxygen uptake efficiency slope (OUES) is the slope when plotting $\dot{V}O_2$ against the logarithm of $\dot{V}_E$ (log$\dot{V}_E$) (Baba *et al.*, 1996). High values of $\dot{V}_E$ have more influence than $\dot{V}O_2$ and the slope represents a more reliable approximation of the efficiency of $\dot{V}O_2$. The OUES is clinically useful for two key reasons. Firstly, it can be generated from submaximal data (Hollenberg and Tager, 2000). In principle, even a few data points after the VT can be used to derive a reproducible OUES. Secondly, several analyses have shown a tight relationship between OUES and $\dot{V}O_{2\,peak}$ (Coeckelberghs *et al.*, 2016; Van Laethem *et al.*, 2005). When OUES is considered in logistic regression models, it is superior to $\dot{V}O_{2\,peak}$ to predict mortality (Coeckelberghs *et al.*, 2016; Davies *et al.*, 2006). The consequence is that in practice, the OUES can be used to estimate maximal exercise tolerance from a submaximal test. This is a particularly useful tool in those who are unwilling or unable to exercise to their physical limit. Normal values are expressed as the percentage of predicted OUES. A normal OUES in the setting of a low

$\dot{V}O_{2\,peak}$ should alert the clinician to the possibility that the test was submaximal due to poor effort. Figure 2.8 shows the OUES measured in a 39 year old healthy recreational runner and a 76 year old patient with severe HF. OUES was 2520 $(mL \cdot min^{-1}) \cdot (L \cdot min^{-1})^{-1}$ for the recreational runner which falls well within the normal range for his age, height and weight whereas the patient with severe HF demonstrated a significant reduced OUES at 1437 $(mL \cdot min^{-1}) \cdot (L \cdot min^{-1})^{-1}$.

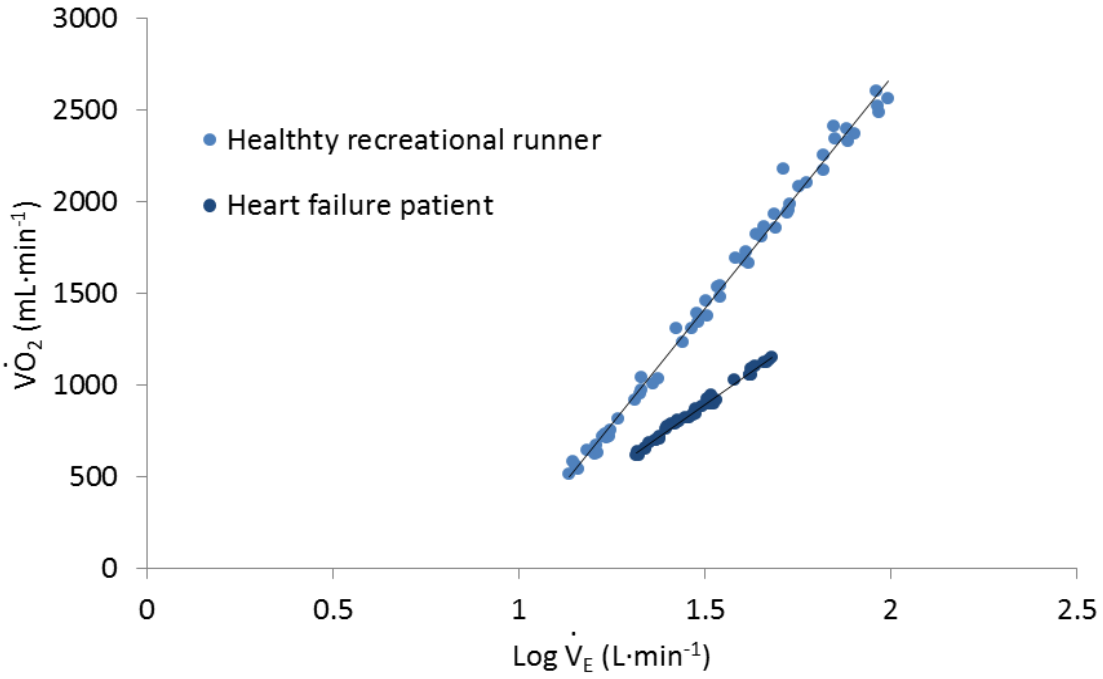


Figure 2.8: OUES for a 39 year old healthy recreational runner, OUES = 2520 $(mL \cdot min^{-1}) \cdot (L \cdot min^{-1})^{-1}$ vs. a 76 year old patient with HF, OUES = 1437 $(mL \cdot min^{-1}) \cdot (L \cdot min^{-1})^{-1}$
OUES – oxygen uptake efficiency slope; $\dot{V}O_2$ – oxygen uptake; $\dot{V}_E$ - ventilation (data from patients seen clinically at Eastbourne DGH)

2.3.4.4 Ventilatory efficiency

Another key CPET variable is ventilatory efficiency ($\dot{V}_E$ /$\dot{V}CO_2$). This variable represents the ventilatory requirement to eliminate a given amount of CO_2 produced by the metabolising tissues and is index of the amount of $\dot{V}_E$ needed to eliminate CO_2. $\dot{V}_E$ increases with an increased work rate. Not all ventilated air is exposed to alveolar gas exchange. The proportion of tidal volume (V_t) that does not contribute to alveolar gas exchange (e.g. those gases that remain within respiratory passages) is known as dead

space (V_D). There are two types of dead space; anatomical and physiological dead space. Physiological V_D is the volume of the lungs which does not contribute to gas exchange, either because it is anatomical V_D or because the alveoli are not perfused (Kinnear and Blakey, 2014). When exercising, V_D is increased due to bronchodilation of the respiratory passages. To maintain sufficient gas exchange, V_t and alveolar ventilation are increased in order to maintain adequate gas exchange. This is termed normal ventilation-perfusion matching (Wasserman *et al.*, 2005). At rest, in an upright position those lung segments in the apices are better ventilated than those in the lung bases. However, gravity would tend to favour blood flow to the bases rather than the apices. The pulmonary vasculature must react to route perfused blood within the pulmonary capillary bed to those alveoli where it is best needed. During exercise, due to an increase in $\dot{Q}$, blood vessels towards the apex of the lungs become involved and perfusion of the lungs improves, resulting in better ventilation-perfusion matching (Kinnear and Blakey, 2014). Figure 2.9 demonstrates the schematic for poor ventilation-perfusion mismatching.

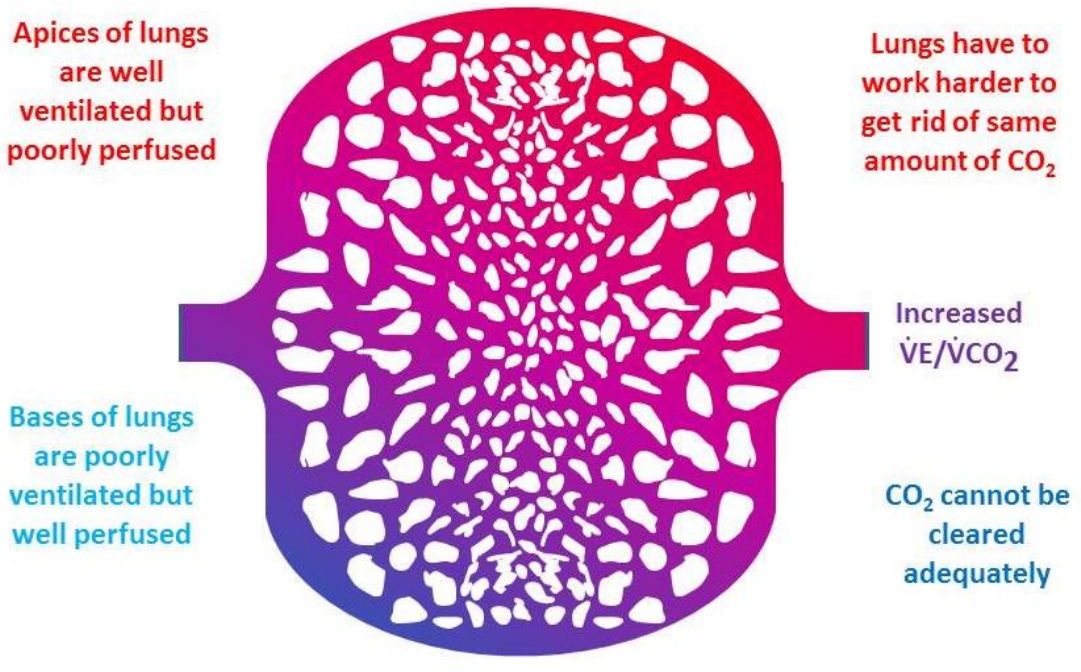


Figure 2.9: A design of the lungs demonstrating ventilation-perfusion mismatching during exercise

A failure in ventilation-perfusion matching causes an increase in so-called 'functional' dead space and implies a high V_D/V_t ratio and increased $\dot{V}_E/\dot{V}CO_2$. The $\dot{V}_E/\dot{V}CO_2$ ratio is

a reproducible, easily obtainable parameter during submaximal exercise whilst conducting a CPET (Arena *et al.*, 2004; Piepoli *et al.*, 2006a; Piepoli *et al.*, 2006c). The $\dot{V}_E/\dot{V}CO_2$ can either be expressed as a ratio (either at the lowest point during exercise or at the VT) or as slope function during exercise. No consensus exists on which methodology should be used (a more detailed analysis is included in section 3.4.3). Normal values increase with age and a value greater than 34 is considered abnormal (Wasserman *et al.*, 2005). A high $\dot{V}_E/\dot{V}CO_2$ ratio means that there is disproportionately high ventilation needed to achieve CO_2 excretion. This can be easily explained by an increase in anatomical or functional dead space ventilation such as hyperventilation, but could also occur if arterial CO_2 declines during exertion, either as a consequence of inappropriate ventilatory reflex responses or as a consequence of metabolic acidosis (Kinnear and Blakey, 2014). Numerous diseases have an effect on the $\dot{V}_E/\dot{V}CO_2$ ratio. Almost all lung diseases cause an increase in the ratio, mainly due to high anatomical ventilatory dead space resulting in a high V_D/V_t ratio which does not decrease with exercise. Therefore, patients with lung disease need more ventilation for any given workload. In HF, $\dot{V}_E/\dot{V}CO_2$ ratio is also elevated in the absence of any lung disease. The reason why is not fully understood but may be due to the functional ventilation-perfusion mismatching due to increase ventilatory drive and the haemodynamic demands associated with the work of breathing and abnormally elevated chemoreceptor and ergoreceptor sensitivity to exercise (Clark *et al.*, 1994; Ponikowski *et al.*, 2001). The $\dot{V}_E/\dot{V}CO_2$ ratio is a strong independent predictor of prognosis in HF and is found to be superior to $\dot{V}O_{2peak}$ especially when patients perform sub-maximal exercise and when patients are on beta-blocker therapy (Arena *et al.*, 2004; Corrà *et al.*, 2004; Francis *et al.*, 2000; Gitt *et al.*, 2002; Guazzi *et al.*, 2012). Figure 2.10 shows the $\dot{V}_E/\dot{V}CO_2$ slope measured in a 39 year old healthy recreational runner and a 76 year old patient with severe HF. $\dot{V}_E/\dot{V}CO_2$ slope = 29 for a healthy recreational runner which is within normal range whereas the 76 year old patient with HF has a $\dot{V}_E/\dot{V}CO_2$ slope at 36.6.

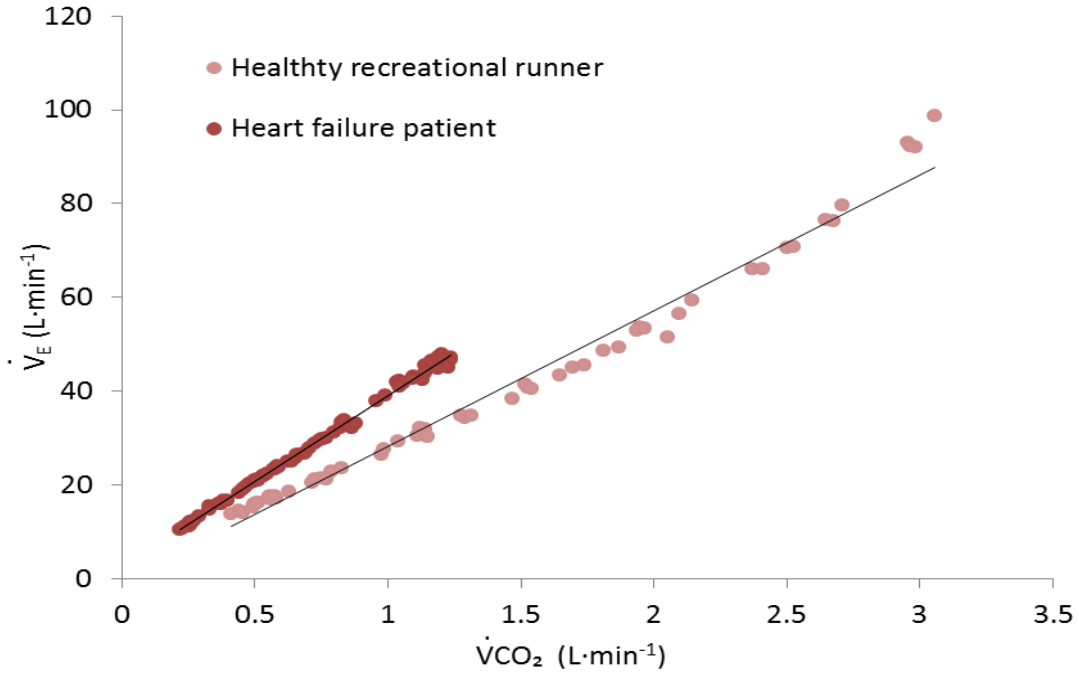


Figure 2.10: $\dot{V}_E$ /$\dot{V}CO_2$ for a 39 year old healthy recreational runner, $\dot{V}_E$ /$\dot{V}CO_2$ slope = 29 vs. a 76 year old patient with HF, $\dot{V}_E$ /$\dot{V}CO_2$ slope = 36.6. $\dot{V}_E$ – ventilation; $\dot{V}CO_2$ - carbon dioxide production (data from patients seen clinically at Eastbourne DGH)

2.3.5 Importance of cardiopulmonary exercise testing

CPET provides diagnostic, prognostic, and functional information. Reproducibility of the parameters measured during exercise testing is important to take into consideration as this may affect interpretation of the results. There are several factors which may affect reliability results which include changes in underlying disease process, changes in medication, patient motivation, patient instruction/encouragement, time of day, testing procedures, and the equipment/calibration process. A number of studies have measured reproducibility of CPET parameters in healthy individuals (Garrard and Emmons, 1986; Nordrehaug *et al.*, 1991), in patients with Chronic Obstructive Pulmonary Disease (COPD) (Belman *et al.*, 1991; Noseda *et al.*, 1989), and in patients with chronic HF (Janicki *et al.*, 1990; Meyer *et al.*, 1997). These studies demonstrated reliability of CPET parameters but mention to use caution when interpreting tests clinically. These are dated studies and have included less than 20 patients each. A larger study including almost 400 patients with

HF evaluated the within-subjects variability of peak $\dot{V}O_2$, $\dot{V}_E$ /$\dot{V}CO_2$ and $\dot{V}O_2$ at the VT and concluded that although some variability was noted and should be taken into account in clinical application on repeated CPETs there appears no familiarisation effect (Bensimhon *et al.*, 2008). Another by study by Barron *et al.*, (2014) examined the test-retest reliability for multiple CPETs in a total of 93 patients with COPD, HF, or with severe mitral valve disease. Results showed excellent test-retest reliability for the majority of CPET variables and concluded that familiarisation is not necessary in the majority of patients and variables are largely unaffected by age, gender, body mass index, aetiology of disease, different protocols, and inter-test interval.

CPET can be useful in a variety of ways; as a preoperative evaluation prior to elective surgery (Balady *et al.*, 2010), to optimise risk stratification in the clinical decision making for invasive procedures, prior medical device therapy, or to assess unexplained exertional dyspnoea (Guazzi *et al.*, 2012). Other potential uses are to determine disease severity and to determine disease progression in patients with HF, chronic pulmonary obstructive disease, congenital heart disease, myocardial disease and patients with valvular heart disease (Guazzi *et al.*, 2012, 2016).

Reduced exercise tolerance is the cardinal symptom in patients with HF. The traditional grading of severity has been done using the New York Heart Association (NYHA) criteria (Table 2.5). This classification system is subjective and poorly reproducible as there is no widespread agreement on how to assign a patient to an NYHA class in clinical practice and has never been found to have prognostic relevance (Raphael *et al.*, 2007). However this classification system remains the base of functional assessment in clinical guidelines. Testing patients on exercise will provide a more enhanced assessment as it unmasks symptoms which may be not apparent at rest and therefore will provide a more enhanced clinical prognosis. The Weber classification uses CPET parameters to describe the objective monitoring of HF disease progression (Weber *et al.*, 1982) (Table 2.4).

Table 2.5 – New York Heart Association classification (The Criteria Committee of the New York Heart Association, 1994)

I	Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain
II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain
III	Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain
IV	Patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased

Patients can be followed up regularly to determine any changes in CPET parameters which might impact decision making for more aggressive medical therapy or intervention. Monitoring patients' progression before and after treatment (pacemaker, transplant, valvular replacement) can be worthwhile to determine the benefits of treatment. CPET can also be used to individually design cardiac rehabilitation programmes targeting specific and defined outcomes for patients, or to distinguish "silent" cardiovascular abnormalities that can develop and cause sudden death in athletes (Corrado *et al.*, 2005).

CPET is becoming increasingly more popular in clinical practice (Huddart *et al.*, 2013) A survey in 2013 performed in England estimated that an excess of 15,000 CPETs are done on a yearly basis for preoperative assessment (Huddart *et al.*, 2013). This number has risen from 2008. Numbers of CPET performed for non-pre-operative patients is unknown. The importance of the utility of CPET in clinical decision making and the true increased benefit is broadly recognised and the growing volume of evidence support this (American Thoracic Society, 2003; Balady *et al*., 2010; Guazzi *et al*., 2012, 2016; Mezzani *et al*., 2009; Nichols *et al*., 2015; Piepoli *et al*., 2006a, 2006b; 2006c; Taylor *et al*., 2015). These statements all agree on the potential benefits CPET can provide in day to day practice but formal guidelines have yet to be defined. Although CPET offers a comprehensive approach to assess patients with cardiovascular disease, it is still an

underused test in daily clinical practice. This may be partly explained by absence of trained personnel who are able to carry out and interpret tests or due to the complexity and the lack of consistency the way tests are performed and reported, or by the overwhelming amount of data CPET software generates, which to most physicians is incomprehensible (Guazzi *et al.*, 2016; Huddart *et al.*, 2013). Formal guidelines would make CPET more accessible in daily practice.

2.4 Echocardiography

Echocardiography is using ultrasound to examine the heart. It is one of the most important and extensively used diagnostic tests performed in cardiology and routinely used in the diagnosis, management and follow-up in patients with cardiac disease (Murphy and Lloyd, 2007). Ultrasound originated by the use of radar technology during World War II, a technology called RADAR (Radio detection and Ranging). In 1946, André Denier proposed the use of ultrasound on the human body (Edler *et al*, 2004). Inge Edler and Helmmuth Hertz were able to develop the first Motion-mode (M-mode) system. In 1953, the first moving ultrasound cardiogram was recorded. In 1979, a scanner was developed enabling 2-dimensional images of the heart for the first time (Edler & Hertz, 1954) (Figure 2.11).

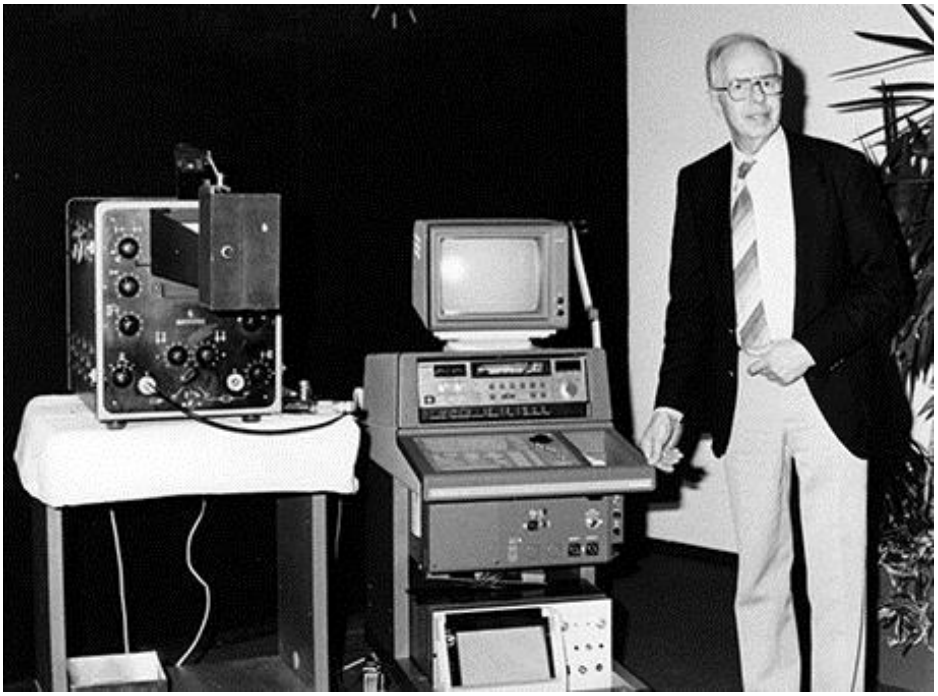


Figure 2.11: Hertz with the 1953 ultrasound reflectoscope on the left and the Sonoline CD on the right, 1985

Echocardiography is a powerful, non-invasive, safe, and painless technique and is widely available. It provides anatomical and functional assessment of cardiac chambers, valves, myocardium, pericardium, and the aorta.

2.4.1 Principles of echocardiography

All methods of ultrasound imaging are founded on the generation of high frequency (>1MHz) acoustic pressure waves from a transducer containing one or more piezoelectric crystals (Ramrakha and Hill, 2012). A pulse is produced and the crystals listen for a reflection which can be sampled over time. The timing of the returning signal reveals the object location because the velocity of sound is constant. The amplitude of the reflecting signal is based on the angle of incidence and the interface of acoustic impedance. High echo reflection is white (bone), less reflection (muscle) is grey and no reflection is black (blood). The signal that returns to the transducer provides depth and intensity of reflection and is transformed electronically into greyscale images. When an ultrasound beam is swept across an area of interest, fast consecutive sampling can be achieved, resulting to display multiple scan lines and creating a moving 2-dimensional image (Kaddoura, 2012).

2.4.2 Key echocardiography techniques

2.4.2.1 Two-dimensional echocardiography

The most widely used technique to interpret an echocardiogram is two-dimensional echocardiography. This technique allows the echocardiographer a visual assessment of the myocardium and the heart valves. There are a number of standard views (windows) obtained during an exam where the patient usually lies in the left lateral position in order to obtain the best possible images. Figure 2.12 illustrates the various positions of the transducer during examination of the heart whereas Figure 2.13 shows the various images obtained from the different echo windows.

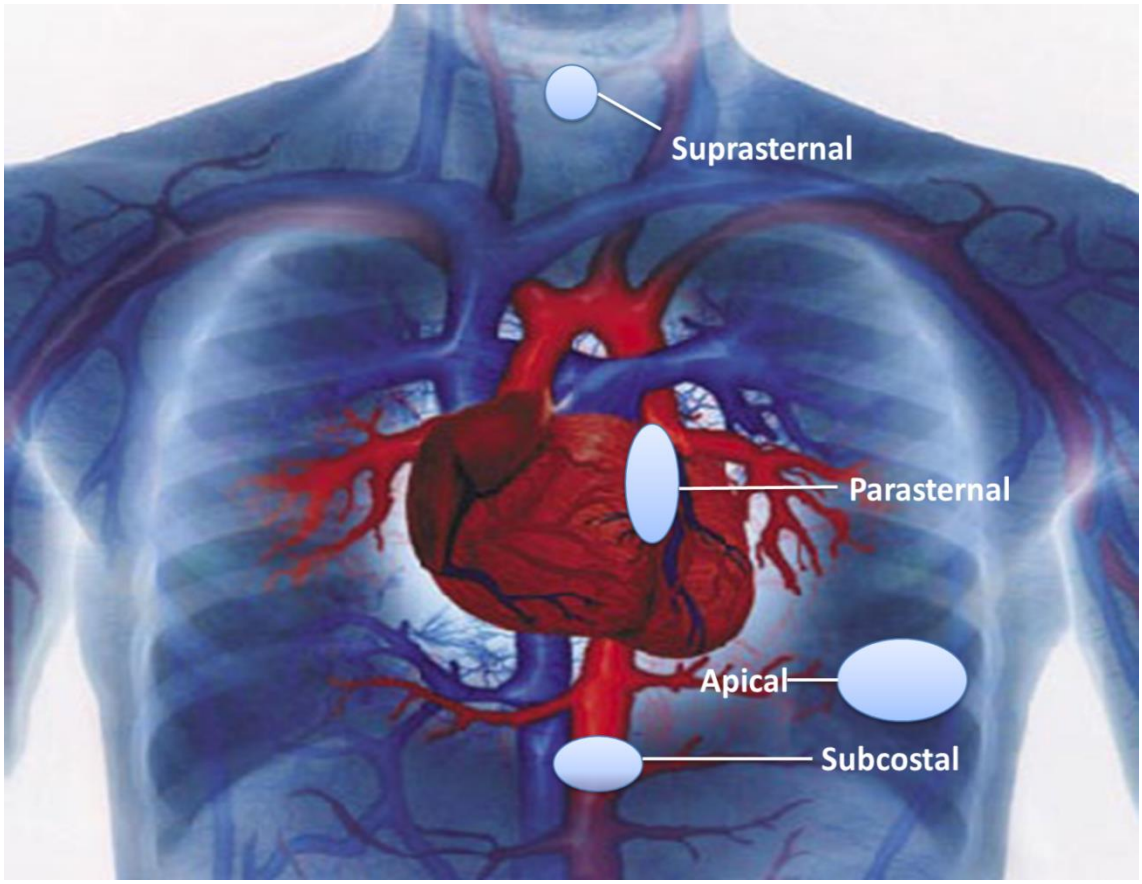


Figure 2.12: Transthoracic echocardiographic windows

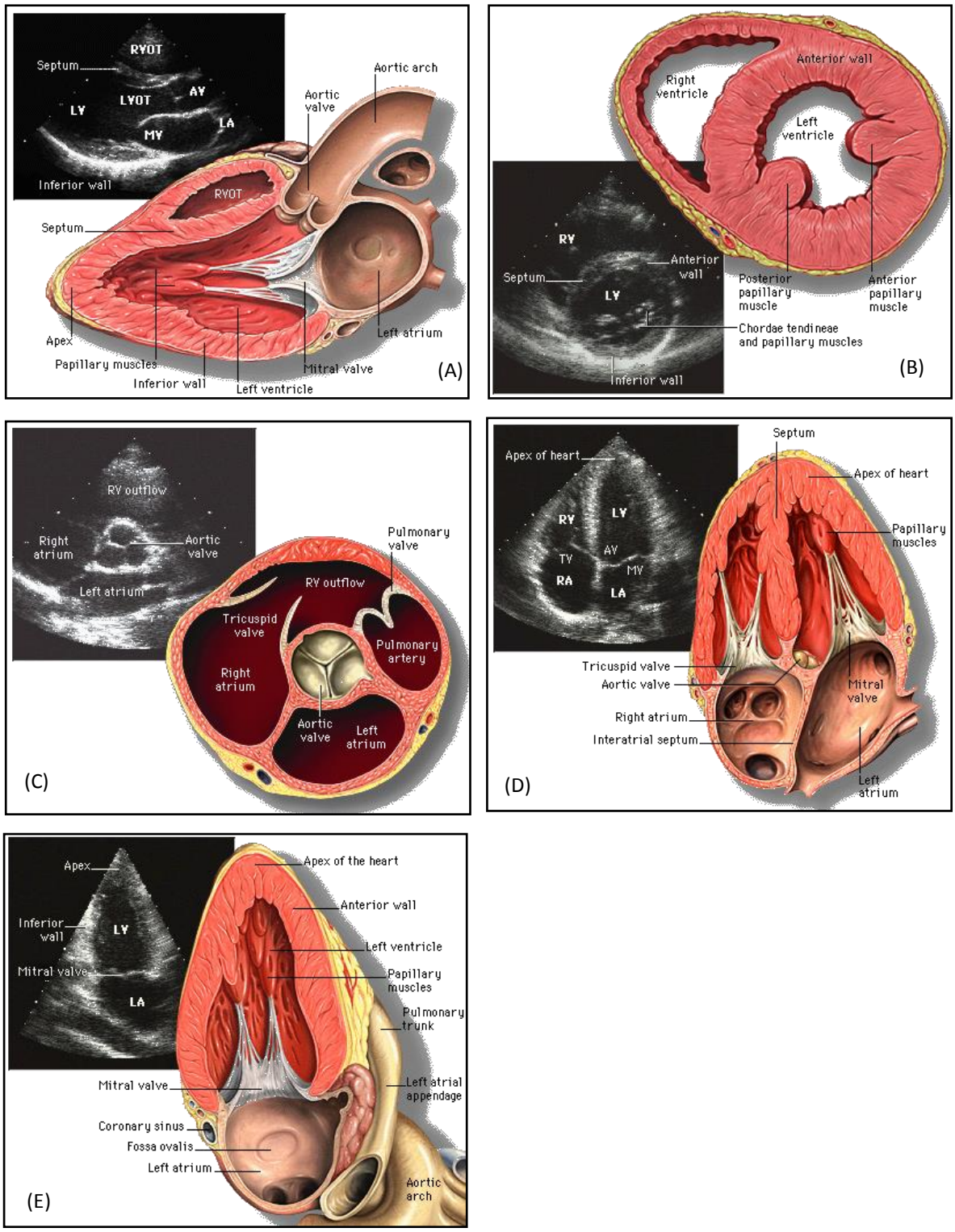


Figure 2.13: Transthoracic echo images: (A) Left parasternal long axis view ; (B) Parasternal short axis view, mitral valve level, (C) Parasternal short axis view, aortic valve level, (D) Apical four chamber view, (E) Apical two chamber view. (RVOT: right ventricle outflow tract, LVOT: left ventricle outflow tract, RA: right atrium, LA: left atrium, RV, right ventricle, LV: left ventricle, TV: tricuspid valve, AV: aortic valve, MV, mitral valve) (Vannan *et al.*, 2006).

2.4.2.2 M-mode

The first available form of echocardiography, and still used regularly today, is M-mode (Figure 2.14). M-mode images describe a single line of ultrasound over time. M-mode will show the structure intersected by the line toward or away from the probe over time. M-mode can display moving structures in greater depth that 2-D and is used to measure the size and the thickness of the cardiac chambers and is also used to time cardiac events (Kaddoura, 2012).

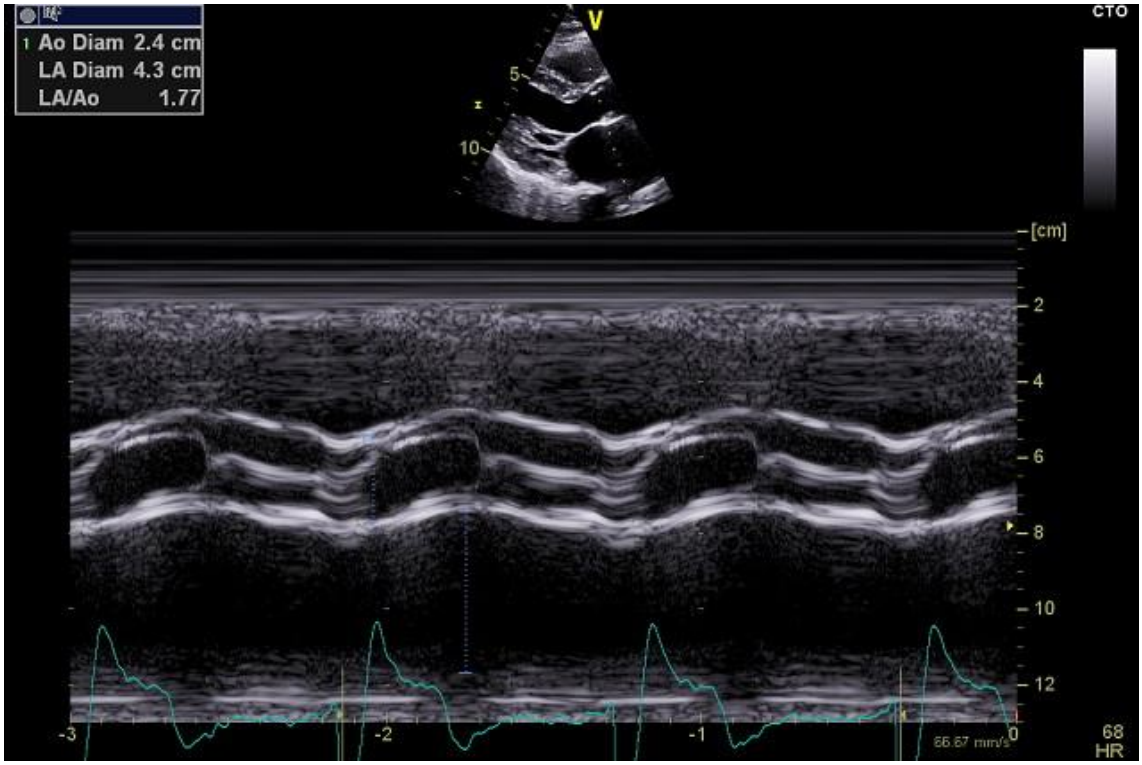


Figure 2.14: M-mode measurements from the aortic valve and left atrium

2.4.2.3 Doppler echocardiography

Doppler echocardiography is the movement of red blood cells and provides haemodynamic information regarding heart and blood vessels. The three commonly used Doppler techniques are: Continuous Wave (CW) Doppler, Pulsed Wave (PW) Doppler and Colour flow mapping. CW Doppler is used to measure high blood velocities at specific sites within the heart and to determine severity of valvular stenosis and regurgitation. PW Doppler allows a flow disturbance to be identified or

blood velocity from a small region to be measured and provide a measurements of the Left ventricular (LV) diastolic function, SV and Q̇. Colour flow mapping as an automated 2-D version of PW Doppler. Blood velocity and direction are measured at numerous points down several scan lines on a 2-D echo image (Kaddoura, 2012). The blue colour indicated blood moving away from the transducer and the red colour indicated blood moving towards the transducer. With this technique, the site and direction of abnormal blood flow can be identified. Figure 2.15 demonstrates a mitral valve in the apical 4- chamber view with moderate mitral regurgitation (MR).

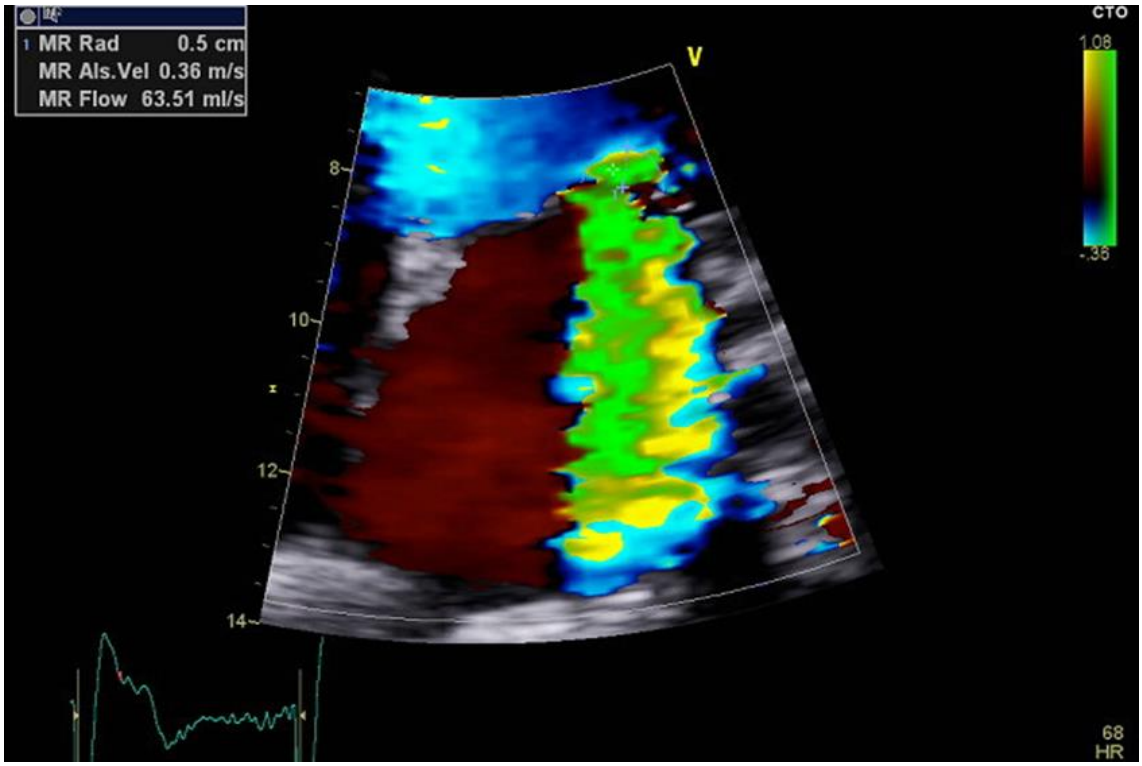


Figure 2.15: Colour Doppler demonstrating a moderate jet of mitral regurgitation in the apical 4-chamber view

2.4.2.4 Tissue Velocity Imaging

The heart narrows, shortens, lengthens, widens and twist during a contraction due to muscle fibers alignments (Buckberg *et al.*, 2008). Echocardiography describes these mechanics using three motions: longitudinal, radial and circumferential motion. It involves the 3-dimensional untwisting motion of the heart. Radial motion is a combination of motions as there no cardiac fibers actually aligned radially. Both radial and longitudinal motion can both be measured using strain speckle tracking analyses

or Tissue Velocity Imaging (TVI) (Buckberg *et al.*, 2008). TVI is a more readily available technique and is often used to measure the longitudinal motion of the heart. This technique is a robust and easy to use. TVI uses Doppler principles to measure the velocity of myocardial motion. A clear disadvantage for TVI is that the technique is angle dependent. Two different methods are available, spectral tissue Doppler and colour tissue Doppler (Figure 2.16 and 2.17). Both methods have been validated in numerous studies (Donovan *et al.*, 1995; Garcia *et al.*, 1996; Lind *et al.*, 2002; Manouras *et al.*, 2009). Both methods measure the peak velocity of the heart in particular longitudinal motion because in the apical views the longitudinally oriented endocardial fibers are most parallel to the ultrasound beam. The cardiac cycle represent three waveforms, systolic longitudinal velocity (S'), early diastolic velocity (E'), and atrial contraction (A'). The technique is easy to use and valuable to help detect a range of disease processes such as diastolic dysfunction, early diagnosis of genetic disease, differentiation between constrictive and restrictive physiology, differentiation of athlete's heart from hypertrophic cardiomyopathy (HCM), assessment of cardiac dyssynchrony and assessment of right ventricular function (Ho and Solomon, 2006). However there are marked differences between both methods. Studies have reported lack of agreement in values obtained from both techniques and therefore should not be used interchangeably. Colour tissue Doppler uses an autocorrelation technique with a smoothing of the Doppler technique and an averaged myocardial velocity is obtained for a given segment. This is the reason colour tissue Doppler returns lower values and may underestimated the true value as compared to spectral tissue Doppler. The advantages for colour tissue Doppler is the increased spatial resolution and the opportunity to evaluate multiple structures and segments in a single view but colour tissue Doppler has an upper limit of measurable velocities (determined by the pulse repetition frequency). Spectral tissue Doppler measures peak velocity instantaneously with a high temporal resolution but has a lower reproducibility (Cho, 2011).

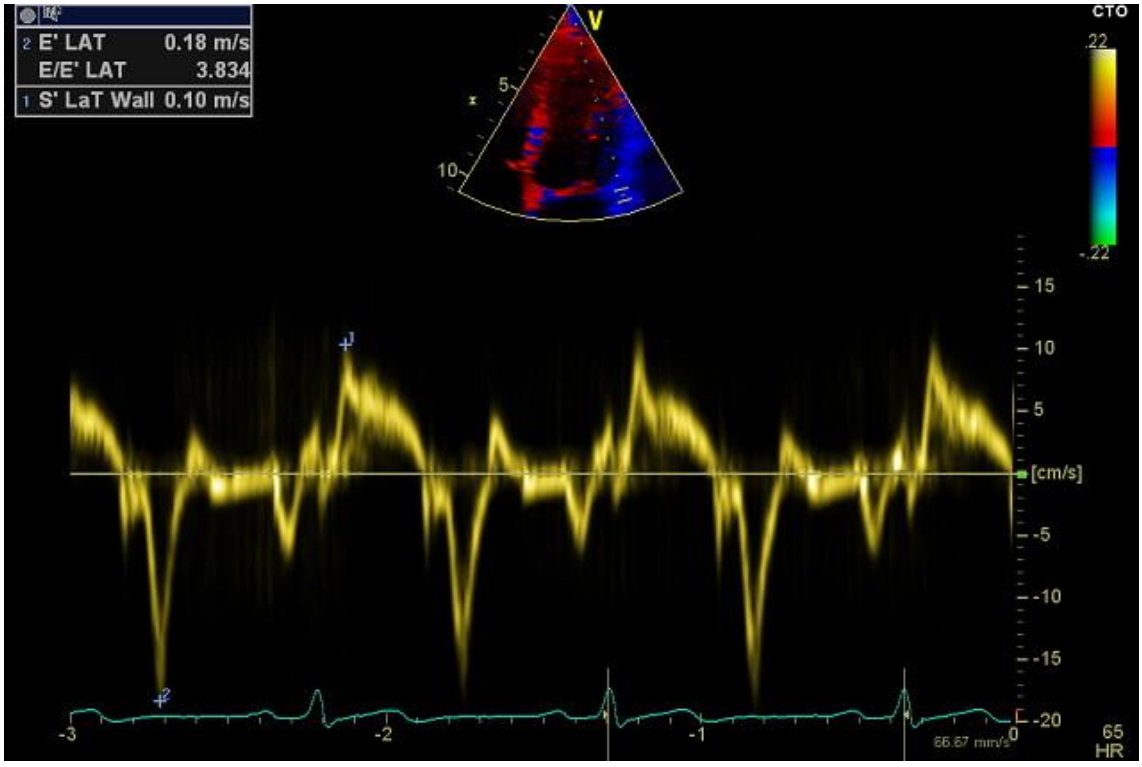


Figure 2.16: Spectral tissue Doppler: an example of normal systolic velocity in the lateral wall

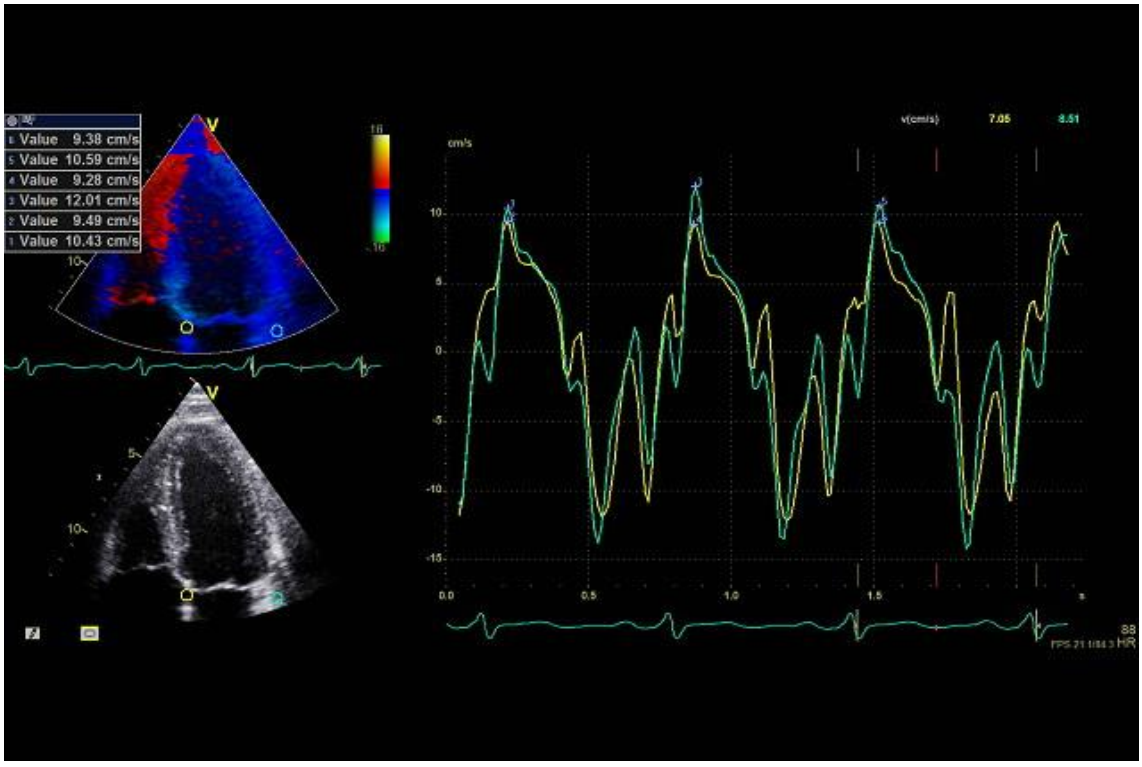


Figure 2.17: Colour tissue Doppler: an example of normal systolic velocity in the lateral and septal wall

2.4.3 Key echocardiography parameters

2.4.3.1 Left ventricular ejection fraction

The most widely used parameter to characterise heart function is left ventricle ejection fraction (LVEF). It is the fraction of outbound blood pumped from the LV with each heartbeat. The most widely used method to assess LV systolic function is the modified Simpson's biplane method (see section 3.4 for details). This method can be challenging, especially when the study pictures are suboptimal. Inter- and intra-observer variability for calculation of LVEF remains high which is troublesome as LVEF is often used for therapeutic decisions making in patients with HF (McGowan and Cleland, 2003). At exercise this method becomes even more challenging as images are more difficult to obtain. The reproducibility of measurement remains sub-optimal, due partly to image quality and anatomical factors (Donal *et al.*, 2011). Resting LVEF correlates poorly to both functional capacity (Carell *et al.*, 1994; Clark *et al.*, 1994; Rubis *et al.*, 2009; Witte *et al.*, 2004) and prognosis (Florea *et al.*, 2000; Grayburn *et al.*, 2005; Guazzi *et al.*, 2010b; Wang *et al.*, 2003, 2005). LVEF is a reflection of whole systolic myocardial displacement and may be more dependent on loading conditions than other measures such as tissue velocity (Donal *et al.*, 2011; Marwick, 2003; Rubis *et al.*, 2009). Furthermore LVEF poorly describes longitudinal myocardial function which is often affected early in a variety of heart diseases. Previous studies have documented only a weak relationship between LVEF either at rest or under stress conditions and exercise tolerance (Rubis *et al.*, 2009). LVEF during dobutamine stress, where loading conditions can be very different, has been shown to predict adverse outcome during echocardiography and nuclear scintigraphy (Otasevic *et al.*, 2006; Paraskevaidis *et al.*, 2001; Ramahi *et al.*, 2001). The inability to increase LVEF during stress echocardiography has been shown to be a strong predictor for mortality (Pedone *et al.*, 2005).

2.4.3.2 Systolic longitudinal velocity

Systolic velocity is a simple and easily obtainable measure on exercise echocardiography and describes the longitudinal function of the LV (Figure 2.16; 2.17). Longitudinal function is important to examine as it is an important indicator for

ventricular dysfunction and is often first affected in cardiovascular disease and often precedes a fall in LVEF. Both systolic and diastolic TVI measures, at rest and during exercise have previously been demonstrated to predict exercise tolerance (McIntosh *et al.*, 2013; Podolec *et al.*, 2008; Rubis *et al.*, 2010). The concept of diastolic reserve has gained considerable interest, particularly in patients with HF and preserved ejection fraction (HFPEF) where changes in the ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/E') predict exercise performance (Grewal, 2009; Podolec *et al.*, 2008). Resting TVI values, particularly those describing diastole, have been shown to have prognostic value (Mogelvang *et al.*, 2009; Wang *et al.*, 2003, 2005). One of the major limitations is the fusion of the E/A during exercise where the diastolic TVI values become impossible to measure. In patients with chronotropic incompetence the E wave will be identifiable as fusion only occurs at higher HR. Systolic longitudinal velocity is better identifiable during exercise as no fusion occurs. A clear disadvantage both during diastole and systole is that the technique is angle dependent. Patients with off axis echocardiographic windows will therefore often have inaccurate TVI values and care needs to be taken when interpreting results. However spectral TVI has a much greater temporal resolution compared to strain imaging and is applicable at high HRs.

2.4.3.3 Myocardial strain imaging

Myocardial deformation is most often assessed using speckle-tracking echocardiography. This technique allows assessment of longitudinal, radial and circumferential strain. The best evaluated strain parameters is longitudinal strain which some studies have found to be superior to LVEF in a number of cardiac diseases for predicting major adverse cardiac events (Kalam *et al.*, 2014). Strain describes the local shortening, thickening and lengthening of the myocardium and allows a detailed assessment of left ventricular wall motion analyses and assessment of regional myocardial function (Dandel *et al.*, 2009). Figure 2.18 demonstrates a mildly reduced strain pattern in a patient with hypertensive heart disease. Strain assessment during exercise is technically challenging but the technique is evolving to allow clinical availability for regional and global cardiac function (Marwick, 2006). Studies have

demonstrated potential usefulness for detecting myocardial ischaemia and in patients with severe aortic stenosis (AS) or MR (Hanekom *et al.*, 2007; Moonen *et al.*, 2009). The future of this technique is promising but more data is required during exercise to support the use of strain during higher HR. The disadvantage when using strain is the high dependency on image quality and the poor application using strain during higher HRs.

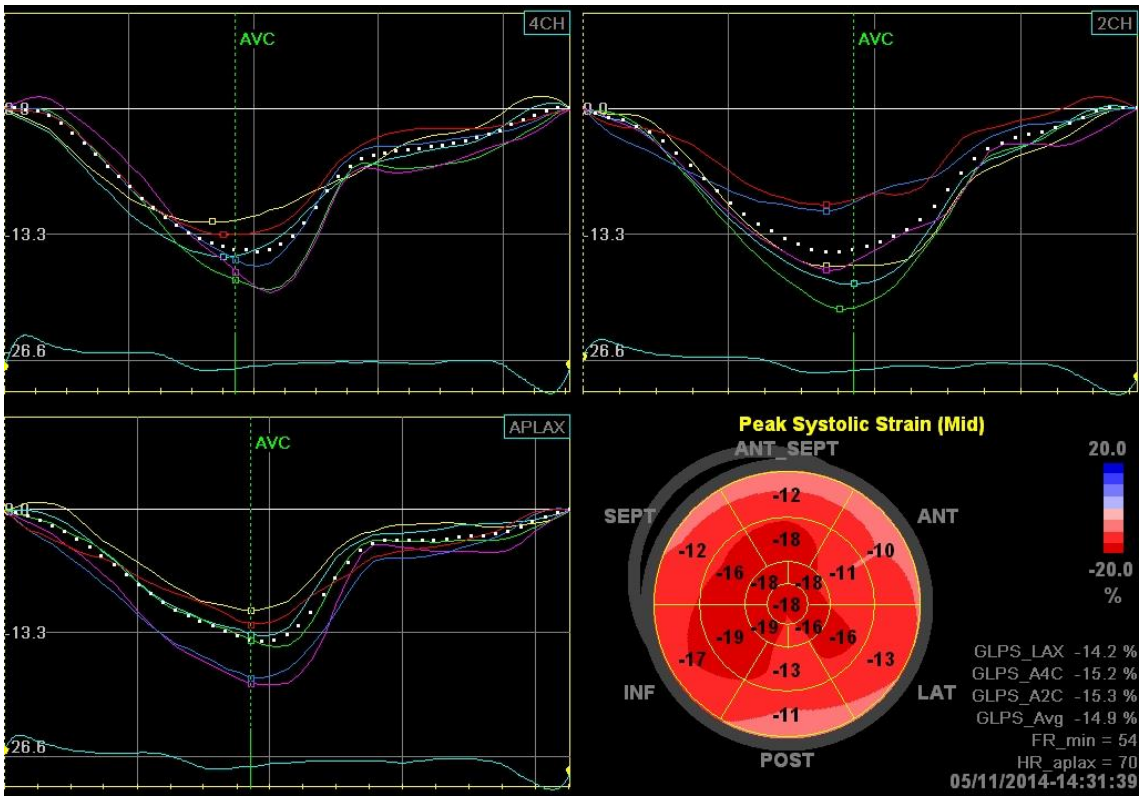


Figure 2.18: An example of strain in a patient with hypertensive heart disease

2.5 Stress echocardiography

Echocardiography in combination with a physical or pharmacological stress is termed stress echocardiography. Stress echocardiography is key for the detection of coronary artery disease and guidelines state that stress echocardiography is the most cost-effective and risk-free imaging choice (Becher *et al.*, 2004; Sicari *et al.*, 2008). Stress echocardiography is used to diagnose subclinical cardiac dysfunction which is not apparent at rest. If patients are unable to exercise, or image quality is submaximal (most often due to body habitus or chest deformities) pharmacological stress echocardiography is ideal, this often uses a dobutamine infusion for the assessment. During stress healthy myocardium increases contractibility and thickening (Marwick, 2003). If patients are able to exercise, this can be done on either a treadmill or cycle ergometer. On a treadmill images have to be obtained within 1 minute after ending the test as ischaemia induced wall motion abnormalities may resolve quickly making the procedure more challenging (Becher *et al.*, 2004). With a semi-recumbent cycle ergometer images are obtained during exercise, providing more time for images to be obtained and patients are better positioned to help obtain echocardiography images at exercise. Changes in global or regional wall motion and thickening can be indicative of myocardial ischaemia which can become apparent under stress when a relative reduction in myocardial blood flow becomes sufficient to cause a reduction in myocardial contraction (Becher *et al.*, 2004; Senior *et al.*, 2005). Resting regional wall motion abnormalities are suggestive of previous myocardial infarction.

2.5.1 Clinical importance of exercise echocardiography in non-ischaemic patients

Exercise echocardiography is used for the diagnosis, risk stratification, follow-up, and evaluation of treatment. Patients with valvular heart disease, HCM, pulmonary hypertension, and diastolic dysfunction during exertion may benefit. Exercise echocardiography is not routinely recommended in the ESC guidelines (Murphy and Lloyd, 2007; Sicari *et al.*, 2008). The evidence for the use of exercise echocardiography in non-ischaemic patients is evolving and over the past 10 years, exercise echocardiography has extended its use in a variety of applications (Pellikka *et al.*, 2007; Picano *et al.*, 2009). However stress echocardiography in non-ischaemic patients is not widely applied regularly in clinical practice often due to technical challenges of exercise echocardiography (Sicari *et al.*, 2008). However recommendations by the European and the American Society of Echocardiography have recently become available stating that in patients where symptoms are discrepant with the severity of the valvular lesion, exercise echocardiography may prove to be valuable tool for identifying those with a poor prognosis (Lancellotti *et al.*, 2016).

The failure to increase contractile reserve during exercise – which refers to the increase in myocardial contractility at rest compared to exercise – exposes patients with underlying LV dysfunction (Leung *et al.*, 1996). Failure to increase contractile reserve is associated with higher mortality, more events and hospitalisations (Pedone *et al.*, 2005). In patients with valvular heart disease, exercise echocardiography can be used to assess dynamic valve function by measuring changes in haemodynamic gradients or the severity of regurgitation during exercise (Bonow *et al.*, 2006; Vahanian *et al.*, 2012). Exercise-induced increase in pulmonary artery pressure over 60 mmHg may be considered for valve surgery (Bonow *et al.*, 2006).

The usefulness of exercise echocardiography is versatile and the application in non-ischaemic patients is rising but guidelines should be agreed upon to incorporate stress echocardiography more widely into clinical practice. A major 5-year prospective study is currently underway including 10.000 patients including those with ischaemic and non-ischaemic heart disease. The aim of the study is to investigate the feasibility and

reproducibility of stress echocardiographic parameters and to assess prognostic value in a variety of patients with cardiac diseases (Picano *et al.*, 2017).

2.6 Combining cardiopulmonary exercise testing and exercise echocardiography

Most measurement to describe patients' symptoms, disease severity, mechanisms and prognosis are obtained at rest (Agricola *et al.*, 2004). Many patients with heart disease often experience no symptoms at rest, but can become limited when exercising. Exercise is the ideal physiological condition to monitor simultaneously cardiac function and symptoms. Evaluating patients during exercise provides a more complete and objective assessment of patients symptoms. CPET objectively describes exercise tolerance and is essential for the assessment of functional impairment and prognosis (Guazzi *et al.*, 2012).

Stress echocardiography is a useful and non-invasive test which provides important information regarding cardiac function. Stress echocardiography is becoming increasingly popular due to its versatility. It is increasingly recognised in the evaluation of non-ischaemic heart disease as it permits simultaneous assessment of myocardial function and haemodynamic response and its diagnostic and prognostic value (Lancellotti *et al.*, 2016). Integrating CPET with exercise echocardiography provides additional unique information not obtained from either test independently and it is relatively straightforward to incorporate an echocardiography into a standard CPET protocol.

Table 2.6 summarises several studies which have emerged demonstrating the feasibility and tolerability when combining both tests. The feasibility and usefulness of combining both tests has mainly been performed in patients with HF either with reduced ejection fraction (HFREF) (Borghi-Silva *et al.*, 2014; Podolec *et al.*, 2008), or in patients with HFPEF (Bandera *et al.*, 2017; Haykowsky *et al.*, 2011; Nedeljkovic *et al.*, 2016; Shimiaie *et al.*, 2015). Single studies have expanded the use in patients with mitral stenosis (MS) (Laufer-Perl *et al.*, 2017) and in patients with HCM (Re *et al.*, 2017). McIntosh *et al.*, (2013) included a range of patients with cardiac diseases and healthy controls (n=101) and found a strong relationship between $\dot{V}O_{2peak}$ and S'

measured at peak exercise. This relationship was greater than any other common echocardiographic parameter observed and demonstrates the relationship between peak longitudinal velocity and $\dot{V}O_{2peak}$. Guazzi (2016) summarised several previous studies focusing on HFPEF patients using exercise assessments and concluded that although more exercise data is needed, the combined use of CPET and exercise echocardiography is a feasible and comprehensive approach to investigate unexplained breathlessness in HFPEF patients. In addition to these studies several abstracts have been presented at international conferences which demonstrate the applications of combined CPET and exercise echocardiography is generating. These abstracts include a feasibility and tolerability study during pregnancy (Boardman *et al.*, 2015), an evaluation performing the combined test on patients with complex valvular disease, severe cardiomyopathy or exertional dyspnoea of unknown origin (Guijarro *et al.*, 2014), assessing exercise performance in patients with AS (Bandera *et al.*, 2014), and detecting early diastolic dysfunction in patients with hypertensive heart disease (Nedeljkovic *et al.*, 2012).

Outcomes variables obtained from CPET and exercise echocardiography are diverse and there is no consensus which parameters are superior in describing cardiac function on exercise. Systolic function and particularly S' has previously shown to be an indicator for ventricular dysfunction as is often first affected in cardiovascular disease and often precedes a fall in LVEF (Yu *et al.*, 2007). S' is a reproducible and relatively easily obtained measurement during exercise. McIntosh *et al.*, (2013) included a range of patients with heart disease and healthy participants and found a very strong relationship between peak S' during exercise and $\dot{V}O_{2peak}$. This study suggests the importance of contractile reserve and highlights that echocardiographic assessment at rest alone is insufficient to predict exercise tolerance. Traditional measurements such as LVEF have failed to show any relationship with $\dot{V}O_{2peak}$ (Rubis *et al.*, 2009). Relatively simple obtainable parameters such as S' and diastolic parameters such as E' and E/E' are available and have shown good correlation with $\dot{V}O_{2peak}$ and prognosis (McIntosh *et al.*, 2013; Podolec *et al.*, 2008; Rubis *et al.*, 2010; van Zalen *et al.*, 2015).

Nedeljkovic *et al.*, (2016) included 87 patients with normal systolic function, patients with hypertension and patients with exertional dyspnoea. Combined exercise echocardiography and CPET was able to identify those patients with "masked" HFPEF by excluding other causes of exertional dyspnoea. If patients demonstrated an increase in E/E' greater than 15 during exercise, they were classified as having HFPEF. These patients had a lower peak $\dot{V}O_2$, lower $P_{ET}CO_2$ values, and a higher $\dot{V}_E/\dot{V}CO_2$ slope.

Bandera *et al.*, (2017) included 102 HFPEF with non-severe MR, exercise-induced severe MR and severe MR at rest. Groups were compared and revealed that patients with severe MR at rest were associated with the greatest LV remodelling, absence of contractile reserve, the highest $\dot{V}_E/\dot{V}CO_2$ slope and the worst mid-term outcome compared to the other 2 groups. The implications for clinical practice are that if there is a discrepancy in symptoms and resting echocardiography findings in these patients a more detailed combined exercise echocardiography with CPET may be able to assist in the assessment of the different phenotypes of MR and the limitation this may cause and may support response to therapy.

Banovic *et al.*, (2015) described a case study in a 24 year old recreational athlete who was sent for routine examination. A bicuspid aortic valve with severe AS was diagnosed. The patient reported excellent exercise tolerance and wanted to continue high intensity training. CPET exercise echocardiography revealed a $\dot{V}O_{2\,peak}$ of 37.1 $mL \cdot kg^{-1} \cdot min^{-1}$ which is on the lower end of normal for the patient. Aortic gradient did not significantly increase with exercise and no symptoms were present during the test. The gradients were obtained in recovery as the test was performed on a treadmill which may have underestimated any increase in gradients due to rapid recovery of HR in younger fitter patients. The CPET also did not follow a classic ramp protocol (a Bruce protocol was used instead which increases the speed and incline every three minutes) which may have negatively influenced the $\dot{V}O_{2\,peak}$. The authors concluded that AS did not cause any haemodynamic compromise and therefore no aortic valve intervention was indicated. Due to the finding of the $\dot{V}O_{2\,peak}$ being on the lower end of the normal scale, the patient was placed under close surveillance and was advised to stop high intensity training.

Borghi-Silva *et al.*, (2014) included 86 patients with HF and investigated the use of a novel parameter, exercise ventilatory power (EVP). This is the peak systolic blood pressure divided by the $\dot{V}_E/\dot{V}CO_2$ slope, combining ventilatory efficiency with systemic haemodynamics during exercise. Results show that reduced EVP provided significant information regarding disease severity and HF associated pathophysiology. Reduced EVP was related with a lower $\dot{V}O_{2peak'}$ and $\dot{Q}$ response coupled with deteriorating right heart function and pulmonary haemodynamics although this parameter needs further investigation.

Podolec *et al.*, (2008) investigated fifty patients with ischaemic HF and found that exercise E/E' was superior to resting E/E' values in predicting exercise tolerance. This study did not however include any systolic parameters as the sole focus was placed on diastolic function. The CPET protocol used was 20 W per 2 minutes instead of a constant ramp protocol which was arguably too high for some patients. This may have underestimated $\dot{V}O_{2peak}$ for a number of patients as 23 patients did not reach a $\dot{V}O_{2peak}$ of more than 14 $mL \cdot kg^{-1} \cdot min^{-1}$. Additionally, diastolic measurements during exercise are often challenging as there is fusion of the E and A waves at higher HRs, yet the authors failed to include an explanation how this technically challenging aspect was tackled.

Shimiaie *et al.*, (2015) included 31 patients with HF (15 HFPEF and 16 HFREF) and 15 controls. Authors concluded that combined CPET exercise echocardiography is feasible and allows a non-invasive evaluation of exercise intolerance. Echocardiography was obtained at individual stages (rest, the VT, and peak exercise). Although the authors explained using the method to determine the VT, this method is used after cessation of exercise and often not possible to obtain during exercise. It is therefore not clear when echocardiographic measurements commenced, how much time was needed to obtain measurements and if measurements were actually obtained during the VT. Echocardiographic measurements were also taken at maximal exercise and again it is not clear how maximal exercise was determined. The time required to acquire all images is challenging and therefore is important to start acquiring images slightly before patients are at maximum exertion. Similar methodologies were used by Laufer-

Perl *et al.*, (2017) who included twenty patients with rheumatic mitral stenosis (MS) and twenty control patients. Results showed that patients with MS have reduced exercise systolic reserve, LV relaxation, SV, HR and $\dot{V}_E$. No correlation between the mitral valve gradient or mitral valve area and $\dot{V}O_{2peak}$ during exercise was found and ventilatory abnormalities were similar to patients with HF.

Re *et al.*, (2017) included 197 patients with HCM and concluded that a different grade of diastolic dysfunction during exercise explains level of functional impairment. A dynamic evaluation of HCM pathophysiology allows the assessment of disease progression which aids the selection of the best available treatment. However all patients were placed on the same ramp protocol of 10 W per minute which is arguably too low for some patients and almost certainly too low for most of the healthy participants. This may underestimate the $\dot{V}O_{2peak}$ as patients who exercise more than 12 minutes may fatigue before their true peak exercise tolerance has been reached (Luks *et al.*, 2013). The focus was placed on diastolic function and the overall peak HR was 131 beats·min^{-1} which would certainly have resulted in fusion of the E and A waves. Authors fail to address this technically difficult problem. Echocardiographic images were obtained every two minutes on an upright cycle ergometer and the peak pictures were obtained in recovery on a bed which may have influenced results as peak pictures were not actually obtained at peak exercise.

Haykowsky *et al.*, (2011) investigated patients with HFPEF in an upright position and found a reduced peak $\dot{V}O_{2peak}$ compared to healthy controls secondary to decreased peak HR, $\dot{Q}$ and $C(a\text{-}\bar{v})O_2$difference. A classic exercise echocardiography protocol was used increasing power by 25 W every three minutes. This protocol would more than likely have influenced the $\dot{V}O_{2peak}$ and potentially other CPET parameters as the work increments would be too high for some patients, resulting in an insufficient length of test to acquire valid data, $\dot{V}O_2$ would have plateaued during the three minutes stages making identification of the VT very challenging. Moreover, the exercise was done on an upright cycle ergometer and the only parameter measured on exercise was the apical 4-chamber view. SV, $C(a\text{-}\bar{v})O_2$difference, volumes were all derived from ESV and EDV – this measurement has variable reliability especially during exercise (as

previously discussed in section 2.4.3.1.) (McGowan and Cleland, 2003; Nikitin *et al.*, 2003).

All of the above studies describe the exciting potential exercise echocardiography combined with CPET may have in the diagnosis and prognosis in cardiac patients. Different studies focused on different parameters, mainly diastolic vs. systolic parameters, this makes comparing studies difficult.

In addition, a variety of different methodologies was used to obtain results and these should be standardised where possible. CPETs need to be performed using a classic ramp protocol aiming to fatigue patients between 8-12 minutes and ramp protocols should be individualised based on age and functional ability. Adding echocardiography measurements during CPET should commence during predefined set time-points which are yet to be determined based on HR and RER. Influence of difference should be determined when images are obtained in the recovery phase lying down compared to during exercise on a semi-recumbent ergometer as differences in position and timing may affect echocardiography parameters.

Table 2.6 Summary of studies using exercise echocardiography combined with cardiopulmonary exercise testing

Study	**Population**	**Method**	**Main findings**
Laufer-Perl *et al.*, 2017	20 patients with rheumatic MS vs. 20 controls	Supine cycle ergometer with a ramp protocol	Combined CPET and exercise echocardiography is a non-invasive detailed assessment. Patients with MS have reduced exercise systolic reserve, relaxation, SV, HR and ventilation. No correlation between gradient or mitral valve area and $\dot{V}O_{2\,peak}$ during exercise. Ventilatory abnormalities similar to HF patients.
Bandera *et al.*, 2017	102 patients with HF and a preserved LVEF with non-severe MR, exercise-induced severe MR and severe MR at rest.	Semi-recumbent cycle ergometer with individualised ramp protocol of maximal 12 W per minute.	Patients with severe MR at rest were associated with the greatest LV remodelling, absence of contractile reserve, the highest $\dot{V}_E$ /$\dot{V}CO_2$ slope and the worst mid-term outcome. Severe dynamic MR causes functional limitation similar to severe MR at rest, characterised by exercise induced pulmonary hypertension.
Re *et al.*, 2017	197 patients with HCM and 40 controls	Upright exercise using a 10 W ramp for all patients.	Different grade of diastolic dysfunction during exercise explains level of functional impairment. A dynamic evaluation of HCM pathophysiology is able to assess disease progression and choose the best available treatment.
Nedeljkovic *et al.*, 2016	87 patients with normal systolic function, hypertension and exertional dyspnoea	Patients with an increase in E/E' greater than 15 during exercise were classified as HFPEF, they had lower peak $\dot{V}O_2$, lower $P_{ET}CO_2$ values, and higher $\dot{V}_E/\dot{V}CO_2$ slopes	Combined exercise echocardiography and CPET was able to identify those patients with masked HFPEF excluding other causes of exertional dyspnoea.

Study	**Population**	**Method**	**Main findings**
Guazzi, 2016	Summary of various studies	Editorial letter including a short summary of studies including exercise in patients with HF and preserved LVEF	Combined CPET and stress echocardiography is a feasible and comprehensive new method for early diagnosis and research investigation of unexplained exertional dyspnoea
Shimiaie *et al.*, 2015	45 patients with either HFPEF, HFREF or controls	Semisupine exercise using an individualised ramp protocol. Measurements were obtained at rest, during unloaded cycling, at the VT, and at peak exercise.	1) Stress echocardiography and CPET is feasible and allows non-invasive evaluation of exercise intolerance. 2) Exercise intolerance in HF patients due to lower cardiac out, LV compliance, and higher peak systemic vascular resistance 3) Chronothropic incompetence and peripheral factors important in the pathogenesis in exercise intolerance
Bandera *et al.*, 2015	Case report of a 62 year old patient with HCM	Semisupine exercise. Rest and peak images pre septum myomectomy and 6 months after	Pre surgery - significant LVOT obstruction during exercise with severely reduced $\dot{V}O_{2\,peak}$. 6 months after surgery a significant improvement was observed in $\dot{V}O_{2\,peak}$, $\dot{V}_E$ /$\dot{V}CO_2$ and no gradient was observed on exercise. CPET exercise echocardiography is able to demonstrate an improvement in functional and echocardiographic findings after surgical therapy.

Study	Population	Method	Main findings
Borghi-Silva *et al.*, 2014	Letter to the editor – including 86 patients with HF	Novel parameter – exercise ventilatory power (peak SBP / $\dot{V}_E/\dot{V}CO_2$ slope) was investigated	Right sided heart function coupled with pulmonary haemodynamic status in HF patient is an important marker. A prognostic threshold was identified.
McIntosh *et al.*, 2013	101 patients with a variety of cardiac diseases	Semisupine exercise using an individualised ramp protocol. Rest and peak measurements were obtained.	Strong relationship between exercise S' and $\dot{V}O_{2peak}$ in patients with varying ages and cardiac diseases and greater than any other echocardiographic measure of cardiac function
Haykowsky *et al.*, 2011	48 patients with HFPEF and 25 healthy controls	Upright exercise increased 25 W every 3 minutes. Exercise echocardiography apical 4-chambers only.	Patients with HFPEF have a reduced peak $\dot{V}O_{2peak}$ compared to healthy controls secondary to decreased peak HR, $\dot{Q}$ and $C(a\text{-}\bar{v})O_2$difference
Podolec *et al.*, 2008	50 patients with chronic, stable HF	Semisupine exercise. Rest and peak images. 20W per 2 minute increments	E/E' at peak exercise is superior to resting assessment of E/E' in predicting exercise capacity

MS – mitral stenosis, SV – stroke volume; End-Tidal carbon dioxide tension; HCM – hypertrophic cardiomyopathy; LVOT – Left ventricular Outflow Tract; HR – heart rate; CPET – cardiopulmonary exercise test, HF – heart failure, $\dot{V}O_2$ — oxygen uptake, S' – systolic velocity, MR – mitral regurgitation; E' –mitral annular early diastolic velocity, E/E' -ratio between early mitral inflow velocity and mitral annular early diastolic velocity; LV – left ventricle; $\dot{V}_E/\dot{V}CO_2$ - Efficiency of ventilation to eliminate carbon dioxide; HFPEF – heart failure and preserved ejection fraction ; HFREF – heart failure with reduces ejection fraction; SBP – systolic blood pressure

2.7 Proposed aims of the thesis

Evaluating patients during exercise provides a comprehensive assessment of overall well-being compared to resting evaluations. The relationship between cardiac contractile reserve and exercise performance using CPET in combination with exercise echocardiography offers a quick, complete and objective assessment which may provide superior information regarding patient's prognosis and diagnosis superior to assessing patients whilst at rest. CPET together with exercise echocardiography is able to assess patients' whilst exercising and thereby provides a better overall assessment of symptoms and prognostic status. The potential benefits of exercise testing and exercise echocardiography as standalone tests are recognised by the European Society of Cardiology (Vahanian *et al.*, 2012) but definitive guidelines are lacking. This thesis will use the highly quantifiable and validated measures from CPET to describe how anatomical and physiological augmentation measured during exercise echocardiography relates to exercise tolerance in a range of patients with heart disease and healthy controls.

The aims of the individual studies are:

1) To determine the relationship between resting echocardiography and exercise parameters in patients with AF
2) A critical evaluation to investigate if any exercise parameters are able to predict prognosis in patients with systolic HF
3) To investigate if systolic longitudinal velocity measures on exercise is able to predict a positive response to cardiac resynchronisation therapy (CRT)
4) To investigate the relationship exercise systolic longitudinal velocity and $\dot{V}O_{2\,peak}$ in patients with severe AS
5) To evaluate the relationship between S' and $\dot{V}O_2$ during exercise

CHAPTER 3

GENERAL METHODS

3.1 Introduction

The materials and methodologies are described below. All visits to the hospital were standardised as explained in section 3.2. Section 3.3 explains the CPET procedure in detail and section 3.4 explains the echocardiography procedures in detail. All studies were approved either by the South East Coast – Brighton and Sussex Research Ethics Committee (formerly known as Brighton East) or the London Ethics Committee (study 5) or the Local audit committee from Eastbourne District General Hospital. Eastbourne local research and development office (R&D) from Eastbourne District General Hospital sponsored study 1 to 4 (Appendix A)

3.2 Patient identification and recruitment

Patients with different types of heart disease and healthy participants were recruited (Table 3.1). Study 1 included patients with paroxysmal AF, study 2 included patients with systolic HF, study 3 included HF patients awaiting CRT, study 4 included patients with severe AS, and the final study included healthy participants. All patients were recruited from Eastbourne District General Hospital. Healthy participants for study 5 were included prior to participation in the 2016 London road marathon.

Table 3.1: Number of patients per study

	Number of patients
○ Study 1: The relationship between resting transthoracic echocardiography and exercise parameters in patients with paroxysmal AF	69
○ Study 2: Prognostic importance of tissue velocity imaging during exercise echocardiography in patients with systolic HF	80
○ Study 3: Contractile reserve measured by systolic velocity and response to CRT in patient with HF	38
○ Study 4: Asymptomatic aortic stenosis: insights from cardiopulmonary exercise testing combined with echocardiography	32
○ Study 5: The relationship between $\dot{V}O_2$ and the rate of myocardial deformation as characterised by longitudinal systolic velocity during exercise in healthy individuals	57

3.2.1 Inclusion and exclusion criteria

The principal inclusion criteria were as below, more specific details are provided in the dedicated studies.

- Study 1: Patients with symptomatic paroxysmal AF suitable for AF ablation
- Study 2: Patients with systolic HF and who had been stable on medical therapy for at least one month prior to study inclusion. The definition of systolic HF was made by the combination of appropriate symptoms and reduced LV function on echocardiography
- Study 3: Patients with a reduced LVEF below 35%, symptomatic HF despite optimal medical treatment, and clinically selected for CRT according to contemporary guidelines
- Study 4: Patients with asymptomatic AS under follow up at Eastbourne DGH
- Study 5: Healthy first time London marathon runners participants

Exclusion criteria differed per study and are described in each chapter separately. The following general exclusion criteria were applied to all studies: inability to perform exercise, poor echocardiography windows, symptomatic coronary disease or evidence of reversible ischaemia, recent decompensating of underlying disease, severe lung disease, uncontrolled hypertension, pregnancy, inability to consent, inability to complete study related investigations, and all standard absolute contra-indications to exercise testing (Table 2.1).

3.3 Standardisation procedures

Prior to start of any procedures height, weight, resting blood pressure, oxygen saturation and HR were recorded to make sure patients were safe to exercise. Guidelines for contraindications to exercise testing were used and are displayed in table 2.2 which include the American Heart Association (Fletcher *et al.*, 2001) and the British Cardiovascular Society (The Society for Cardiological Science and Technology, 2008).

All patients underwent CPET on a semi-recumbent cycle ergometer with simultaneous echocardiography, described in section 3.6. All testing for studies 1-4 were carried out

at the Cardiology department at Eastbourne District General Hospital. Testing for study 5 occurred at St. Bartholomew Hospital, London. At Eastbourne the testing area was in a dedicated room next door to the Coronary Care Unit. In London two rooms were used in the echocardiography department. On both occasions the testing rooms were equipped with emergency equipment including a defibrillator, emergency drugs and an alarm to notify other members of staff. The room was clean, and fully air-conditioned to provide adequate testing conditions. Temperature was between 20-24 °C for every test. Optimal temperature for a CPET test is 22°C (Pina *et al.*, 1995). All tests were conducted with two members of staff present, one fully trained exercise physiologist with immediate life support training and either a cardiologist or a cardiac nurse with advanced life support training. Patients were asked not to perform strenuous exercise 48 hours prior testing and not to consume alcohol or caffeine 2 hours prior the test. Patients continued their medication as normal prior testing. The study protocols conformed to the guidelines of the 1975 Declaration of Helsinki. Participants were informed of all procedures, benefits, and risks relating to the study before providing written informed consent.

3.4 Procedures for cardiopulmonary exercise testing

A semi-recumbent cycle ergometer (ERG 911 S/L, Schiller, Switzerland) was used in order to obtain echocardiography images at rest and exercise (Figure 3.1). At the start of the test a 3-minute rest period was included followed by a 3-minutes warm up period. Exercise protocols were individually determined based on functional status, age and fitness. Work rate (5-30 W) increased every minute until voluntary exhaustion. It is recommended a ramp protocol to fatigue the patient last approximately 8-12 minutes (Balady *et al.*, 2010; Buchfuhrer *et al.*, 1983; Piepoli *et al.*, 2006c). If the chosen ramp protocol is too steep, it is difficult to determine the VT and the $\dot{V}O_{2\,peak}$ may be less than the true $\dot{V}O_{2\,peak}$. If the ramp is too slow this may fatigue the patient before their true peak exercise tolerance has been reached (Luks *et al.*, 2013). All participants pedalled at a self-selected constant cadence between 60 and 90 revolutions per minute and were verbally encouraged to continue until voluntary exhaustion. HR, blood pressure and oxygen saturation were monitored throughout.

$\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ were continuously measured and derived using a calibrated breath-by-breath analyser (Power Cube, Schiller/Ganshorn, Switzerland or Quark, Cosmed, Italy) (figure 3.2).

Figure 3.1: A semi-recumbent cycle ergometer

Figure 3.2 The Schiller/Ganshorn Powercube (right) and the Cosmed Quark (left)

All tests were terminated if any of the testing guidelines criteria were met (modified from (Fletcher *et al.*, 2001; Gibbons *et al.*, 2002) (Table 3.2).

Table 3.2: Indications for terminating exercise testing (modified from (Fletcher *et al.*, 2001; Gibbons *et al.*, 2002))

Absolute indicators	**Relative indicators**
• Drop in SBP > 10 mm Hg from baseline despite an increase in workload, when accompanied by other evidence of ischaemia	• Drop in SBP > 10 mm Hg from baseline despite an increase in workload, in the absence of other evidence of ischaemia
• Moderate-to-severe angina	• Increasing chest pain
• Increasing central nervous system symptoms (e.g. dizziness, near-syncope, ataxia)	• Fatigue, shortness of breath,, wheezing, leg cramps, or claudication
• Signs of poor perfusion	• Arrhythmias other than sustained VT
• Sustained VT	• Hypertensive response (SBP > 250 mm Hg and/or DBP > 115 mm Hg
• Technical difficulties monitoring ECG or SBP	• Development of bundle-branch block that cannot be distinguished from VT
• Participant desire to stop	• ST or QRS changes (2 mm)
• ST elevation (>1.0 mm) in leads without diagnostic Q-waves	

SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure; VT – Ventricular Tachycardia; VT – ventricular tachycardia

$\dot{V}O_{2\,peak}$ was defined as the average oxygen consumption ($\dot{V}O_2$) measured in the last 30 seconds of exercise. The $\dot{V}O_{2\,peak}$ and $\dot{V}O_2$ at VT were calculated as a percentage (% predicted $\dot{V}O_{2\,peak}$ and % predicted $\dot{V}O_2$ at VT) based on the predicted maximum $\dot{V}O_2$ calculated from Wasserman's formula (Wasserman *et al.*, 2005)(Table 3.3).

Table 3.3: Wasserman calculation of predicted $\dot{V}O_{2\,peak}$ ($mL \cdot min^{-1}$)(Wasserman *et al.*, 2005)

Men
Cycle factor = 50.72 – 0.372 · age
Calculate normal weight = 0.79 · height – 60.7
If actual weight = normal weight:
• Predicted $\dot{V}O_{2\,peak}$ = actual weight · cycle factor
If actual weight is less than normal weight
• Predicted $\dot{V}O_{2\,peak} = \left(\frac{\text{normal weight + actual weight}}{2}\right) \cdot$ cycle factor
If actual weight exceeds normal weight:
• Predicted $\dot{V}O_{2\,peak}$ =(normal weight · cycle factor) + 6 · (actual weight – normal weight)
Women
Cycle factor = 22.78 – 0.17 · age
Calculate normal weight = 0.65 · height – 42.8
If actual weight = normal weight:
• Predicted $\dot{V}O_{2\,peak}$ = (actual weight + 43) · cycle factor
If actual weight is less than normal weight
• Predicted $\dot{V}O_{2\,peak} = \left(\frac{\text{normal weight + actual weight + 86}}{2}\right) \cdot$ cycle factor
If actual weight exceeds normal weight:
• Predicted $\dot{V}O_{2\,peak}$ =(normal weight + 43) · cycle factor + 6 (actual weight – normal weight)

3.4.1 V-slope method

The VT is determined using the V-slope method (Beaver *et al.*, 1986). The VT is identified as the $\dot{V}O_2$ at which the change in slope of the relationship of $\dot{V}CO_2$ to $\dot{V}O_2$ occurs. $\dot{V}CO_2$ increases linearly but when exercise intensity increases beyond a break point can be recognised (Figure 3.3). For more detail see section 2.3.3.2. To confirm this breakpoint the ventilatory equivalents and $P_{ET}O_2$ and $P_{ET}CO_2$ are used. This method involves the simultaneous analyses of multiple variables ($\dot{V}_E$ /$\dot{V}O_2$, $\dot{V}_E$ /$\dot{V}CO_2$, $P_{ET}O_2$,$P_{ET}CO_2$) and is termed the dual criteria. The first criterion is the relationship between the ventilatory equivalents and $\dot{V}O_2$, the VT is the point where O_2 reached the minimum value and begins to rise with no associated increase in the $\dot{V}_E/CO_2$ (Figure 3.4). The second criterion used is the relationship between the end tidal gas tensions and $\dot{V}O_2$. VT is identified as the point where $P_{ET}O_2$ began to rise whilst $P_{ET}CO_2$ remains constant (Wasserman *et al.*, 2005). Figure 3.3 and 3.4 are examples how to determine the VT from a 34 year old healthy participant. Absolute $\dot{V}O_{2\,peak}$ was 2.5 L·min^{-1} or 35.6 mL·kg^{-1}·min^{-1} in relative terms. The VT occurred around 1.6 L·min^{-1}, which is 58% of predicted $\dot{V}O_{2\,peak}$. Figure 3.3 demonstrates the V-slope method and Figure 3.2 demonstrates the use of the ventilatory equivalents for O_2 and CO_2 to identify the onset of the VT.

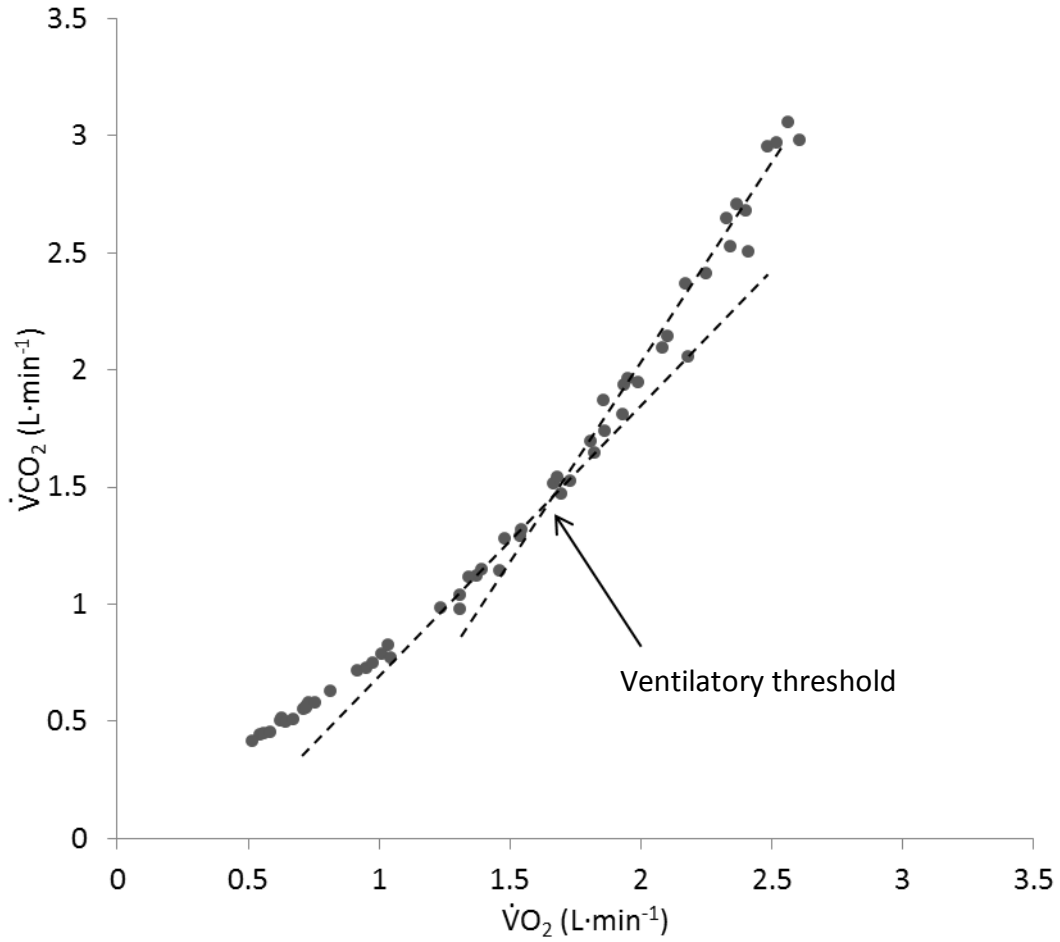


Figure 3.3: The V-slope method: $\dot{V}CO_2$ as a function of $\dot{V}O_2$ during an incremental exercise test from a 34 year old male. The arrow shows the intercept in the graph which occurs around 1.6 $L \cdot min^{-1}$, which in this case occurs at 58% of predicted $\dot{V}O_{2\,peak}$. VT – ventilatory threshold; $\dot{V}O_2$ – oxygen uptake; $\dot{V}CO_2$ – carbon dioxide production (Data from patient seen clinically at Eastbourne DGH)

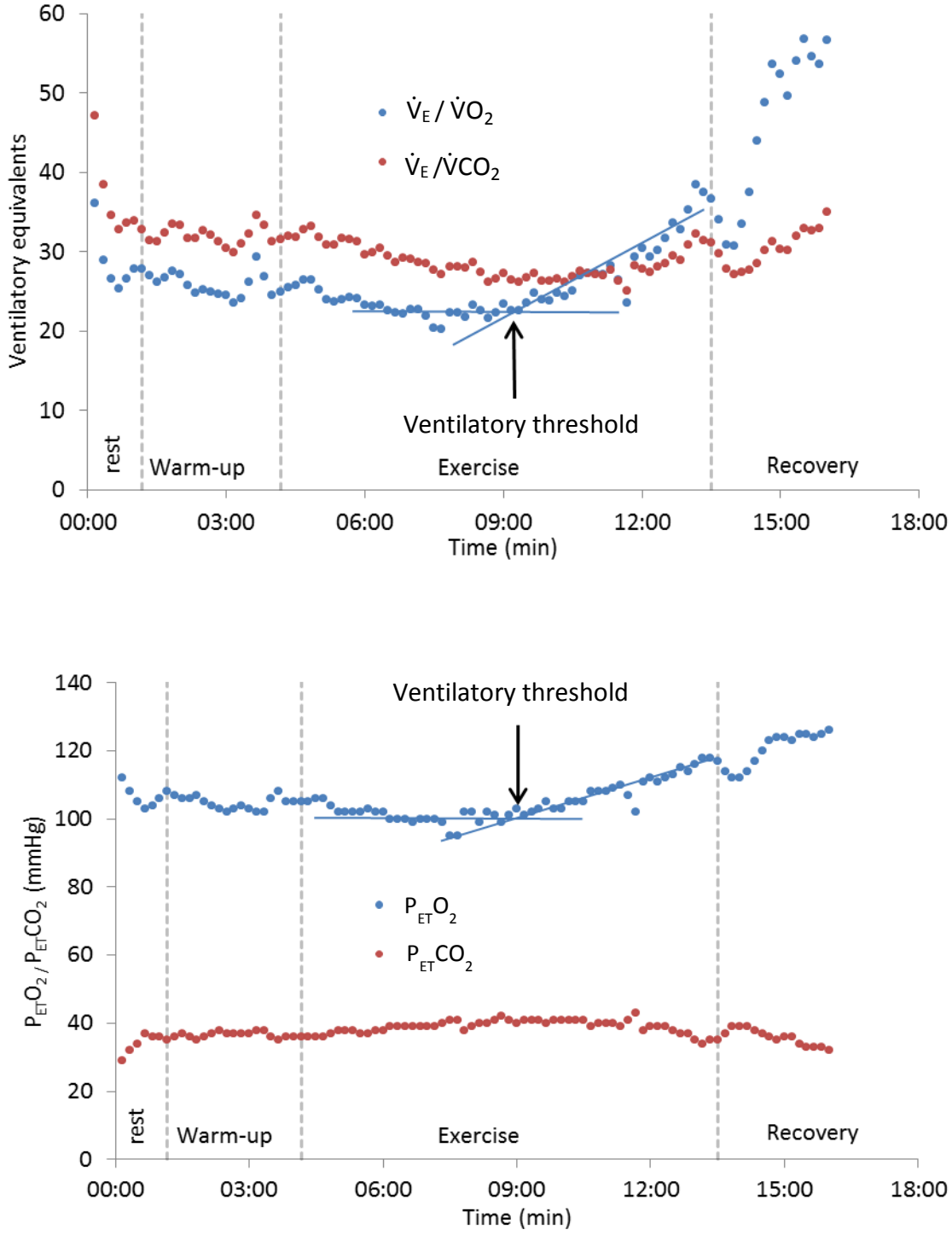


Figure 3.4: Determination of the ventilatoy threshold (VT) using the dual criteria. The relationship between the ventilatory equivalents ($\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$ and $\dot{V}O_2$. VT is recognized as the point were $\dot{V}_E/\dot{V}O_2$ begins to increase whilst the $\dot{V}_E/\dot{V}CO_2$ remains constant (top). The bottom graph demonstrated the relationship between the end tidal gas tensions ($P_{ET}O_2$ and $P_{ET}CO_2$) and $\dot{V}O_2$. VT is recognized as the point where $P_{ET}O_2$ begins to increase as $P_{ET}CO_2$ remains steady
(Data from patient seen clinically at Eastbourne DGH)

3.5 Differences between semi-recumbent vs. upright cycle ergometry

3.5.1 Introduction

CPET is performed during exercise such as running or cycling that involves a large muscle group. $\dot{V}O_{2peak}$ is influenced by the active muscle mass during testing. $\dot{V}O_{2peak}$ obtained on a cycle ergometer tends to be 8-12% lower when compared to treadmill exercise (Wasserman *et al.*, 2005). Due to lower muscle mass recruitment required during cycling. Upright and semi–recumbent cycling may cause differences in $\dot{V}O_2$ values but the exact variation between both positions has not yet been established. Exercise echocardiography guidelines acknowledge the limitations of obtaining images during upright cycling (Sicari *et al.*, 2008). Therefore a specifically designed semi recumbent cycle ergometer can be used to obtain the best possible images during exercise (Figure 3.1). This semi-recumbent cycle ergometer allows the echocardiographer to obtain adequate echocardiographic images whilst patients are cycling. A study by Badruddin *et al.*, (1999) compared the accuracy of supine bicycle exercise echocardiography to treadmill exercise in detecting myocardial ischaemia. The recumbent ergometer was favoured by patients and echocardiographers and the detection of ischaemia was more frequent and more extensive. The semi-recumbent cycle ergometer is able to tilt to the left which supports obtaining good quality images. A hip belt and a stable shoulder support are available to ensure a comfortable position is ensured if the ergometer is turned on its side.

A recent study by Forton *et al.*, (2016) determined the effect of body position in healthy participants and found that body position did not affect $\dot{V}O_{2peak}$ or the $\dot{V}_E/\dot{V}CO_2$ slope. It was noted however that maximum workload was lower in the semi-recumbent group compared to upright exercise. Bonzheim *et al.*, (1992) included patients with coronary artery disease and found no differences in peak HR or $\dot{V}O_{2peak}$ values, but at sub-maximal exercise, HR, systolic blood pressure, $\dot{V}O_2$ and rating of perceived exertion were greater in the upright than in the semi-recumbent position. Another small study including patients with mild hypertension demonstrated similar results in heart response at submaximal exercise. However higher peak HR and higher $\dot{V}O_{2peak}$ values were observed when patients where testing was performed on a

upright compared to a semi-recumbent cycle ergometer with similar blood pressures responses for both cycle ergometers (Walsh-Riddle and Blumenthal, 1989). Patients with HF might have different haemodynamic responses as sitting upright reduces venous return when EDV is increased (Kramer *et al.*, 1982). A study comparing supine vs. upright exercise in patients with HF found higher $\dot{V}O_{2\,peak}$, greater peak HRs and lower peak mean arterial pressure for the upright ergometer but no differences in $\dot{Q}$ or stroke indexes were observed. This study did not include a semi-recumbent position. In order to combine CPET successfully with exercise echocardiography it is important to determine variation in exercise responses to upright and semi-recumbent cycle ergometry and examine the influence that the semi-recumbent position may have on exercise parameters.

3.5.2 Methods

A small validity study was carried out to determine any differences between two ergometers. Six healthy individuals performed two different CPETs on either the semi-recumbent or the upright cycle ergometer. The order was randomised for participants. Averages of the exercise response were calculated and level of agreement was determined between the recumbent and the upright cycle ergometer parameters (peak work rate, $\dot{V}O_2$, $\dot{V}O_2$ at VT, $\dot{V}_E$ /$\dot{V}CO_2$, OUES). Variables were tested for normality and correlation coefficients were calculated. A Bland-Altman assessment for agreement was used to compare the two cycle ergometers. A range of agreement was defined as mean bias ± 2 standard deviations (SD). Bland-Altman plots were computed for relative $\dot{V}O_{2\,peak}$, $\dot{V}_E$ /$\dot{V}CO_2$ and OUES.

3.5.3 Results

Six healthy participants were included (2 males, 4 females). Average age was 38.8 ± 9.5 year, with an average height of 170 ± 7.5 cm. Weight was on average 68.5 ± 16.2 kg on the recumbent cycle ergometer and 68.4 ± 15.9 kg whilst tested on the upright cycle ergometer. Table 3.4 shows the main CPET parameters for both ergometers. CPET parameters were compared and are displayed below in table 3.4,

differences are expressed in percentages. Peak work rate and OUES showed the greatest difference between the semi-recumbent and the upright cycle ergometer.

Table 3.4: CPET parameters for the semi-recumbent and the upright cycle ergometer

	Semi-recumbent	**Upright**	**% difference**
Peak work rate (W)	222	228	2.6%
$\dot{V}O_{2\,peak}$ absolute ($L \cdot min^{-1}$)	2.56	2.52	-1.3%
$\dot{V}O_{2\,peak}$ relative ($mL \cdot kg^{-1} \cdot min^{-1}$)	36.8	36.6	-0.6%
% predicted $\dot{V}O_2$	122	122	0.0%
$\dot{V}O_2$ at VT ($mL \cdot kg^{-1} \cdot min^{-1}$)	23.3	23.7	1.6%
$\dot{V}_E / \dot{V}CO_2$ slope	29.12	29.20	0.3%
$\dot{V}_E / \dot{V}CO_2$ at VT	27.2	27.7	1.7%
OUES $(mL \cdot min^{-1}) \cdot (L \cdot min^{-1})^{-1}$	2668	2568	-3.9%

$\dot{V}O_2$ – oxygen uptake; VT – ventilatory threshold; $\dot{V}_E / \dot{V}CO_2$ - Efficiency of ventilation to eliminate carbon dioxide ; OUES – oxygen uptake efficiency slope

Pearson correlation coefficient was calculated for $\dot{V}O_{2peak}$ ($r=0.95$; $p<0.05$), $\dot{V}_E / \dot{V}CO_2$ slope ($r=0.77$; $p<0.05$) and for OUES ($r=0.87$; $p<0.05$). The Bland-Altman plots chart the difference in $\dot{V}O_{2peak}$, $\dot{V}_E / \dot{V}CO_2$ values, and OUES between both ergometers (upright minus the recumbent cycle ergometer) (Figure 3.5). The values on the semi-recumbent cycle ergometer were slightly higher compared to the upright cycle ergometer for $\dot{V}O_{2peak}$ - 0.2 $mL \cdot kg^{-1} \cdot min^{-1}$; for $\dot{V}_E / \dot{V}CO_2$ slope - 0.08 and for the OUES - 995 $(mL \cdot min^{-1}) \cdot (L \cdot min^{-1})^{-1}$. For 95% of participants, difference in $\dot{V}O_{2peak}$, $\dot{V}_E / \dot{V}CO_2$, and OUES were within two SD of the mean difference.

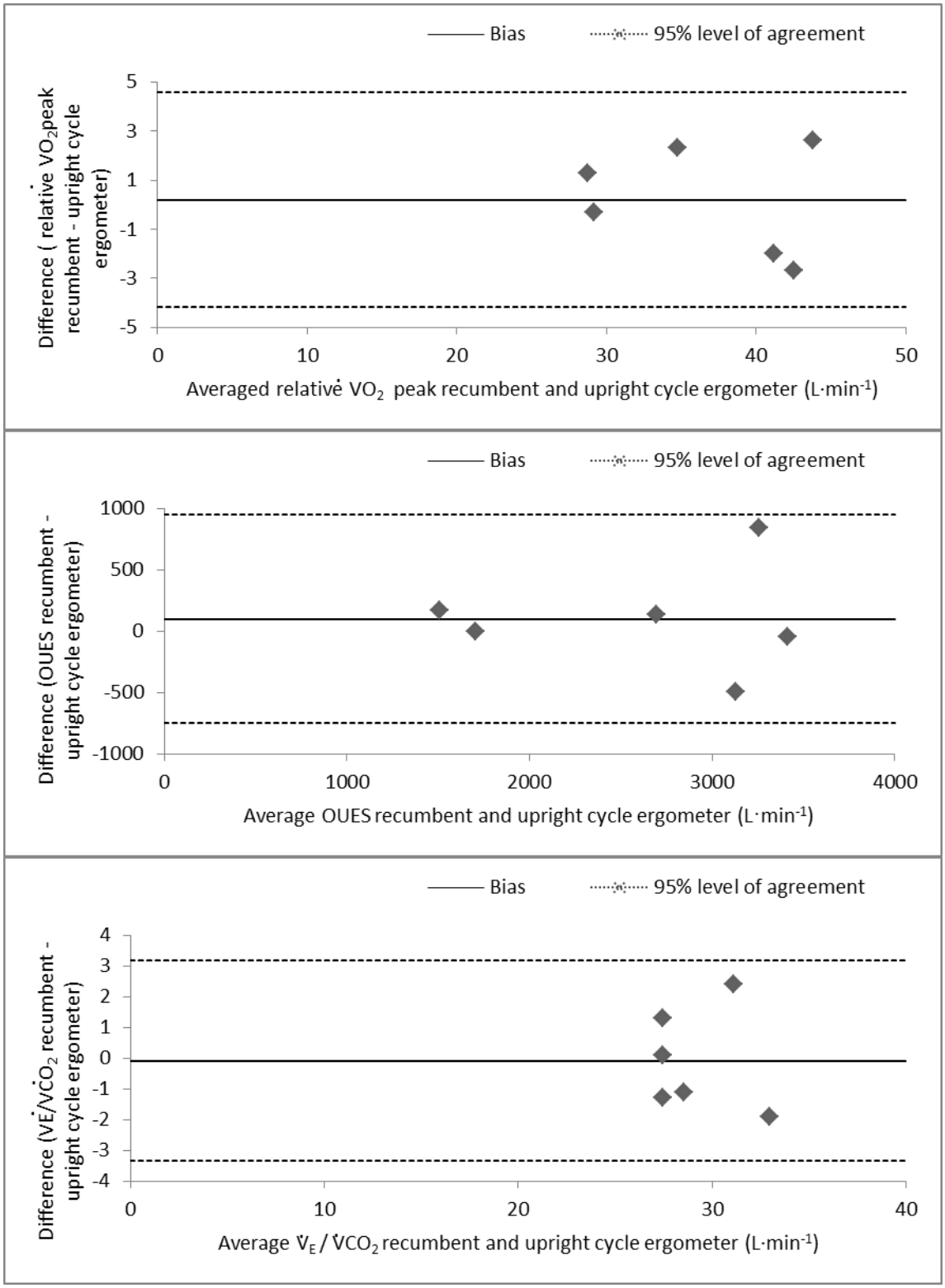


Figure 3.5: Top: Bland-Altman plot for $\dot{V}O_{2\,peak}$; Middle: Bland-Altman plot for OUES; bottom Bland-Altman plot for the $\dot{V}_E$ /$\dot{V}CO_2$ slope. *percentage difference upright compared to the recumbent cycle ergometer. $\dot{V}O_{2\,peak}$ – peak oxygen uptake; $\dot{V}_E$ /$\dot{V}CO_2$ slope - Efficiency of ventilation to eliminate carbon dioxide ; OUES – oxygen uptake efficiency slope.

3.5.4 Conclusion

Peak work rate and the OUES showed the greatest percentage differences between both cycle ergometers. Bland-Altman plots of OUES demonstrates a reasonable uniformly scattered plot, whereas the $\dot{V}_E/\dot{V}CO_2$ slope and $\dot{V}O_{2\,peak}$ show less scatter, suggestive of reduced agreement between measurements. However the limits of agreements are small for all three parameters ($\dot{V}O_{2\,peak}$: -4.1 to 4.5; OUES: -750 to 949; $\dot{V}_E/\dot{V}CO_2$ slope: -3.4 to 3.2) suggestive only a small difference in measurements were observed. Overall results suggest a good relationship and a reasonable agreement between the upright and the semi-recumbent cycle ergometer for this validation study.

3.6 THE VALIDITY OF $\dot{V}O_{2PEAK}$ PREDICTED PARAMETERS AND VARIABILITY USING DIFFERENT $\dot{V}_E/\dot{V}CO_2$ METHODOLOGIES

Modified for publication in the British Journal of Cardiology (van Zalen *et al.*, 2017)

van Zalen, J., Sugihara, C., Sulke, N., Patel, N., Brickley, G., Beale, L., Lloyd, G. (2017). Pitfalls in the interpretation of cardiopulmonary exercise testing data. *The British Journal of Cardiology.* 24, 98-99.

Appendix E

3.6.1 Introduction

CPETs provide objective information on exercise tolerance. However in daily practice, CPET data can be difficult to interpret. Both $\dot{V}O_{2peak}$ and the OUES are affected by many cardiac and non-cardiac diseases and are validated independent predictors for hospitalisation and death (Coeckelberghs *et al.*, 2016; Piepoli *et al.*, 2006c; Weisman and Zeballos, 1994). Percentage predicted $\dot{V}O_2$ is often used when reporting a CPET and a reduction in this parameter prompts an investigation into the decrease in exercise tolerance. Several different formulas are available to predict normal exercise tolerance. The appropriate reference range depends on the method of measurement (Koch *et al.*, 2008). Each of these parameters is most usually expressed at a percentage predicted after allowance for a number of demographic factors such as age and body morphology which are calculated using a number of different formulae. These formulae could provide a variety of results as they use different input functions and mathematical assumptions. The 2003 ATS/ACCP statement (American Thoracic Society, 2003) acknowledged the absence of optimal CPET reference values and recommends that each exercise laboratory select an appropriate set of reference values, but failed to state how to make this selection. There is little data relevant to the majority of patients referred for cardiovascular investigation.

The $\dot{V}_E/\dot{V}CO_2$ provides important insights into the amount of respiratory effort required to maintain homeostasis, which in HF patients is an independent predictor for prognosis (Arena *et al.*, 2004; Corrà *et al.*, 2002). An increase in $\dot{V}_E/\dot{V}CO_2$ is important to identify. This parameter has been widely reported as a slope across the whole of exercise (Tabet *et al.*, 2003), as a ratio at the VT (Wasserman *et al.*, 2005), or at its nadir value (Myers *et al.*, 2009) but there is currently no agreement how the $\dot{V}_E/\dot{V}CO_2$ should be expressed. The AHA statement state that the $\dot{V}_E/\dot{V}CO_2$ slope should be used incorporating all data points whereas Myers *et al.*, (2009) found that the lowest $\dot{V}_E/\dot{V}CO_2$ ratio during exercise is a powerful independent of $\dot{V}O_2$peak and the $\dot{V}_E/\dot{V}CO_2$ slope marker of prognosis in HF patients. Sun *et al.*, (2002) concluded that in 474 healthy adults the lowest $\dot{V}_E/\dot{V}CO_2$ ratio during exercise was the most reproducible and stable for age, gender, exercise mode and laboratory site. However the $\dot{V}_E/\dot{V}CO_2$

slope has received considerably more attention over the years (Agostoni *et al.*, 2010; Arena *et al.*, 2007; Corrà *et al.*, 2002; Tsurugaya *et al.*, 2006), but it has been suggested that the $\dot{V}_E/\dot{V}CO_2$ ratio is more stable as the $\dot{V}_E/\dot{V}CO_2$ slope is more subject to transient to hyperventilation early in exercise.

This validation study explored the potential variability in the results of CPET data from typical cardiac patients including HF patients awaiting CRT implantation, patients scheduled for AF ablation for paroxysmal AF and a group of healthy participants. The aim of this investigation was to determine the correlations between well- known formulae which are used to calculate predicted $\dot{V}O_{2peak}$ and predicted OUES and to determine the inter-relationships between different methods to determine $\dot{V}_E/\dot{V}CO_2$ in cardiac patients and healthy individuals. A reduction in $\dot{V}O_{2peak}$ or a raised $\dot{V}_E/\dot{V}CO_2$ has significant consequences for the interpretation of the test and it is therefore crucial to understand.

3.6.2 Methods

CPET using cycle ergometry was performed in a total of 111 patients. Included patients were patients with HF (n=33), patients with paroxysmal AF (n=69) and a group of healthy controls (n=11). CPETs were performed on a semi-recumbent cycle ergometer (Ergoline 911, Schiller, Switzerland) with a commercially available gas exchange metabolic analyser (Power Cube, Schiller, Switzerland or Quark, Cosmed, Italy). The exercise test protocol comprised a period of rest, followed by unloaded cycle exercise, and then exercise against load increased every 1 minute to voluntary exhaustion. The load increment was individually selected for each patient with the aim of achieving 8-12 minutes of exercise. The following formulae were used to predict $\dot{V}O_{2peak}$; Wasserman (Wasserman *et al.*, 2005), Neder (Neder *et al.*, 1999), Hansen (American Thoracic Society, 2003), Jones (Jones *et al.*, 1985), Koch (Koch *et al.*, 2008)) and two formulae were used to predict OUES; Hollenberg (Hollenberg and Tager, 2000), Buys (Buys *et al.*, 2014). The $\dot{V}_E/\dot{V}CO_2$ was measured using three methodologies: a slope throughout the duration of exercise, as a ratio at the VT and at the nadir during exercise. Baseline characteristics of all participants were summarised. Variables are reported as mean ± SD. Correlations were assessed using Pearson's correlation

coefficient when data was normally distributed and Spearman's rank when data was not normally distributed. To establish differences between non parametric data the Kruskal Wallis Test was used. A p-value of less than 0.05 was considered significant. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) statistical software (version 22, IBM Corp, New York, USA).

3.6.3 Results

There was a very strong positive relationship between the unadjusted $\dot{V}O_{2\,peak}$ and OUES (rho 0.95. p<0.001). However when $\dot{V}O_{2\,peak}$ and OUES were compared to the prospectively chosen formulae the correlation was considerably lower for both $\dot{V}O_{2\,peak}$ and OUES. There were marked differences between the adjusted estimates of peak exercise tolerance generated by different formulae. The Buys formula returned the largest number of low values for peak exercise tolerance, and the Neder formula delivered the largest number of high estimates. Nevertheless, all except the Wasserman formula returned an extreme estimate for peak exercise tolerance for at least one patient (Figure 3.6).

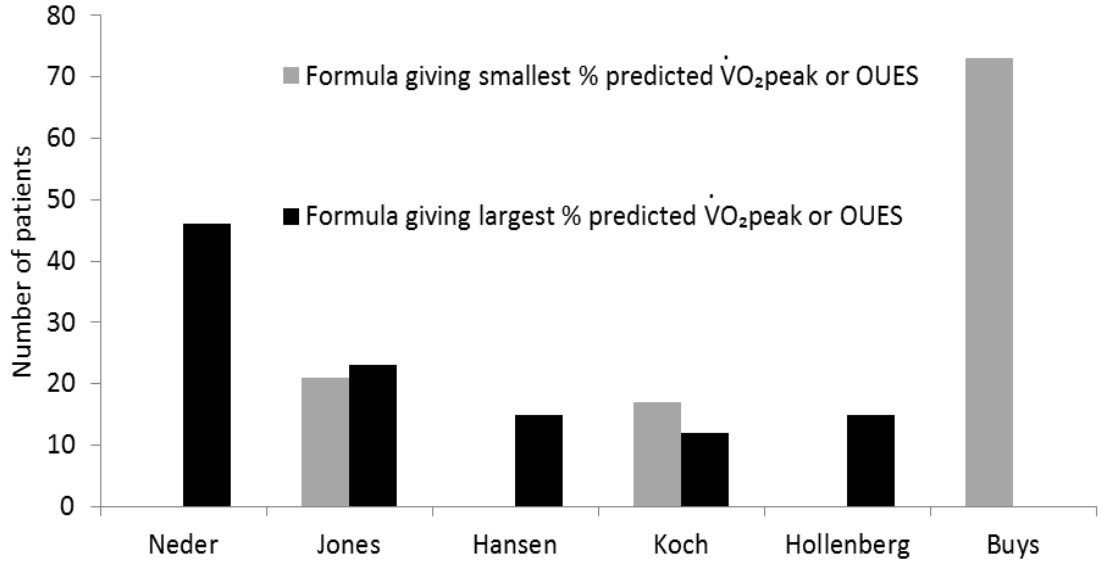
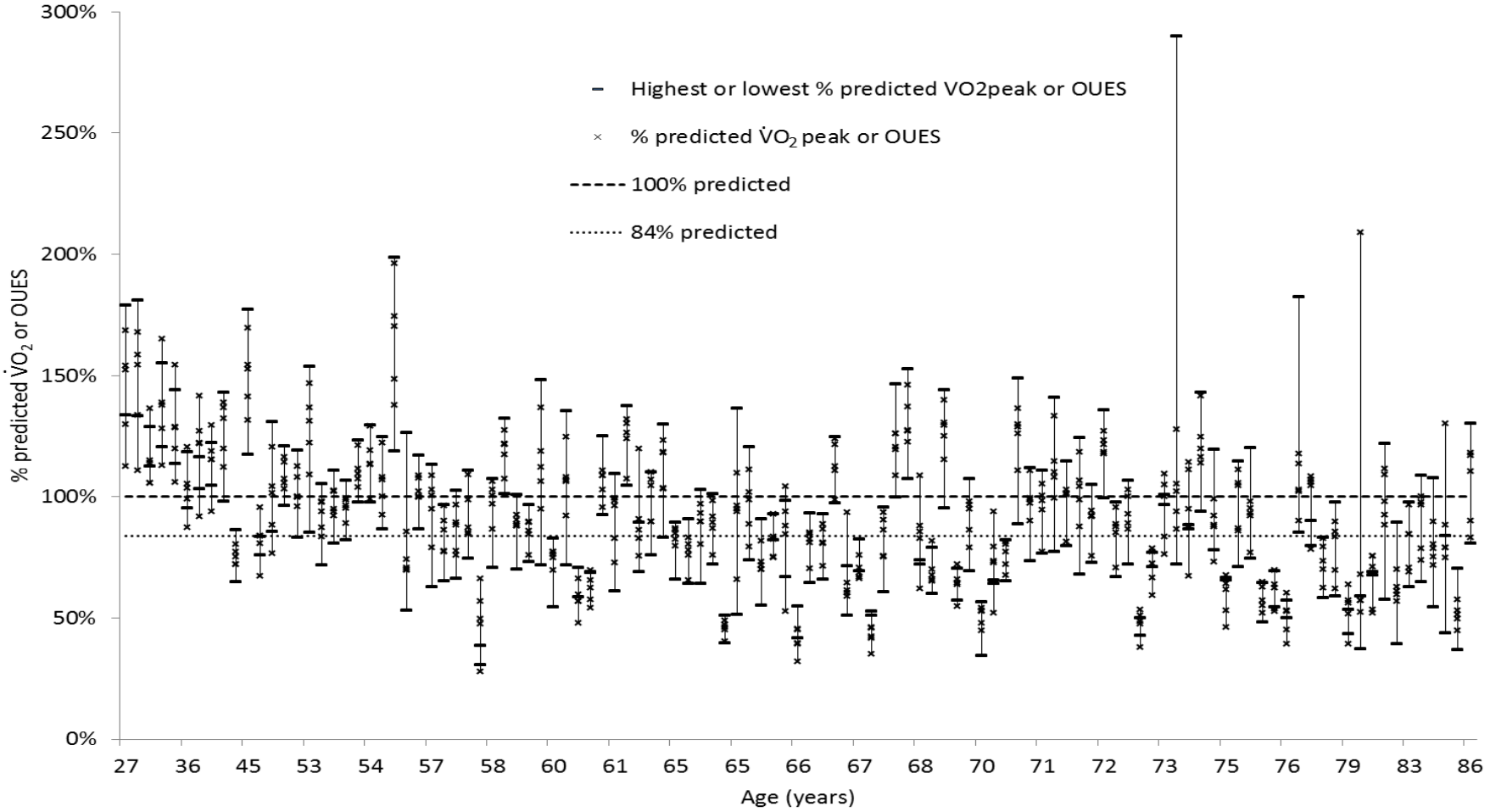


Figure 3.6: The frequency different formulas either returned the largest or smallest % predicted $\dot{V}O_{2\,peak}$ or OUES value. $\dot{V}O_{2\,peak}$ - peak oxygen consumption; OUES - oxygen uptake efficiency slope.

The median difference between the largest and smallest % predicted values was 36 absolute percentage points. In 61 out of 111 (55%) patients, at least one formula suggested <100% predicted peak exercise tolerance, whilst another stated the opposite. The ATS/ACCP statement suggests a threshold of >84% for normal predicted $\dot{V}O_{2\,peak}$ (American Thoracic Society, 2003). In 44 out of 111 (40%) patients, one formula suggested predicted peak exercise tolerance was >100%, whilst another suggested it was <84% predicted. Figure 3.7 shows output of all 7 formulae displayed for each individual. These are ordered in age order to emphasize that there is variation observed across age groups.

Figure 3.7: Predicted $\dot{V}O_{2\,peak}$ (Wasserman, Neder, Hansen, Jones, Koch) or OUES (Hollenberg, Buys) displayed per individual ordered by age.



$\dot{V}O_{2\,peak}$ - peak oxygen consumption; OUES - oxygen uptake efficiency slope

The three methods of measuring $\dot{V}_E/\dot{V}CO_2$ were strongly correlated with one another (rho=0.75, rho=0.85). A significant difference between the three methods measuring $\dot{V}_E/\dot{V}CO_2$ was found (p=0.01) and the lowest ratio $\dot{V}_E/\dot{V}CO_2$ and the $\dot{V}_E/\dot{V}CO_2$ at the VT are significant lower compared to the $\dot{V}_E/\dot{V}CO_2$ slope (p=0.04 and p=0.03 respectively). A $\dot{V}_E/\dot{V}CO_2$ slope lower than 30 is considered normal (Guazzi *et al.*, 2012) and a cut-off at 34 is generally used as a prognosticator for a poor prognosis (Balady *et al.*, 2010). In 60 individuals (55%) the $\dot{V}_E/\dot{V}CO_2$ was measured over 30 in at least one of the measuring method and 26 individuals had a $\dot{V}_E/\dot{V}CO_2$ over 34. In 31 patients a methodology suggested a $\dot{V}_E/\dot{V}CO_2$over 30 whilst another suggested the opposite and in 4 patients one method measured suggested a $\dot{V}_E/\dot{V}CO_2$ above 34, whilst another suggested it was below 30. In the patients with HF 22 out of 33 HF patients had a $\dot{V}_E/\dot{V}CO_2$over 30 and 16 patients had an elevated $\dot{V}_E/\dot{V}CO_2$ greater than 34. In 6 HF patients one method measures a $\dot{V}_E/\dot{V}CO_2$ over 30 whilst another was below 30. The slope methods returned the highest values (55 times), followed by the ratio at the VT (54 times) and the lowest $\dot{V}_E/\dot{V}CO_2$ ratio only gave twice the highest return. The lowest $\dot{V}_E/\dot{V}CO_2$ returned the largest numbers of low values (77 times) followed by the slope methods (28 times) and the ratio returned the lowest $\dot{V}_E/\dot{V}CO_2$ value only 6 times (Figure 3.8).

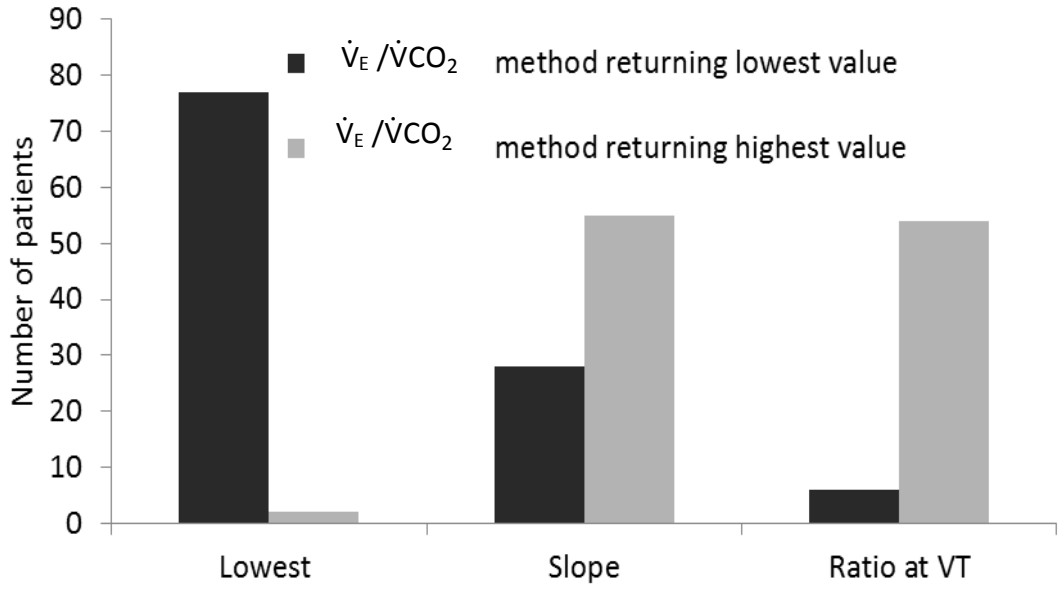
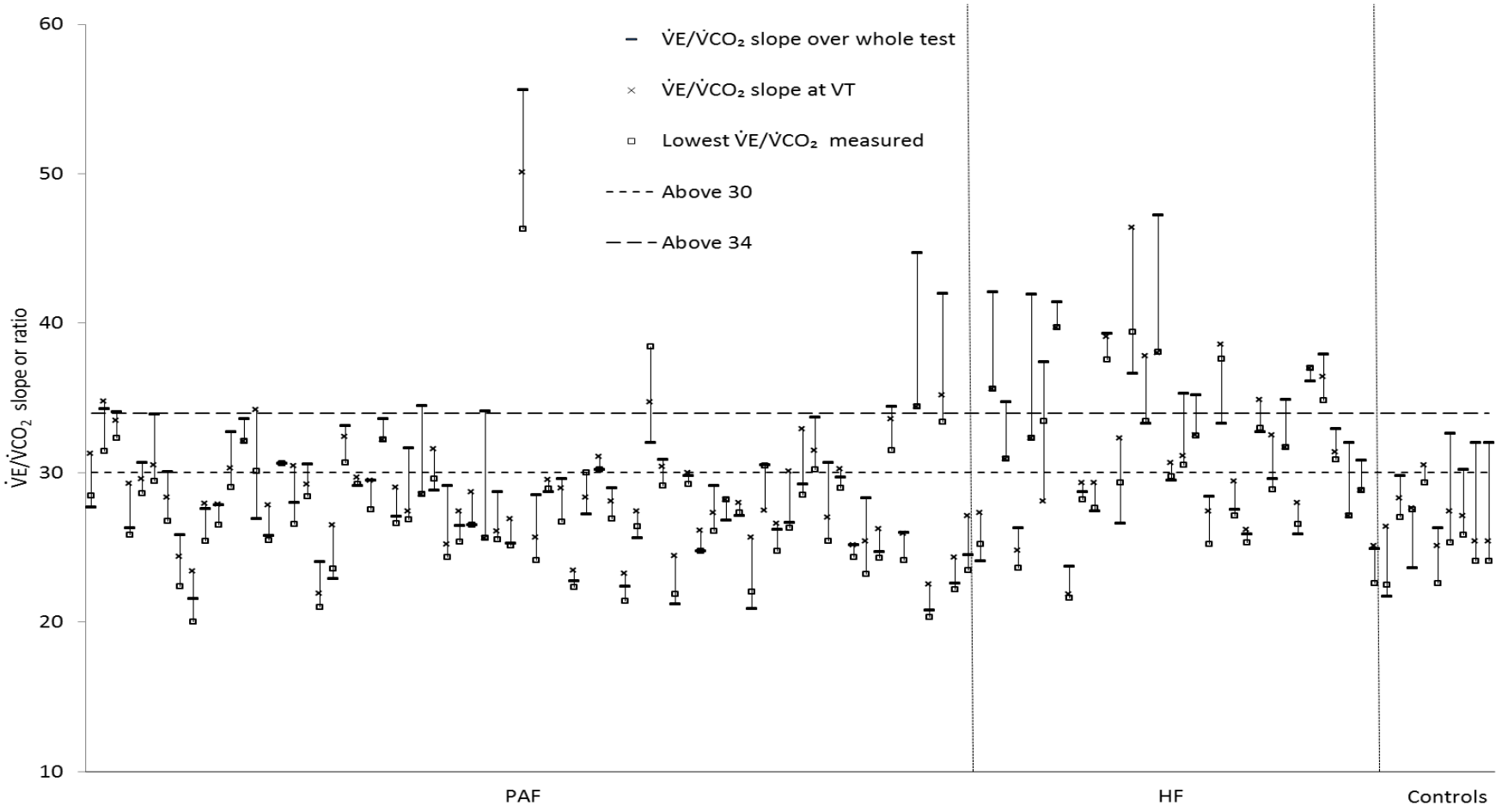


Figure 3.8: The frequency different formulas either returned the largest or $\dot{V}_E/\dot{V}CO_2$ slope or ratio value

Figure 3.9: $\dot{V}_E$ /$\dot{V}CO_2$ values displayed as a slope throughout the duration of exercise, as a ratio at the VT and at the nadir during exercise



$\dot{V}_E$ /$\dot{V}CO_2$ - Efficiency of ventilation to eliminate carbon dioxide

3.6.4 Discussion

The results demonstrate that despite good agreement between the absolute measured parameters, either the predictive calculations incorporating patient demographics, or the method of calculation introduce a much higher degree of variability. This may have significant and important implications for the interpretation of CPET reports in the clinical setting and in comparing studies published in the literature. There is uncertainty around the appropriate reference ranges for CPET. Guidelines have variously recommended the Jones (Jones *et al.*, 1985), the Hansen (American Thoracic Society, 2003) and the Wasserman (Mezzani *et al.*, 2009) formula. The validity of reference ranges has been noted to be uncertain at the extremes of age, height, weight and in women (Wasserman *et al.*, 2005). All formulae use similar demographic factors and make adjustment in the same direction. However, when applied to a cardiac patient, the formulae give different results. For example, one patient in this study achieved a $\dot{V}O_{2peak}$ of 290% predicted in the Jones formula, but only 72% predicted by the Koch formula. The ATS/ACCP statement (American Thoracic Society, 2003) noted several methodological limitations in studies reporting reference ranges. These included small sample size, retrospective study design, lack of randomisation and inclusion of smokers. Furthermore, the commonly-used Wasserman formula is a modified form of the Hansen formula. However, the rationale and evidence base for the modification has not yet been published or peer-reviewed. Studies with large number of HF patients have demonstrated that the Wasserman equation outperformed actual measure $\dot{V}O_{2peak}$ in predicting adverse events (Arena *et al.*, 2009; Osada *et al.*, 1998; Stelken *et al.*, 1996). However these studies did not directly compared the formulae, as the formulae were only tested against adverse events. Moreover, studies (de Almeida *et al.*, 2014; Debeaumont *et al.*, 2016) are still emerging computing new predicting equations to better fit certain populations, demonstrating the need for an improved validated predicting equation. Across various populations, from normal controls to those with advanced HF, different references ranges for peak exercise tolerance can give markedly differing results.

Ventilatory efficiency has shown prognostic power in mortality in HF patients but its determination has not yet been standardised. This study shows that the different methodologies of $\dot{V}_E/\dot{V}CO_2$ are closely related to each other but the ratios either at the VT or at the lowest point were significantly lower compared to the $\dot{V}_E/\dot{V}CO_2$ slope. A few studies have compared the different approaches but these have been limited to its prognostic ability rather than the causes of the differences in methodology chosen (Bard *et al.*, 2006; Myers *et al.*, 2009). It is important to agree on the use of a single measurement that is able to provide significant prognostic information regarding patient's ventilatory efficiency.

3.6.5 Conclusion

Until more research is done to clarify the formulae that best predict clinical outcome in these populations, physicians should consider % predicted $\dot{V}O_2$ and OUES parameters in their clinical decision-making with caution. Likewise the different methods measuring the $\dot{V}_E/\dot{V}CO_2$ showed significant variation which is important as the reference ranges used to interpret $\dot{V}_E/\dot{V}CO_2$ are diverse. Proper reference ranges with consistent methodology should be developed which will permit the accurate, reliable, and reproducible use of CPET in daily cardiac assessment. In the meantime CPET results should be interpreted with caution.

3.7 Procedures for echocardiography

Echocardiography was performed using either a GE Vivid 7 platform or a GE Vivid E9 (Vingmed-General Electric, Horten, Norway) equipped with a phased-array 3.5 MHz transducer. Standard echocardiographic views were obtained (Figure 3.10). Two-dimensional, spectral Doppler and TVI were obtained at rest and during exercise for all studies. Echocardiography was performed or analysed predominately by the author. Full British Society of Echocardiography accreditation in adult echocardiography was obtained during the course of this thesis (Appendix B).

Figure 3.10: Echocardiography machine: the GE Vivid 7 (Left) and GE Vivid E9 (right)

LV volumes and LVEF were calculated using Simpson's biplane method (Goerke and Carlsson, 1967) and the recommended method for volume measurements is the biplane method of disks (modified Simpson's rule) (Figure 3.11). Images were obtained from the 4 and 2-chamber views. The principle underlying this method is that the total left ventricular volume is calculated from the summation of a stack of elliptical disks. The method used calculates the LVEF by measuring EDV and ESV. LVEF is calculated as follows: LVEF = (EDV – ESV) / EDV (Figure 3.11).

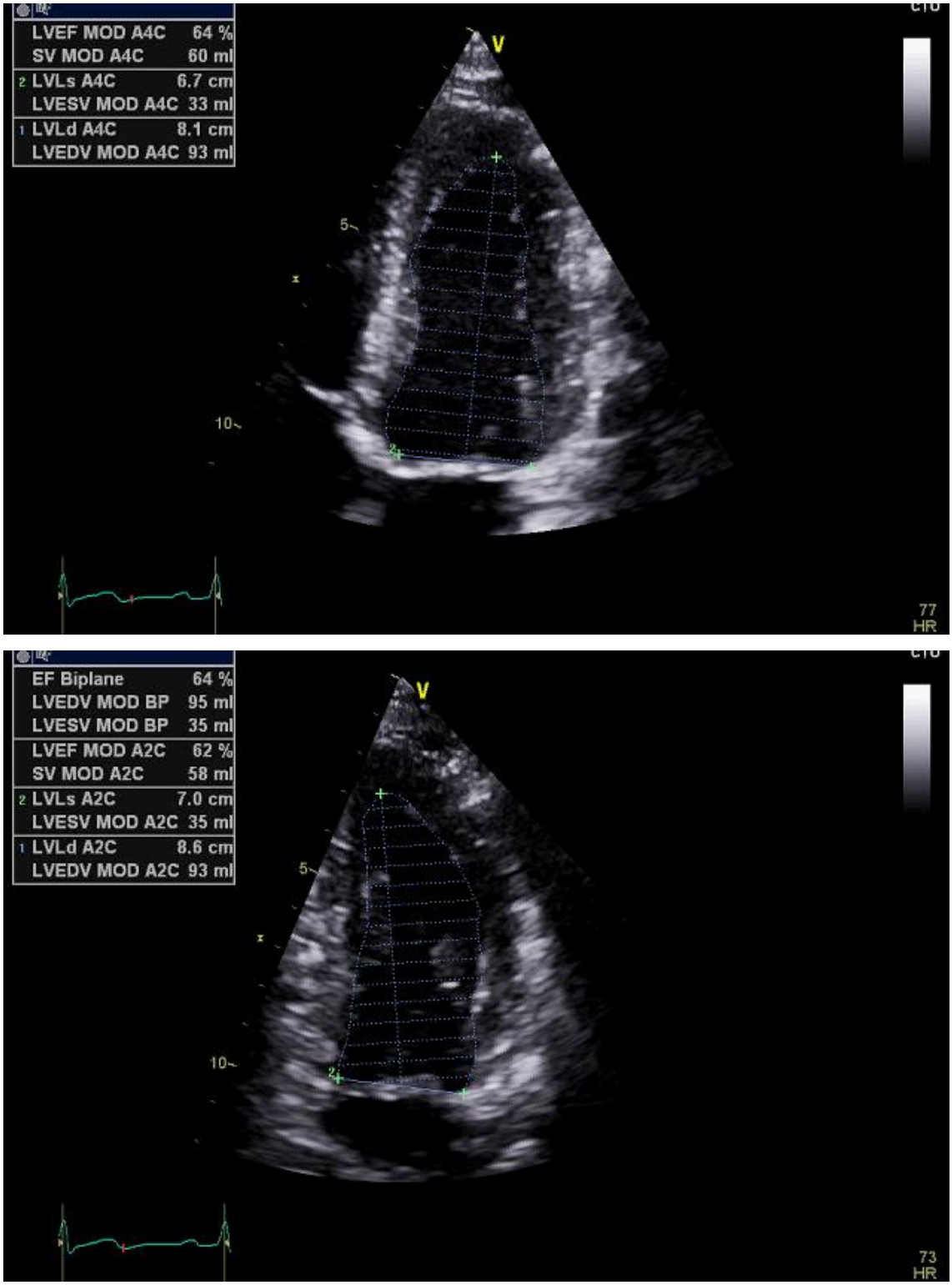


Figure 3.11: The modified Simpson's method measuring the LVEF in a healthy individual. 4-ch chamber view (top) and 2-chamber view (bottom)

Doppler echo provides haemodynamic information regarding the heart and blood vessels and is able to measure the severity of valvular stenosis, detects valvular regurgitation and can reveal intracardiac shunts (Kaddoura, 2012). CW Doppler is used to measure high velocities. Figure 3.12 demonstrates CW Doppler through the aortic valve in a patient with severe AS.

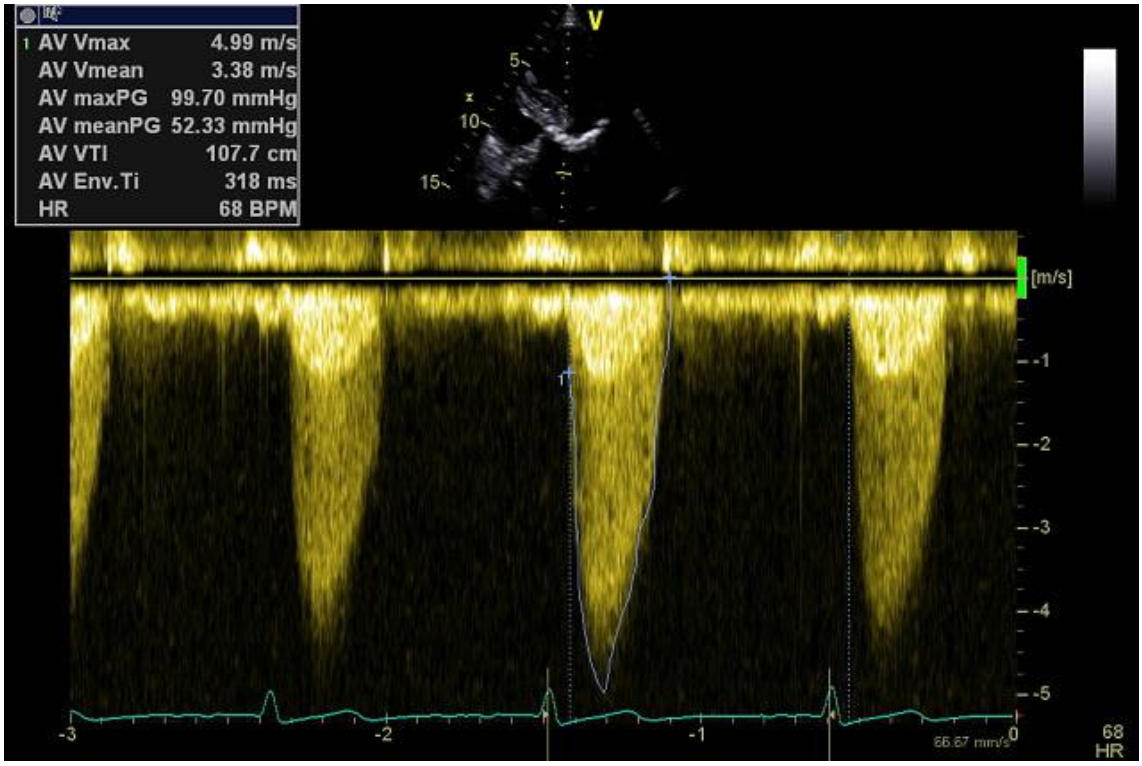


Figure 3.12: Continuous Wave Doppler through the aortic valve demonstrating severe aortic stenosis

PW Doppler was used to accurately measures flow at a specific sampling point. Mitral valve flow pattern were determined using PW Doppler sample volume at the tip of the mitral leaflets (Figure 3.13).

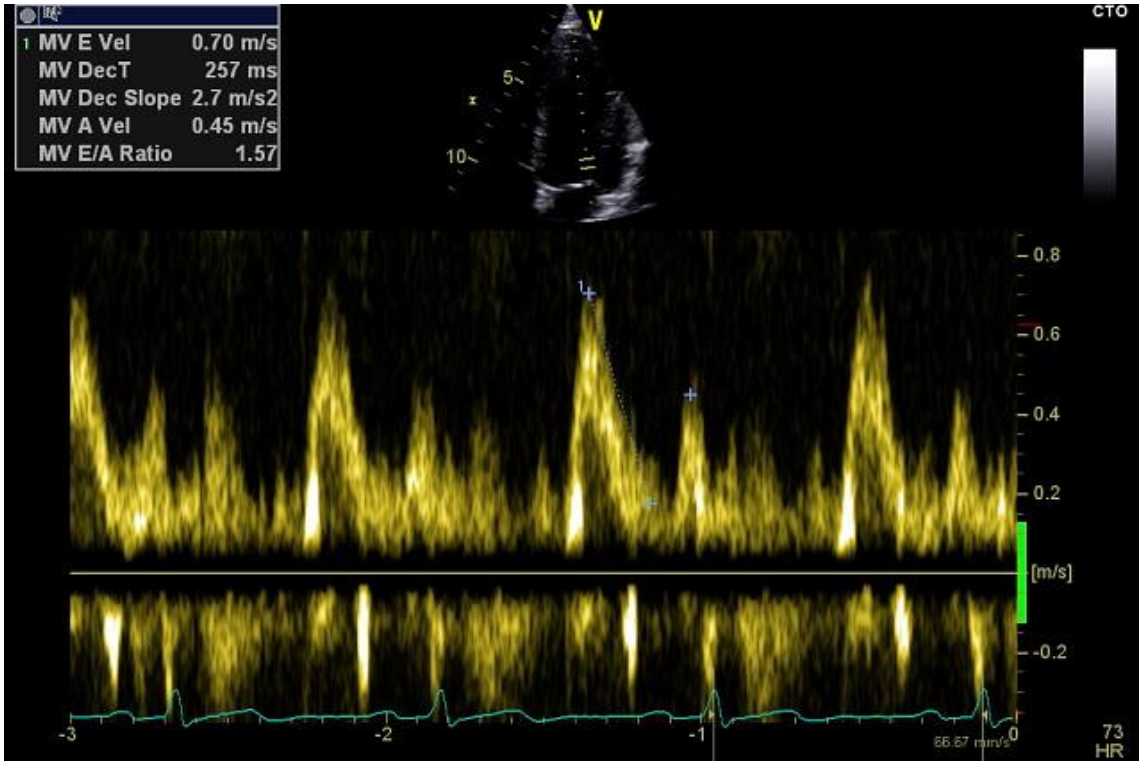


Figure 3.13: Transmitral Doppler mitral inflow demonstrating a normal mitral flow pattern

Pulsed wave Doppler for Q̇ assessment was obtained from apical 5-chamber view one centimetre below the aortic valve (Figure 3.14)

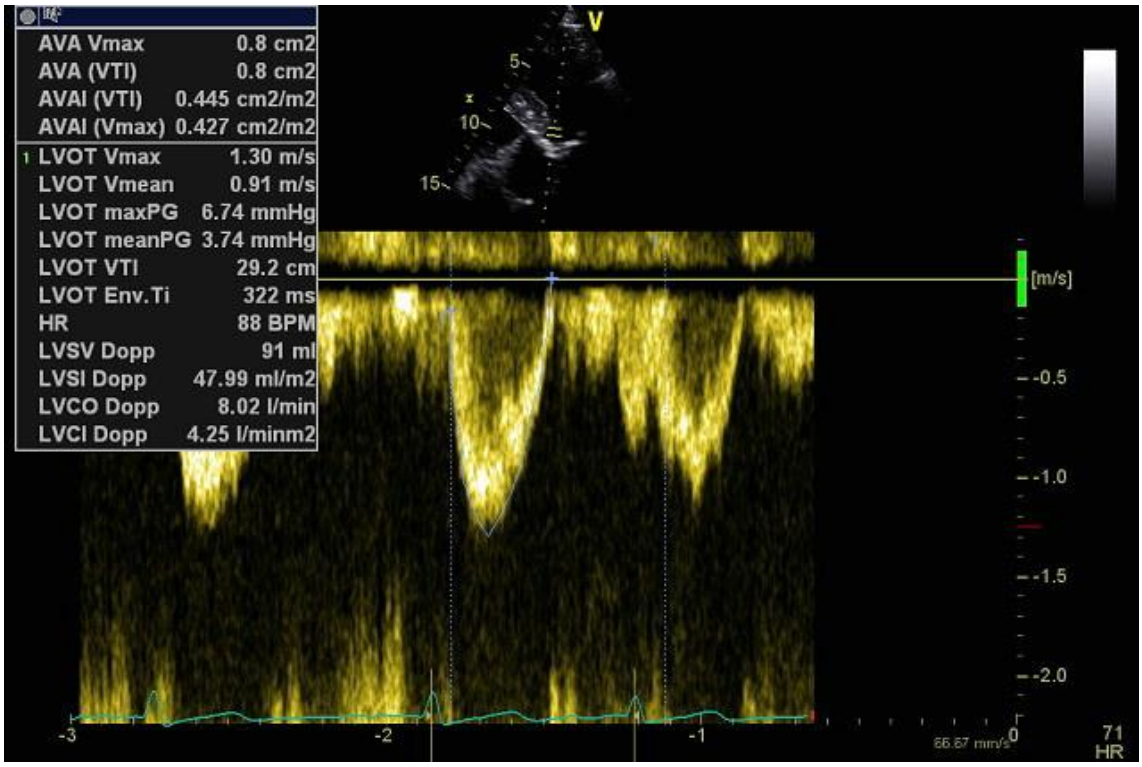


Figure 3.14: Pulse wave Doppler at the level of left ventricular outflow tract

TVI imaging was performed with the sample volume placed at mitral annulus in either the 4-chamber view or in all the 3-apical views. Exercise S' (defined as the highest velocity during systole after the end of isovolumetric contraction) was obtained from the mitral annulus. At least 3 cardiac cycles were obtained and S' was averaged for each segment and all available S' were averaged. Where a reproducible TVI recording was not achieved, all available recordings were used to calculate the average. Myocardial velocity during early diastole (E') was measured on the lateral wall and where possible in the septal wall. Images were obtained in real time and analysed after each study. Images were stored offline.

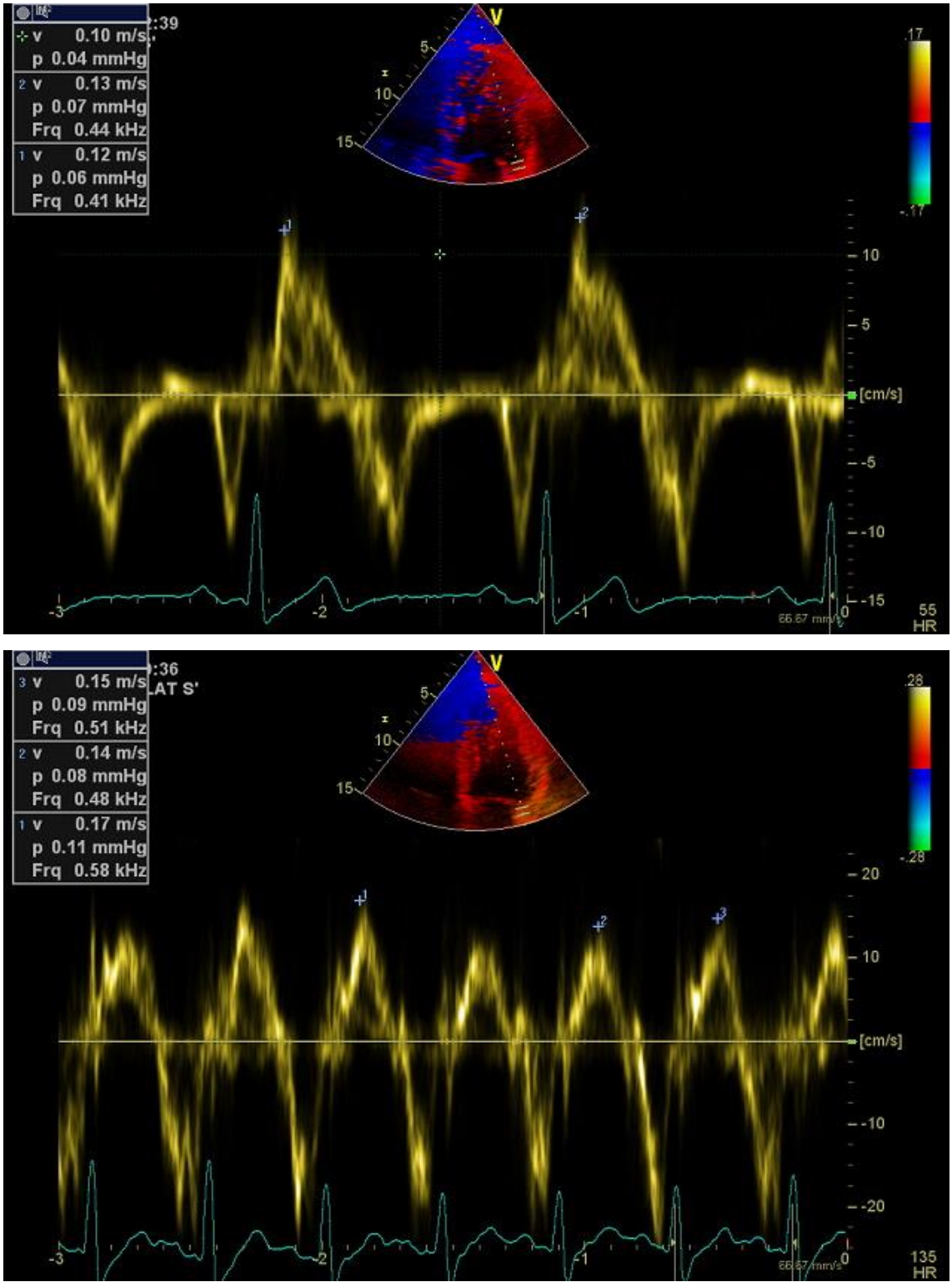


Figure 3.15: Spectral tissue Doppler at rest (top) and peak exercise (bottom) obtained from the lateral basal segment demonstrating an increase in systolic longitudinal function

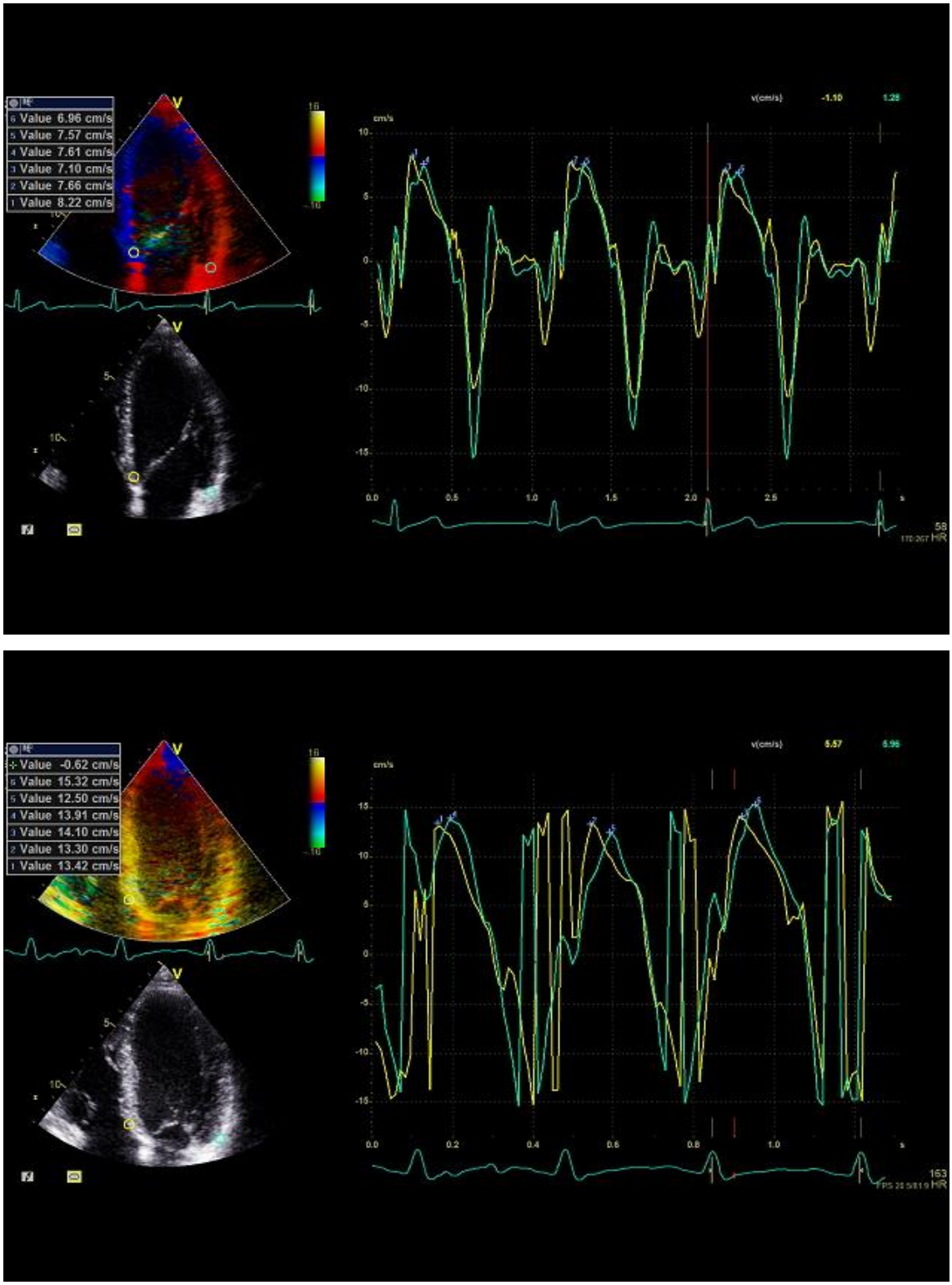


Figure 3.16: Tissue Colour Doppler at rest (top) and peak exercise (bottom) obtained from the septal and lateral basal segments demonstrating an increase in systolic longitudinal function

3.7.1 Inter- and intraobserver variability

Echocardiographic inter- and intraobserver variability was carried out for echocardiographic and CPET parameters. For the echocardiographic measurements 22 patients with HF were randomly selected as part of two different studies. Both studies reported that exercise S' had excellent inter- and intraobserver reliability compared to exercise LVEF, exercise E' and E/E' (chapter 5 and 6 for more detail). Interobserver and intraobserver variability were excellent for S' at exercise unlike LVEF at exercise which was less reliable; this is in agreement with previous studies (McGowan and Cleland, 2003; Nikitin *et al.*, 2003).

Interobserver variability including CPET parameters was analysed for 15 participants from study 5 (chapter 8) and demonstrates excellent agreement for measures of $\dot{V}O_{2\,peak,}$ and the OUES. Interobserver agreement was slightly reduced for the $\dot{V}O_2$ at the VT and the $\dot{V}_E$ /$\dot{V}CO_2$ slope (see chapter 8 for more detail). This is in agreement with previous literature studies in the literature (Cohen *et al.*, 1991; Sinclair *et al.*, 2009).

3.8 Exercise echocardiography in combination with CPET

Patients resting echocardiogram pictures were obtained whilst strapped in on the semi-recumbent ergometer. Patients were asked to continue to take their medication as usual. At the start of the test a 3 minute rest period was included followed by a 3 minute warm up period. Exercise protocols were individually determined based on functional status. Work rate (5, 10, 15 or 20 W) increased every minute until voluntary exhaustion aiming for 6-10 minutes of exercise. HR, BP and oxygen saturation were monitored throughout. $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ were continuously measured and derived using a calibrated breath-by-breath analyser (Schiller Powercube AT-104 PC, Ganzhorn, Baar, Switzerland). Echocardiography measurements commenced when patients were close to finishing the test when the RER was exceeding 0.95 and if patients were not taking beta blockers in combination with a peak predicted HR>85%. All measurements were taken within 90 seconds of finishing exercise. Patients were verbally encouraged to exercise until maximal exertion. $\dot{V}O_{2peak}$ was expressed as the highest value from an average of 30s during the final stage of the exercise test. Figure 3.17 and 3.18 demonstrate the set up for a CPET exercise echocardiogram.

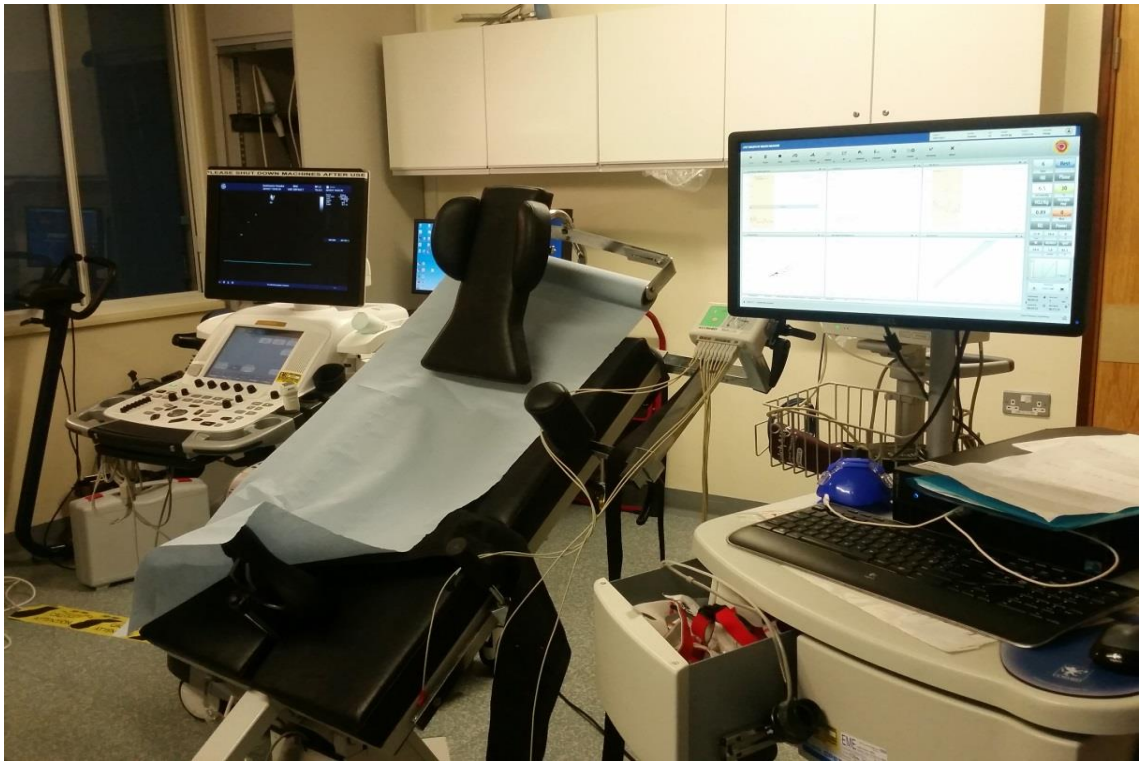


Figure 3.17: The set up for a CPET exercise echocardiogram including a GE Vivid E9 and a Cosmed Quark CPET system

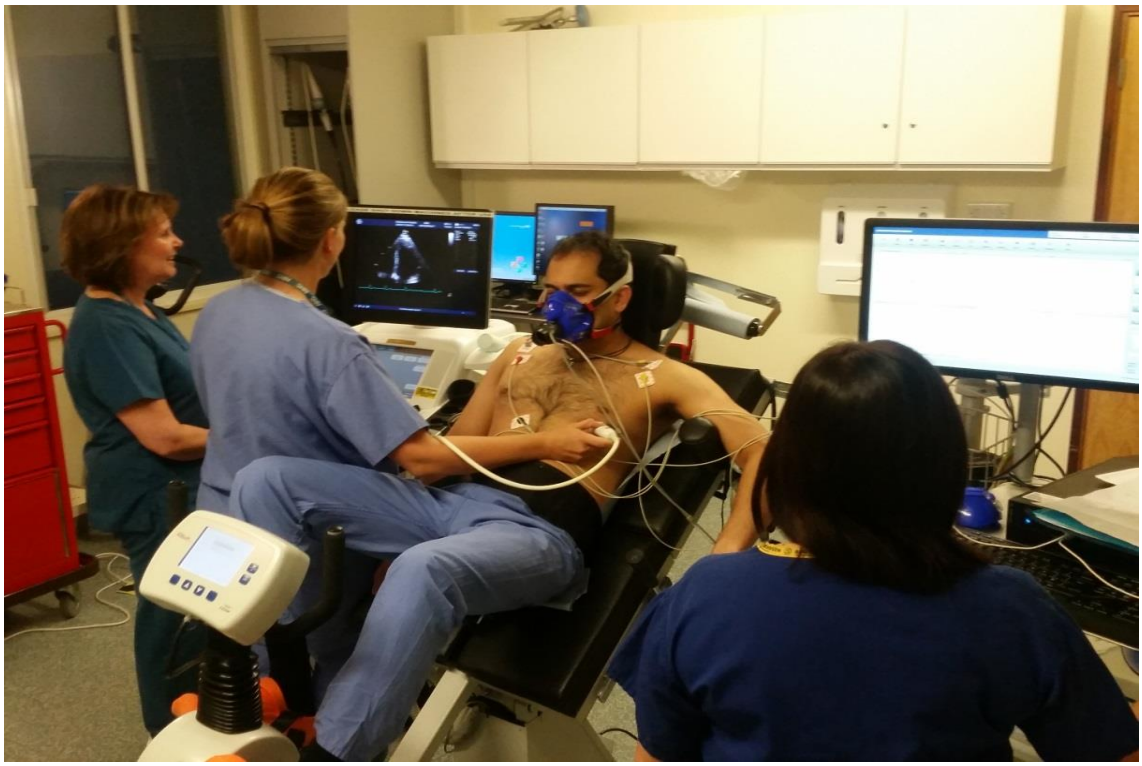


Figure 3.18: A CPET exercise echocardiogram in action (published with permission from volunteer)

CHAPTER 4

THE RELATIONSHIP BETWEEN RESTING TRANSTHORACIC ECHOCARDIOGRAPHY AND EXERCISE PARAMETERS IN PATIENTS WITH PAROXYSMAL AF

Presented at the Euroecho conference; 2015, Seville; Spain

van Zalen, J., Sugihara, C., Patel, N., Sulke, A.N., Lloyd, G. (2015) The relationship between resting transthoracic echocardiography and exercise capacity in patients with paroxysmal atrial fibrillation. *European Heart Journal - Cardiovascular Imaging* 16 suppl 2: S202

Appendix D

4.1 Abstract

Resting transthoracic echocardiograms are commonly used in the assessment of patients with AF. The aim of the study was the examine the relationship between LV or left atrial (LA) function and objectively assessed exercise parameters obtained using CPET. Standard resting echocardiograms and CPETs were performed on 69 patients scheduled for AF ablation. Unadjusted peak exercise tolerance strongly correlated with submaximal exercise tolerance (rho = 0.94; $p < 0.001$). There was no significant univariate correlation between resting echocardiography parameters and peak exercise tolerance. Sensitivity analyses confirmed that after demographic factors were controlled for, in multivariate generalised linear models, no resting echocardiography data had any significant association with exercise tolerance. In patients with paroxysmal AF, conventional resting echocardiography data had no relationship with objectively assessed exercise tolerance. The role of resting echocardiography was not better than demographic factors alone in predicting $\dot{V}O_{2peak}$.

4.2 Introduction

Resting transthoracic echocardiography is routinely performed in the assessment of cardiac patients. It provides anatomical and functional assessment of the heart function, cardiac chamber size, valve function, myocardium, and assessment of the aorta size. AF is the most frequently observed cardiac arrhythmia in the world (Chugh *et al.* 2014). In the UK an estimated 1.3% of the population have AF. The prevalence rises dramatically with age; the median age for people living with AF is 75 years. It is estimated that for people aged 50-59 years the prevalence is 0.5% and this number doubles with each advancing decade, almost 9% of people ages 80-90 years suffer from the condition (Benjamin *et al.*, 1998; Davis *et al.*, 2012). AF can be classified in four different categories: first detected AF, paroxysmal AF, persistent AF and permanent AF. First detected AF is when only one episode of AF is diagnosed, if the patient experiences more documented episodes of AF then this is termed recurrent. If a recurrent episode spontaneously self-terminated within seven days it is classified as paroxysmal AF. An episode which requires cardioversion to return to sinus rhythm is termed persistent AF and if an episode is sustained longer than seven days and cardioversion has failed, or if no longer attempted, then it is classified as permanent AF (Fuster *et al.*, 2006). The prevalence of paroxysmal AF is not well documented and clinical experience suggests that paroxysmal AF could develop to permanent AF with estimates reaching between 15 to 30% in a 1-3 year time period (Ruigómez *et al.*, 2005). Patients with paroxysmal AF are often asymptomatic and for the majority of patients the main echocardiographic abnormalities found are dilatation of the LA (Tsang *et al.*, 2001) or LV diastolic dysfunction (Tsang *et al.*, 2002) and these may have prognostic value (Aljaroudi *et al.*, 2012; Takemoto *et al.*, 2005; Tsang *et al.*, 2003). The presence of diastolic impairment of the left ventricle and loss of atrial function are both implicated in the generation of symptoms in patients with AF. CPET offers the best tool to assess the overall physiological effect of cardiac dysfunction. CPET is non-invasive, safe (Skalski *et al.*, 2012), reliable and reproducible (Barron *et al.*, 2014). CPET data has been robustly linked to hard clinical end-points such as hospitalisation and death (Guazzi *et al.*, 2010a; Guazzi *et al.*, 2010b), regardless of age (Arena *et al.*, 2011). The population studied are patients with paroxysmal AF. The reason for investigating

patients with paroxysmal AF is that the patients included have a wide range of co-morbidities and a variety of symptoms and have a range of exercise tolerance and are therefore a varied and diverse patient population to investigate. The objectives of this study were to determine whether patients with paroxysmal AF show any relationships between echocardiography and CPET. It was therefore hypothesised that resting echocardiographic parameters would not show any relationship with any CPET parameters.

4.3 Methods

4.3.1 Study patients

This prospective observational study was conducted at Eastbourne District General Hospital. The study protocol was developed by the investigators and was approved by the institutional review board and the National Ethics Committee. All patients gave written informed consent before starting study procedures. 69 patients were recruited into a study assessing the effects of AF ablation, and underwent resting echocardiography and CPET prior to any intervention. Inclusion criteria included above 18 years of age and symptomatic paroxysmal AF suitable for AF ablation. Exclusion criteria included prior cardiac or thoracic surgery, inability to undergo general anaesthesia for AF ablation, pregnancy, cardiac rhythm disorders other than AF and the presence of pre-existing permanent pacemakers or implantable loop recorders that did not allow for continuous monitoring for AF occurrence, or were not MRI-safe.

4.3.2 Resting echocardiography

Transthoracic echocardiography was performed with an ultrasound machine (Vivid 7 or Vivid 9, GE Healthcare, USA). A complete dataset (as per guidelines from the British Society of Echocardiography)(Wharton *et al.*, 2015) was collected. Additional measures collected were:

- TVI was used to determine S', E' and A' velocities at the lateral and septal mitral annulus in the apical 4 chamber view. A' velocities were only measured in sinus rhythm.

- Patient age, gender, height and weight at the time of the echocardiogram

Further measures were derived from the above dataset:

- SV was calculated as LV outflow tract (LVOT) Velocity Time Integral (VTI) · (π (LVOT dimension))^2
- Body Surface Area (BSA) was calculated from Du Bois' formula(Du Bois and Du Bois, 1989)
- SV and LA volume was indexed by dividing by BSA
- TVI parameters were averaged for lateral and septal annulus

4.3.3 Cardiopulmonary Exercise Test

CPETs were performed on a semi-recumbent cycle ergometer (Ergoline 911, Schiller, Switzerland) with a commercially available gas exchange metabolic analyser (Power Cube, Schiller, Switzerland or Quark, Cosmed, Italy). The exercise test protocol comprised a 1-2 minutes period of rest, followed by 3 minutes unloaded bicycle exercise, followed by exercise against load increased every 1 minute until voluntarily exhaustion. The load increment was individually selected (10-25 W) for each patient with the aim of achieving 8-12 minutes of exercise excluding the warm-up.

4.3.4 Statistical Analysis

Categorical variables are reported as observed number of patients (%). A p-value of less than 0.05 was considered significant. Continuous variables in which the Shapiro-Wilk test rejected the null hypothesis of normality were considered non-parametric variables, and are reported as median interquartile range (IQR). Other variables are reported as mean ± SD. Correlation was examined using Pearson's product correlation coefficient (r), or Spearman's rank correlation coefficient (rho) in the case of non-parametric variables. A correlation below 0.3 was considered weak, and above 0.5 was considered a strong correlation. In a *post-hoc* analysis, the relationship between peak exercise tolerance and resting echocardiography parameters was examined in a multivariable generalised linear model.

4.4 Results

The demographics of the 69 patients studied are presented in table 4.1. All patients had paroxysmal AF, and approximately half were hypertensive. The prevalence of other comorbidities was also high. Average exercise tolerance fell within the normal predicted range. Table 4.2 shows the main CPET and echocardiographic parameters.

Table 4.1: Demographics, comorbidities and CPET results of study patients

Demographic factor	
Age (years)	64.3 ± 9.6
Height (cm)	171 (IQR 164 to 181)
Weight (kg)	84.2 ± 16.1
Body Mass Index, BMI ($kg \cdot m^{-2}$)	27 (IQR 24 to 31)
Female	38 (55%)
Hypertension	34 (49%)
Hyperlipidaemia	19 (28%)
Diabetes	7 (10%)
CAD	11 (16%)
Prior MI	3 (4%)
Prior CVA or TIA	6 (9%)
Asthma	4 (6%)
COPD	2 (3%)
Prior Cancer	6 (9%)

CAD – coronary artery disease; MI – myocardial infarction; CVA – cardiovascular attach; TIA – transient ischaemic attack, COPD – chronic obstructive pulmonary disease, $\dot{V}O_2$ – oxygen uptake, $\dot{V}_E$ – ventilation, $\dot{V}CO_2$ – carbon dioxide elimination

Table 4.2: Cardiopulmonary exercise testing and echocardiography parameters

CPET parameters	
% predicted $\dot{V}O_{2\,peak}$	99.7% (IQR 87.7% to 113.0%)
$\dot{V}O_{2\,peak}$ ($L \cdot min^{-1}$)	1.66 (IQR 1.33 to 2.15)
$\dot{V}O_{2\,peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	20.7 (IQR 16.6 to 24.8)
OUES ($(mL \cdot min^{-1}) \cdot (L \cdot min^{-1})^{-1}$)	2021 ± 677
$\dot{V}O_2$ at VT ($L \cdot min^{-1}$)	1.03 (IQR 0.76 to 1.24)
% VT from predicted max	59.4 ± 9.9
$\dot{V}_E / \dot{V}CO_2$ ratio at VT	28.0 ± 4.1
Echocardiography - systolic function	
Mean S' velocity ($cm \cdot s^{-1}$)	7.7 ± 1.2
Biplane EF (%)	61 ± 6
SV (mL)	77 ± 24
Adjusted SV ($mL \cdot m^{-2}$)	39 ± 12
Echocardiography - LV diastolic function	
Mean E' velocity ($cm \cdot s^{-1}$)	9.4 ± 2.5
Mean E/E'	9.4 ± 2.6
Echocardiography - Left atrium	
Mean A' velocity ($cm \cdot s^{-1}$)	8.3 ± 1.7
LA volume biplane (mL)	67 ± 19
LAVI ($mL \cdot m^{-2}$)	34 ± 9
LA area (cm^2)	20.8 ± 4.4

$\dot{V}O_2$ – oxygen uptake, OUES – oxygen uptake efficiency slope, $\dot{V}_E$ – ventilation, $\dot{V}CO_2$ – carbon dioxide elimination, S' – systolic velocity, EF – ejection fraction, SV – stroke volume, E' –mitral annular early diastolic velocity, E/E' -ratio between early mitral inflow velocity and mitral annular early diastolic velocity, A' - myocardial velocity associated with atrial contraction, LA – left atrium, LAVI – left atrial volume index

There was a large range in observed values seen across all parameters with the exception of LVEF (61±6%). Echocardiographic measures of systolic function (S', LVEF, SV) had no observed correlations with each other. Measures of LA size showed a strong relationship between area and volume ($r=0.92$; $p<0.0001$) but a much lower correlation with diameter ($r=0.44$; $p<0.0001$). There was no significant linear relationship observed between LV diastolic function (E' and E/E') and LA functional parameters (LA volume).

No single echocardiographic primary parameters showed a significant correlation with any CPET parameters. SV showed a significant correlation (Table 4.3) with $\dot{V}O_{2\,peak}$ and OUES, however although significant this correlation is weak. A significant correlation between OUES, systolic longitudinal velocity and LA size and volume, again the correlation coefficient was weak. Correlations between the primary measures of TTE with CPET parameters are displayed in Table 4.3.

As the primary echocardiographic measures demonstrated no relationship or low correlation with peak exercise tolerance (Table 4.3), a number of *post hoc* sensitivity analyses were performed. Correlation coefficients were calculated for all 35 echo parameters against $\dot{V}O_{2\,peak}$. There was no single echocardiographic parameter highly correlated with $\dot{V}O_{2\,peak}$. The univariate correlations between all echo parameters and $\dot{V}O_{2\,peak}$ are shown in Table 4.4.

Eight (of 35) echo parameters correlated with $\dot{V}O_{2\,peak}$, however all the correlation coefficients were low. As expected, age, gender, height and weight were more strongly correlated with $\dot{V}O_{2\,peak}$ than any echo parameter. All significant univariate correlations (including height, weight, age and gender) were entered into a generalised linear model for $\dot{V}O_{2\,peak}$. Age and gender had significant effects within this model ($p<0.001$); no other covariate had any significant effect. Furthermore, this model (including echo data) was inferior in the prediction of $\dot{V}O_{2\,peak}$ to a generalised linear model including only age, gender, height and weight as covariates. Substituting $\dot{V}O_2$ at VT as the response variable did not have any significant effect, and a model including demographic covariates proved superior to one including resting echocardiographic data.

Table 4.3: Correlation coefficients (Pearson's r and Spearman's rho) for the relationship between echocardiography primary measures and primary CPET parameters

	% pred $\dot{V}O_{2peak}$	$\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	% VT from predicted max	OUES $(mL \cdot min^{-1}) \cdot (L \cdot min^{-1})^{-1}$
Mean S' ($cm \cdot s^{-1}$)	rho = 0.09 p = ns	rho = 0.10 p = ns	r = -0.01 p = ns	**r = 0.24** **p = 0.05**
Biplane EF (%)	rho = 0.07 p = ns	rho = 0.09 p = ns	r = 0.18 p = ns	r = -0.04 p = ns
SV (mL)	rho = 0.12 p = ns	**rho = 0.39** **p = 0.001**	r = 0.13 p = ns	**r = 0.38** **p = 0.001**
Adjusted SV ($mL \cdot m^{-2}$)	rho = 0.12 p = ns	**rho = 0.30** **p = 0.01**	r = 0.17 p = ns	r = 0.17 p = ns
Mean E' ($cm \cdot s^{-1}$)	rho = 0.01 p = ns	rho = 0.15 p = ns	r = -0.01 p = ns	r = 0.21 p = ns
Mean E/E'	rho = -0.07 P = ns	**rho = -0.28** **p = 0.02**	r = -0.07 p = ns	r = -0.27 p = ns
Mean A' ($cm \cdot s^{-1}$)	rho = 0.01 p = ns	rho = -0.08 p = ns	r = 0.08 p = ns	r = -0.01 p = ns
LA volume (mL)	rho = 0.05 p = ns	rho = 0.11 p = ns	r = -0.05 p = ns	**r = 0.35** **p = 0.004**
LAVI ($mL \cdot m^{-2}$)	rho = 0.06 P = ns	rho = 0.03 p = ns	r = -0.04 p = ns	r = 0.11 p = ns
LA area (cm^2)	rho = 0.01 P = ns	rho = 0.11 p = ns	r = -0.07 p = ns	**r = 0.32** **p = 0.007**

S' – systolic velocity, EF- ejection fraction, SV – stroke volume, E' –mitral annular early diastolic velocity, E/E' -ratio between early mitral inflow velocity and mitral annular early diastolic velocity, A' - myocardial velocity associated with atrial contraction, LA – left atrium, LAVI – left atrial volume index

Table 4.4: Parameters considered in post-hoc exploratory analyses. Spearman's correlation coefficient (rho) for resting echocardiography data plus gender, age, height and weight against $\dot{V}O_{2\,peak}$. The 10 (of 35) echocardiography parameters with $p < 0.05$ are shown.

Parameter	Spearman's correlation coefficient	p-value
LA volume biplane	0.32	0.01
LA width	0.29	0.02
LA area	0.32	0.01
Lateral S'	0.27	0.02
Lateral MAPSE	0.33	0.01
Mean E/E'	-0.25	0.04
Lateral E/E'	-0.30	0.04
Gender (male)	0.67	<0.001
Age	-0.53	<0.001
Height	0.72	<0.001
Weight	0.54	<0.001

LA – left atrium, S' – systolic velocity, MAPSE – mitral annular plane systolic excursion, E/E' -ratio between early mitral inflow velocity and mitral annular early diastolic velocity

4.5 Discussion

This study shows there are no or very weak relationship between resting echocardiography and CPET data in patients with AF. This is in agreement with the hypothesis set out at the start of the study. This is an important finding as often a lot of emphasis is placed upon resting measurements when assessing patients. For patients with AF there is a conventional wisdom which implies that as LV systolic and diastolic function decline the importance of an 'atrial kick' to maintain $\dot{Q}$ increases (Alpert *et al.*, 1988). Hence both LV performance and atrial function should play a role in defining exercise tolerance. This study is the first to systematically examine the association of these routine echocardiographic indices with objectively assessed exercise tolerance in patients with a history of AF and without clinically important valvular or myocardial disease. It is surprising to observe no predictive value from resting echocardiography data and this requires careful consideration. Donal *et al*. (2008) found a correlation between $\dot{V}O_{2\,peak}$ and LA volume (r = 0.53), and $\dot{V}O_{2\,peak}$ and E/E' (r = 0.45) in 75 patients with NYHA II/III HF and an EF of <35%. In our study, we found no significant correlation between $\dot{V}O_{2\,peak}$ and LA volume (rho = 0.11) or E/E' (rho = 0.15). Donal *et al*. (2008) included patients with symptomatic HF and the mean age was 55, whereas the mean age in our study was 64. The age difference may have influenced the end result. In 243 HF patients with a mean age of 62, the observed relationship between E/E' and $\dot{V}O_{2peak}$ was closer to what we observed (r = 0.22) (Guazzi *et al.*, 2010a). Another study reported that in 486 patients, mainly referred to exclude CAD, resting E/E' and LA strain had independent correlations with exercise tolerance (Kusunose *et al.*, 2012). Again, the mean age in this study was 56. In addition, exercise duration was determined using the Bruce protocol on treadmill exercise tolerance tests, not CPETs. Importantly, the independent effects of E/E' and LA strain were small (partial r of 0.15 and 0.25 respectively) and for statistical reasons no other echocardiographic indices such as LV systolic function or LA size were included in the multivariate model, making it difficult to consider the effect of collinearity between these and the chosen covariates. Overall, it appears that even if the resting echocardiographic indices of LA size, LA function or LV diastolic function do offer incremental diagnostic information, the overall effects of these are small. It is

possible that any relationship between resting echocardiography and exercise tolerance is confined to patients with symptomatic HF and may be less evident in older patients or in patients specifically AF. Unadjusted $\dot{V}O_{2\,peak}$ has excellent prognostic predictive tolerance. $\dot{V}O_{2\,peak}$ is, however, heavily influenced by age, gender and body size. This study demonstrated that resting echocardiography was not better than demographic factors alone in predicting $\dot{V}O_{2\,peak}$.

4.5.1 Study Limitations

The study population is drawn from patients awaiting ablation for paroxysmal AF. On average, they had preserved LVEF and normal exercise tolerance. As such, our findings may not be applicable outside of this group. However, AF is common, with an estimated population prevalence of 2%, which is predicted to increase (European Heart Rhythm Association *et al.*, 2010). With respect to cardiac patients, at least 5% of over 55s can be expected to have AF (Heeringa *et al.*, 2006), with the risk of AF climbing with comorbid cardiovascular disease (Kannel *et al.*, 1982). Our patients were older, and had more comorbidities than is usually reported in similar studies.

4.6 Conclusions

This study demonstrated that resting echocardiography and CPET parameters are not related to each other and echocardiography parameters were unable to predict CPET. Height and weight were superior when predicting $\dot{V}O_{2\,peak}$ values. Both echocardiography and CPET provide a set of unique parameters and provide the clinician with valuable information about cardiac function and exercise tolerance. Testing patients at rest does not always provide a good overall assessment of patients symptoms as those often come on during exercise. This leads to the importance of using echocardiography whilst patients are exercising and this may be a more realistic method to assess cardiac function and obtain a true objective functional assessment. This study suggests that exercise tolerance and resting echocardiographic parameters do not show any relationships and the role of resting echocardiography in the assessment of patients with AF should be confined to underlying structural heart disease or severe LV dysfunction.

CHAPTER 5

PROGNOSTIC IMPORTANCE OF TISSUE VELOCITY IMAGING DURING EXERCISE ECHOCARDIOGRAPHY IN PATIENTS WITH SYSTOLIC HEART FAILURE

Presented at the European Society of Cardiology conference 2012
Presented at the British Society of Echocardiography – winner of the young investigator award

van Zalen, J., Podd, S., Raju, P., McIntosh, R., Beale, L., Brickley, G., Sturridge, L., Patel, N., Lloyd, G. (2013) Using Tissue Doppler systolic velocities to determine contractile reserve in heart failure patients is a strong predictor for survival and hospitalisation. *European Heart Journal - Cardiovascular Imaging* 13; suppl 1 (Club 35 poster)

Appendix D

Published in Echo Research and Practice

van Zalen, J.J., Patel, N.R., Podd, S., Raju, P., McIntosh, R., Brickley, G., Beale, L., Sturridge, LP., Lloyd, G. (2015). Prognostic importance of tissue velocity imaging during exercise echocardiography in patients with systolic heart failure. *Echo Research and Practice* 2(1); 19-27

Appendix E

5.1 Abstract

Resting echocardiography measurements are poor predictors of exercise tolerance and symptoms in patients with HF. Exercise echocardiography may provide additional information and can be expressed using LVEF, or diastolic parameters (E/E'), but LVEF has some major limitations. S' provides a measure of longitudinal systolic function, which is relatively easy to obtain and shows a good relationship with exercise tolerance. The objective of this study was to investigate the relationship among S', E/E', $\dot{V}O_{2peak}$ and LVEF obtained during exercise echocardiography and both mortality and hospitalisation. A secondary objective was to compare S' measured using a simplified two-wall model. A total of 80 patients with stable HF underwent exercise echocardiography and simultaneous CPET. Volumetric and TVI measurements were obtained, as was $\dot{V}O_{2peak}$. Of the total number of patients, 11 died and 22 required cardiac hospitalisation. S' at peak exertion was a powerful predictor for death and hospitalisation. Cut-off points of 5.3 $cm \cdot s^{-1}$ for death and 5.7 $cm \cdot s^{-1}$ for hospitalisation provided optimum sensitivity and specificity. This study suggests that, in patients with systolic HF, S' at peak exertion calculated from the averaged spectral TVI systolic velocity of six myocardial segments, or using a simplified measure of two myocardial segments, is a powerful predictor of future events and stronger than LVEF, diastolic velocities at rest or exercise and $\dot{V}O_{2peak}$. Results indicate that measuring S' during exercise echocardiography might play an important role in understanding the likelihood of adverse clinical outcomes in patients with HF.

5.2 Introduction

Systolic HF is a major cause of mortality and morbidity, and its prevalence is increasing due to the ageing population (Townsend *et al.*, 2012). It is conventionally defined by demonstrating typical clinical symptoms and signs associated with compatible findings on a resting echocardiogram (McMurray *et al.*, 2012). Patients with systolic dysfunction respond to a range of physical and medical therapies, but nonetheless have a poor prognosis (Meta-analysis Global Group in Chronic Heart Failure, 2012). Resting echocardiography and particularly LVEF has been shown to be a poor predictor of exercise tolerance (Benge *et al.*, 1980; Carell *et al.*, 1994). Several studies have suggested the additional value exercise echocardiography has on exercise tolerance and symptoms (Carell *et al.*, 1994; Rubis *et al.*, 2009; Witte *et al.*, 2004) and prognosis (Florea *et al.*, 2000; Grayburn *et al.*, 2005; Wang *et al.*, 2003, 2005). Exercise echocardiography adds prognostic value in patients with myocardial ischaemia secondary to coronary artery disease (Bountioukos *et al.*, 2004; Sicari *et al.*, 2008). Furthermore echocardiographic data during exercise provides additional information regarding patients' overall exercise capacity (Agricola *et al.*, 2004). HF patients demonstrating an increase in LVEF of 5% (in absolute terms) or more during exercise echocardiography have a better prognosis (Bax *et al.*, 1999; Pedone *et al.*, 2005; Werner *et al.*, 1994). LVEF can be challenging to obtain reliably and has some major limitations including a lack of reproducibility, dependence on loading conditions and it only describes maximum displacement at the end of systole meaning the longitudinal component of systolic function is not completely described. Systolic annular velocities obtained during exercise echocardiography shows a strong relationship with exercise tolerance (Ciampi *et al.*, 2013; Rubis *et al.*, 2009) and the change in early diastolic velocity has also proven predictive (Sekiguchi *et al.*, 2009). The relationship between both systolic and diastolic velocities and prognosis however remains undetermined. Therefore the objective of this study was to investigate whether S', E/E', $\dot{V}O_{2peak}$ and LVEF, all of which describe different aspects of cardiac function, would relate to mortality and cardiac hospitalisation in an established cohort of patients with systolic HF. It was hypothesised that peak S' and $\dot{V}O_2$ would be the strongest prognostic parameters for mortality and hospitalisation.

5.3 Methods

This was a retrospective longitudinal study of 80 patients with systolic HF participating in cohort studies undertaken at our institution using the same echocardiography and CPET protocols (McIntosh *et al.*, 2013) (explained in more detail below). All patients were medically treated for systolic HF and had been stable on medical therapy for at least one month prior to study inclusion. The definition of systolic HF was made by the combination of appropriate symptoms and a depressed LV on resting echocardiography. Exclusion criteria included unstable angina, symptomatic angina, evidence of reversible ischaemia, percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) within the last 6 months, severe lung disease or poor echocardiographic windows. Informed written consent was obtained and all studies were approved by the local ethical committee.

5.3.1 Echocardiography

Echocardiography was performed using a GE Vivid 7 platform (Vingmed-General Electric, Horten, Norway) equipped with a phased-array 3.5 MHz transducer. Two-dimensional, spectral Doppler and TVI were obtained at rest and during exercise. LV volumes and LVEF were calculated using Simpson's biplane method in the apical four-chamber and two-chamber views. Transmitral Doppler was obtained by placing a PW Doppler sample volume at the tips of the mitral leaflets. PW Doppler for $\dot{Q}$ assessment was taken in the 5-chamber view one centimetre below the aortic valve. TVI imaging was performed with the sample volume placed at mitral annulus in the 3-apical views. Exercise S' (defined as the highest velocity during systole after the end of isovolumetric contraction) was obtained from 6 peri-annular sites of the mitral annulus (septal, lateral, inferior, anterior, posterior, anteroseptal). At least 3 cardiac cycles were obtained and S' was averaged for each segment and all available S' were averaged. At instances where a reproducible TVI recording was not achieved, all available recordings were used to calculate the average. Myocardial velocity during early diastole (E') was measured on the lateral wall because this was laid down in one of the study protocol (because of the inclusion of a proportion of patients who had undergone previous

cardiac surgery, in whom septal diastolic velocity might not have been representative). Images were obtained in real time and analysed after each study. Images were stored offline.

5.3.2 Cardiopulmonary exercise test

A semi-recumbent cycle ergometer (ERG 911 S/L, Schiller, Baar, Switzerland) was used. Peak $\dot{V}O_{2\,peak}$ was used as the main outcome variable as it has been previously shown to be a strong predictor of mortality in systolic HF patients (Arena *et al.*, 2004; Poggio *et al.*, 2010). Patients were asked to continue to take their medication as usual when tested. At the start of the test a 3 minute rest period was included followed by a 3 minutes warm up period. Exercise protocols were individually determined based on functional status. Work rate (5, 10, 15 or 20 W) increased every minute until voluntary exhaustion aiming for 6-10 minutes of exercise. HR, blood pressure and oxygen saturation were monitored throughout. $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}_E$ were continuously measured and derived using a calibrated breath-by-breath analyser (Schiller Powercube AT-104 PC, Ganzhorn, Baar, Switzerland). Echocardiography measurements commenced when patients were close to finishing the test when the RER was exceeding 0.95 and if patients were not taking beta blockers in combination with a peak predicted HR>85%. All measurements were taken within 90 seconds of finishing exercise. Patients were verbally encouraged to exercise until maximal exertion. $\dot{V}O_{2\,peak}$ was expressed as the highest value from an average of 30s during the final stage of the exercise test.

5.3.3 Follow up

All-cause mortality and cardiac hospitalisation end points were evaluated by cross referencing with the hospital information system (which is linked to the UK registry of death), the clinical case notes, contacting the primary care physician and where necessary contacting the patient by telephone. No patient was lost to follow-up. Where hospitalisations had occurred, all best endeavours to evaluate the notes were made to ensure that the hospitalisation was HF related. Data on re-admission were based on the primary diagnosis at discharge.

5.3.4 Statistical analyses

All data is presented as mean ± SD or percentage for continuous variables and categorical data are presented as absolute values and percentages. Pearson correlation coefficients or Spearman coefficients were used to determine the relationship between echocardiographic variables and exercise tolerance. Differences were investigated using the student t-test for continuous data and the chi-square test for categorical data. All variables were assessed for univariate statistical significance using a Cox's proportional hazard regression model for mortality and hospitalisation. All significant predictors of outcome were entered into a multivariate Cox's proportional model (forward selection) to identify the strongest predictors of mortality or cardiac hospitalisation. Another Cox's regression analysis was carried out interchanging the average systolic velocities for the average of the septal and lateral walls. Data from the Cox's regression analysis is presented as hazard ratios with 95% confidence intervals. Receiver operating characteristics (ROC) curves were used to determine the optimal prognostic threshold value (highest combination of sensitivity/specificity) for mortality and hospitalisation. Interobserver variability was undertaken from 12 randomly selected participants and intraclass correlations (ICC) were calculated. All statistical analyses were carried out SPSS version 20.0; SPSS inc, Chicago, USA. A p-value of <0.05 was considered significant.

5.4 Results

Baseline characteristics can be found in table 5.1. A total of eighty patients were included in the study, 11 patients died and 22 required non-elective hospital admissions during a median follow up of 24 months (range 3 - 40 months). Of the remaining number of patients, 50 patients suffered from ischaemic heart disease, of these 16 patients had a previous CABG and 13 patients had a previous PCI. A proportion of patients (n=23) previously underwent CRT prior inclusion to the research study, 30 patients had been clinically approved to receive CRT and the remaining 27 did not qualify for CRT at the time of the study. Although no significant difference were found for the presence of ischaemic heart disease, there was a trend observed for hospitalisation (p=0.25) and survival (p=0.15). No differences in age, gender,

electrolytes, hypertension, left bundle branch block, diabetes, non-significant valvular heart disease, presence of CRT, previous CABG or PCI were observed between those with and without events. A difference was observed for the use of angiotensin II Receptor Blocker (ARB) and diuretics for patients who had been hospitalised. No other difference in drug history was observed (Table 5.1).

Of 480 available segments from TVI analysis, 92% was positively identified at rest vs. 81% during exercise echocardiography. All six myocardial segments were evaluated in 58 patients at rest and 34 patients during exercise. The septal and lateral systolic velocities were identified in all 80 patients at rest and in 78 patients during exercise. The apical long axis view was most frequently not evaluable, in particular the anteroseptal segment. Nevertheless, in 79 patients at rest and in 72 patients during exercise at least 4 segments were accurately identified. The mean TVI value of all six segments correlated well with the mean of the septal and the lateral wall for rest ($r=0.93$, $p<0.001$) and exercise ($r=0.94$, $p<0.001$). Maximal exercise tolerance described using $\dot{V}O_{2peak}$ was significantly higher in survivors than non-survivors (1.2 ± 0.4 L·min^{-1} vs. 0.9 ± 0.3 L·min^{-1}, $p=0.04$) However no difference was found between patients who were hospitalised and those who were not (1.2 ± 0.5 L·min^{-1} vs. 1.1 ± 0.3 L·min^{-1}. A regression analysis showed a weak relationship between $\dot{V}O_{2peak}$ and resting and exercise LVEF ($r=0.35$, $p<0.05$; $r=0.5$, $p<0.05$ respectively), while a moderate correlation was found for exercise S' ($r=0.66$, $p<0.001$). Echocardiographic, exercise and functional parameters for survivors and non survivors, as well as those who were and were not hospitalised is presented in table 5.2. There was a significant difference in systolic velocities at rest and exercise, LVEF at rest and exercise, E/E' at rest and exercise, $\dot{V}O_{2peak}$, and end diastolic dimensions between survivors and non-survivors. Fewer differences were observed between those who were and were not hospitalised, although once again S', LVEF at rest and end diastolic dimensions remained significant.

Table 5.1: Baseline clinical characteristics. Data is expressed as mean ± SD or as number (%) of patients

	All patients	Survivors (n=69)	Non-Survivors (n=11)	No hospitalisation (n=58)	Hospitalisation (n=22)
Age (years)	72 ± 9	71 ± 9	74 ± 7	71 ± 10	74 ± 7
Male	51 (64%)	44	7	39	12
IHD	50 (63%)	41	9	34	16
Hypertension	23 (29%)	19	4	16	7
LBBB	42 (53%)	38	4	32	10
Diabetes Mellitus	15 (19%)	14	1	10	5
Valvular heart disease	9 (11%)	7	2	6	3
CRT	23 (29%)	19	4	15	8
CABG	16 (20%)	15	1	11	5
PCI	13 (16%)	10	3	9	4
ACE inhibitor	50 (63)	42	8	32	18
Beta-blocker	57 (71%)	49	8	43	14
Digoxin	8 (10%)	7	1	6	2
Amiodarone	17 (21%)	13	4	11	6
ARB	24 (30%)	21	3	21*	3

	All patients	Survivors (n=69)	Non-Survivors (n=11)	No hospitalisation (n=58)	Hospitalisation (n=22)
Diuretic	59 (74%)	49	10	39*	20
Statin	54 68%)	49	5	39	15
Serum creatinine	105 ± 35.9	103 ± 34	121 ± 45	101 ± 32	118 ± 42
Serum sodium ($mmol \cdot l^{-1}$)	139 ± 3.0	139 ± 3	140 ± 3	140 ± 3	139 ± 3
Resting HR ($beats \cdot min^{-1}$)	68 ± 15	67 ± 15	71 ± 16	68 ± 16	67 ± 11
Exercise HR ($beats \cdot min^{-1}$)	99 ± 23	99 ± 22	96 ± 16	102 ± 24	91 ± 20
Rest $\dot{Q}$ ($L \cdot min^{-1}$)	3.9 ± 1.4	3.9 ± 1.4	3.7 ± 1.3	3.9 ± 1.4	3.9 ± 1.6
Exercise $\dot{Q}$ ($L \cdot min^{-1}$)	6.7 ± 2.2	6.9 ± 2.3	5.4 ± 1.6	6.9 ± 2.3	6.3 ± 2.0

* $P < 0.05$

ACE - angiotensin-converting-enzyme, ARB - Angiotensin II Receptor Blocker, CABG – coronary artery bypass graft, PCI – percutaneous coronary intervention, CRT – Cardiac Resynchronisation Therapy, IHD – ischaemic heart disease, LBBB - left bundle branch block; HR – Heart rate; $\dot{Q}$ – cardiac output

Table 5.2: Mean echocardiographic, exercise and functional parameters (Mean ± SD)

	Survivors (n=69)	Non-Survivors (n=11)	No hospitalisation (n=58)	Hospitalisation (n=22)
S' at rest ($cm \cdot s^{-1}$)	5.4 ± 1.6	3.7 ± 1.2*	5.3 ± 1.7	4.5 ± 1.5[§]
S' at exercise ($cm \cdot s^{-1}$)	7.1 ± 2.2	4.4 ± 1.3*	7.2 ± 2.4	5.5 ± 1.6[§]
LVEF at rest (%)	33 ± 11	24 ± 6[§]	33 ± 10	27 ± 11*
LVEF at exercise (%)	40 ± 14	28 ± 8*	39 ± 14	35 ± 13
E' at rest ($cm \cdot s^{-1}$)	6.4 ± 2.6	5.4 ± 2.1	6.4 ± 2.6	5.9 ± 2.3
E' at exercise ($cm \cdot s^{-1}$)	10.1 ± 4.6	7.1 ± 2.3	10.2 ± 4.7	8.5 ± 3.8
E/E' at rest	12.6 ± 7.4	18.7± 9.0*	12.6 ± 7.9	15.0 ± 7.2
E/E' at exercise	12.1 ± 7.2	18.2 ±7.1*	12.2 ± 7.7	14.8 ± 6.8
$\dot{V}O_{2\,peak}$ ($L \cdot min^{-1}$)	1.2 ± 0.4	0.94 ± 0.3*	1.2 ± 0.5	1.1 ± 0.3
$\dot{V}O_{2\,peak}$ ($mL \cdot kg^{1} \cdot min^{-1}$)	15.1 ± 4.4	12.5 ± 2.9	15.1 ± 4.4	13.8 ± 3.9
EDV (mL)	158 ± 59	180 ± 63	161 ± 61	162 ± 54
ESV (mL)	108 ± 46	139 ± 56	109 ± 48	121 ± 49
EDD (mL)	5.8 ± 0.8	6.5 ± 0.9[§]	5.8 ± 0.8	6.3 ± 0.9[§]
ESD (mL)	4.8 ± 0.9	5.6 ± 1.4	4.7 ± 1.0	5.6 ± 0.9[*]
LA diameter (cm)	3.9 ± 0.8	4.4 ± 0.6	3.9 ± 0.8	4.2 ± 0.6
NYHA	2.2 ± 0.8	2.5 ± 0.7	2.2 ± 0.7	2.2 ± 0.8

*Survivors vs. non-survivors or hospitalisation vs. no hospitalisation P<0.01
[§] Survivors vs. non-survivors or hospitalisation vs. no hospitalisation P<0.05
LVEF - Left ventricular ejection fraction, S' – systolic velocity. E' - myocardial velocity early diastole. E/E' – transmitral to basal early diastolic velocity ratio, $\dot{V}O_{2\,peak}$ - peak oxygen uptake, EDV – end diastolic volume, ESV – end systolic volume, EDD – end diastolic dimensions, ESD – end systolic dimensions, LA – left atrium, NYHA – New York Heart Association class

Table 5.3: Univariate predictors of mortality and cardiac admission

Mortality	**HR (95% CI)**	**P-value**	**Hospitalisation**	**HR (95% CI)**	**P-value**
Rest S' ($cm \cdot s^{-1}$)	0.46 (0.29 – 0.75)	0.002	Rest S' ($cm \cdot s^{-1}$)	0.67 (0.50 – 0.90)	0.008
Exercise S' ($cm \cdot s^{-1}$)	0.47 (0.31 – 0.71)	<0.0001	Exercise S' ($cm \cdot s^{-1}$)	0.65 (0.52 – 0.83)	<0.0001
LVEF at rest (%)	0.91 (0.85 -0.98)	0.01	LVEF at rest (%)	0.94 (0.90 – 0.98)	0.008
LVEF at exercise (%)	0.93 (0.88-0.98)	0.01	E/E' at exercise	1.05 (1.00 – 1.09)	0.04
E/E' at rest	1.07 (1.00-1.14)	0.03	EDD (cm)	1.82 (1.03-3.20)	0.04
E/E' at exercise	1.07(1.01 – 1.12)	0.01	ESD (cm)	2.23 (1.31 – 3.77)	0.003
$\dot{V}O_{2\,peak}$ ($L \cdot min^{-1}$)	0.10 (0.01 – 0.76)	0.03	Creatinine	1.01 (1.00 – 1.02)	0.04
ESV (mL)	1.01 (1.00 – 1.02)	0.05	Diuretics	0.23 (0.05-1.00)	0.05

LVEF - Left ventricular ejection fraction, S' – systolic velocity. E' - myocardial velocity early diastole. E/E' – transmitral to basal early diastolic velocity ratio. $\dot{V}O_{2\,peak}$ - peak oxygen uptake, ESV – end systolic volume

Significant univariate predictors are given in table 5.3. None of the clinical characteristics in table 5.3 were univariate predictors for death; for hospitalisation only diuretics were a univariate predictor.

Aetiology of HF was not a univariate predictor for either mortality or hospitalisation. After all the variables that predicted mortality and hospitalisation (Table 5.3) on univariate Cox regression analysis were entered into a forward multivariate Cox regression model, only exercise S' emerged as a significant predictor of mortality (HR: 0.36; 95% CI: 0.19-0.67; p = 0.001) and hospitalisation (HR: 0.62; 95% CI: 0.45-0.85; p=0.003). This model retained its predictive power when exercise S' was substituted by the average septum and lateral S' for mortality (HR: 0.42; 95% CI: 0.24-0.73; p=0.002) and hospitalisation (HR: 0.54; 95% CI: 0.37-0.81; p=0.003). A ROC analysis was carried out for mortality and systolic velocity had the largest area under the curve of 0.86 (95% CI 0.75-0.96). A cut off of 5.3 $cm \cdot s^{-1}$ for exercise S' showed a sensitivity and specificity of 82% and 80% respectively for mortality. Similarly, for hospitalisation, a ROC analyses for exercise S' has an area under the curve of 0.71 (95% CI 0.58-0.83), which resulted in a cut-off of 5.7 $cm \cdot s^{-1}$ representing a sensitivity of 59% and a specificity of 74%. Kaplan-Meier curves were generated using these cut offs (Figure 5.1).

Interobserver variability measured by ICC was stronger for exercise S'; ICC: 0.96; (95% CI: 0.88-0.99) compared to exercise LVEF; ICC; 0.57 (95% CI:-0.82-0.92), exercise E'; ICC: 0.83; (95% CI: 0.38-0.95), and exercise E/E'; ICC: 0.84 (95% CI: 0.40-0.96). Similarly, for the intraobserver variability the ICC was stronger for TVI derived parameters, exercise S'; ICC: 0.97; (95%CI: 0.86-0.99), and exercise E' exercise E'; ICC: 0.99; (95% CI: 0.94-0.99) compared to exercise LVEF; ICC: 0.88; (95% CI: 0.50-0.96), and exercise E/E'; ICC: 0.85; (95% CI: -0.24-0.98).

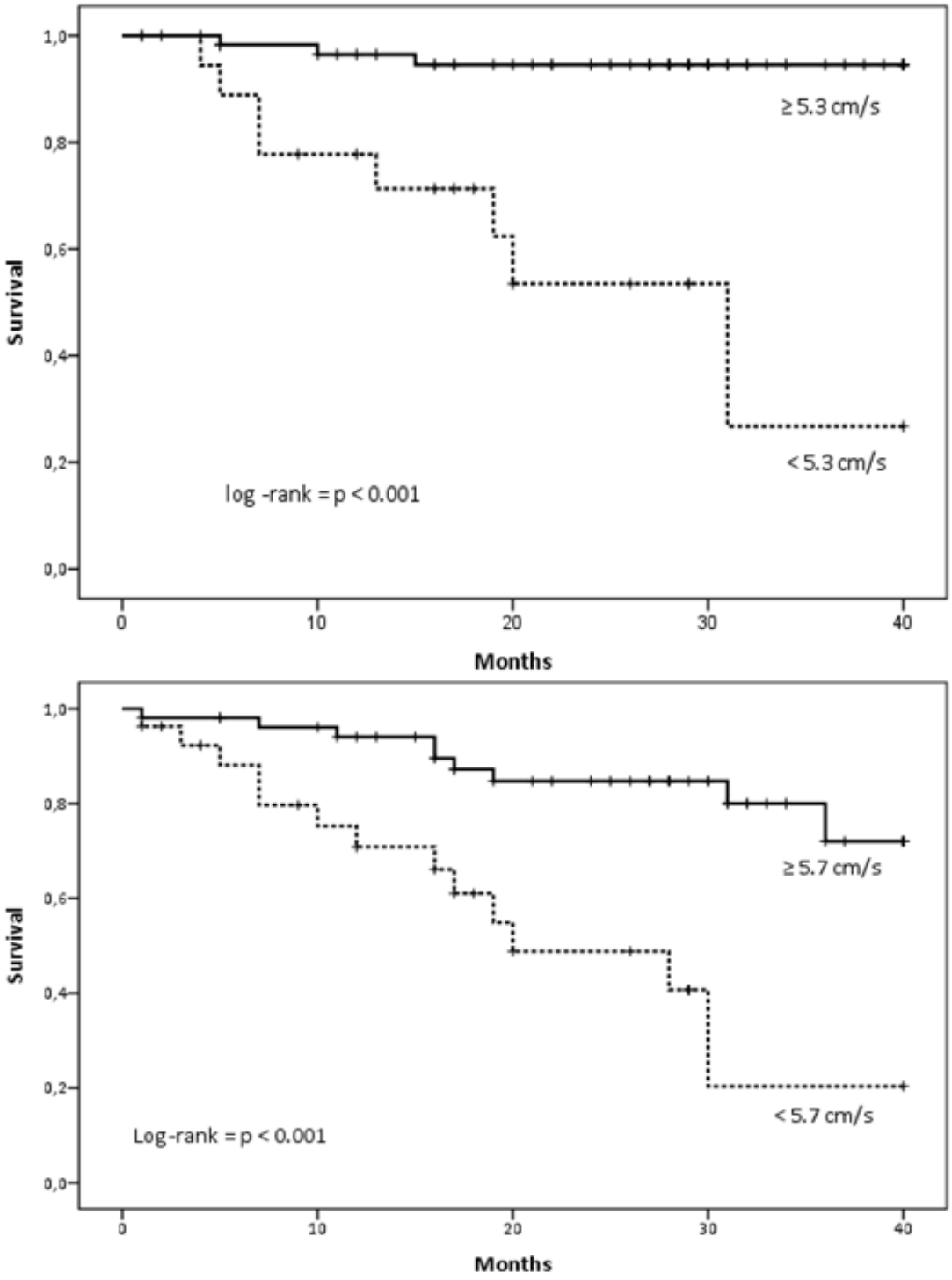


Figure 5.1: Kaplan-Meier curves for mortality (top) and hospitalisation (bottom)

5.5 Discussion

This study suggests that in patients with systolic HF, S' at peak exertion calculated from the averaged spectral TVI systolic velocity of six myocardial segments, or using a simplified measure of two myocardial segments, is a powerful predictor of future events and stronger than LVEF or diastolic velocities at rest or peak exercise, and $\dot{V}O_{2peak}$. It retains its prognostic value after adjustment for clinical data, peak exercise tolerance, functional parameters and other echocardiographic data. Exercise S' cut off points of 5.3 $cm \cdot s^{-1}$ for death and 5.7 $cm \cdot s^{-1}$ for hospitalisation provided optimum sensitivity and specificity which were 82% and 80% or mortality and 59% and 74% for hospitalisation. This only party agrees with the hypothesis set out for this study as both exercise S' and $\dot{V}O_{2peak}$ were hypothesised to have strong prognostic value. Surprisingly, exercise S' proved a stronger predictor than $\dot{V}O_{2peak}$ despite being moderately co-correlated, and $\dot{V}O_{2peak}$ having been highly predictive of mortality in other studies (Francis *et al.*, 2000; Guazzi *et al.*, 2010a). This study confirms the limitation of resting echocardiography in predicting either prognosis or exercise tolerance in systolic HF patients (Guazzi *et al.*, 2010b; Mogelvang *et al.*, 2009; Nikitin *et al.*, 2006; Wang *et al.*, 2003, 2005). Interobserver and intraobserver variability were excellent for S' at exercise unlike LVEF at exercise which was less reliable; this is in agreement with previous studies (McGowan and Cleland, 2003; Nikitin, *et al.*, 2003).

The most widely used parameter to characterise HF is resting LVEF, but this measurement can be challenging. The reasons why LVEF related poorly to both functional tolerance (Carell *et al.*, 1994; Clark *et al.*, 1994; Rubis *et al.*, 2009; Witte *et al.*, 2004) and prognosis (Florea *et al.*, 2000; Grayburn *et al.*, 2005; Guazzi *et al.*, 2010b; Wang *et al.*, 2003, 2005) are complex. The reproducibility of measurement remains sub-optimal, due partly to image quality and anatomical factors (Donal *et al.*, 2011). LVEF is a reflection of whole systolic myocardial displacement and may be more dependent on loading conditions than on other measures such as tissue velocity (Donal *et al.*, 2011; Marwick, 2003; Rubis *et al.*, 2009). Furthermore LVEF poorly describes longitudinal myocardial function which is often affected early in a variety of heart diseases. Previous studies have documented only a weak relationship between

LVEF either at rest or under stress conditions and exercise tolerance which is in agreement with our findings (Rubis *et al.*, 2009). LVEF during dobutamine stress, where loading conditions can be very different, has been shown to predict adverse outcome during echocardiography and nuclear scintigraphy (Otasevic *et al.*, 2006; Paraskevaidis *et al.*, 2001; Ramahi *et al.*, 2001). The inability to increase LVEF during stress echocardiography has been shown to be a strong predictor for mortality (Pedone *et al.*, 2005).

Both systolic and diastolic TVI measures, at rest and during exercise have previously been demonstrated to predict exercise tolerance (McIntosh *et al.*, 2013; Podolec *et al.*, 2008; Rubis *et al.*, 2010). A moderate relationship between $\dot{V}O_{2peak}$ and S' was demonstrated and both resting and exercise recorded TVIs were univariate predictors of mortality. The concept of diastolic reserve has gained considerable interest, particularly in patients with HF and preserved ejection fraction where changes in E and E' velocities predict exercise performance (Grewal, 2009; Podolec *et al.*, 2008). Resting tissue velocity data, particularly those describing diastole such as E' and A', have been shown to have prognostic value (Mogelvang *et al.*, 2009; Wang *et al.*, 2003, 2005). A large study by Grewal, (2009) found an independent association between left ventricular diastolic dysfunction and exercise tolerance. Systolic function was not reported as all patients had a preserved LV. Similar incremental prognostic results have been observed in both systolic HF (Wang *et al.*, 2005) and HF with preserved LVEF (Grewal, 2009; Little and Oh, 2009) for E' and E/E'. One complication when analysing all this data is the relatively close relationship between S' and E' making it difficult to determine which is the dominant influence. So while the primary end point of these studies may relate to diastolic reserve, there is also a significant positive association with systolic function that may not be fully appreciated. One of the main determinants of early diastolic motion (caused by mitral annular descent) is the release of energy stored during systole, and therefore, S' and other systolic measures also inevitably describe in part the behaviour of the myocardium during early diastole (Notomi *et al.*, 2006; Pacileo *et al.*, 2003).

Strain imaging is an alternative for describing myocardial deformation (Dandel *et al.*, 2009). An important disadvantage for TVI derived strain is the low spatial resolution which results in low reproducibly and therefore it is not routinely used in clinical practice (Dandel *et al.*, 2009). 2-dimensional strain speckle tracking has the clear advantage of being angle independent, but requires higher frame rates which may not be sufficient to properly track the increased HRs at exercise. This may result in under sampling, especially during exercise. Recent studies have suggested a potential benefit of speckle track derived strain and strain rate in detecting reversible ischaemia during dobutamine stress echocardiography, but routine use especially during exercise echocardiography is limited due to the limited range of HRs which can be sampled (Moonen *et al.*, 2009; Sicari *et al.*, 2008).

TVI imaging is available on most echocardiography platforms and peak systolic and diastolic velocities are reproducible and easy to obtain both at rest and on exercise (Nikitin *et al.*, 2004). The ability to achieve systolic velocities with a high degree for inter- and intra-reproducibility was confirmed in this study, unlike LVEF. The biggest challenge in achieving averaged TVI measurements is that all walls cannot always be assessed in all patients due to image quality. In this study, more than half of the echocardiographic TVI measures were not satisfactorily obtained from all six myocardial walls, hence the simplified protocol where only average readings for the septal and lateral walls were tested. This simplified protocol gave results that were not significantly different from the average of all six walls. This may be because although an underlying segment may be akinetic, unlike deformation imaging, it still shows an apical long axis velocity because it is tethered to other contracting segments. Thus the annular velocity at any one point is an aggregate of myocardial contractility in that and adjacent segments.

5.5.1 Study limitations and areas for further research

A significant weakness of this study is that E' was measured only in the lateral wall and not averaged over multiple segments and thus may have misrepresented patients with regional wall motion abnormalities. Møller *et al.*, (2001) reported that E/E' was a

strong independent predictor of death and hospital readmission in a cohort of patients with previous myocardial infarction. Strain analysis either by TVI or by speckle tracking was not used in this study and this might have provided further insights into global and regional deformation. The only CPET variable analysed was $\dot{V}O_{2peak}$. Although $\dot{V}O_{2peak}$ correlated with exercise S', it failed to reach statistical significance as a predictor of hospitalisation. There might be a closer relationship with a submaximal parameter such as OUES or $\dot{V}O_2$ at the VT. All patients were considered clinically stable from an ischaemic point of view at enrolment and hence formal wall motion scoring was not undertaken. It is possible that this might have produced similar results due to inducible ischaemia. The study population was small and selective as patients were elderly and over half of the patients suffered from stable ischaemic heart disease. Death and hospitalisations were analysed separately as in retrospective analysis, and it can be more challenging to interpret hospitalisation data with absolute certainty and hence a single combined end point was not deemed appropriate.

5.6 Conclusion

While contractile reserve is recognised as a predictor of adverse cardiac events, this is the first study to demonstrate that the measurement of peak systolic myocardial velocities derived from TVI during exercise predicts death and hospital admissions to a greater extent than either diastolic reserve or LVEF. A simplified two wall protocol, which makes evaluation even more straightforward, gave equivalent results. Resting echocardiographic and clinical parameters were less supportive in predicting future events in this study including $\dot{V}O_{2peak}$. While prospective studies should test the hypotheses and particularly the cut off points identified in this study, the results suggest that measuring S' during exercise echocardiography might have an important role in understanding the likelihood of adverse clinical outcomes in HF patients.

CHAPTER 6

CONTRACTILE RESERVE AND RESPONSE TO CARDIAC RESYNCHRONISATION THERAPY IN PATIENT WITH HEART FAILURE

Presented at the Heart Rhythm UK conference 2016, Birmingham

van Zalen, J., Patel, N., Beale, L., Brickley, G., Lloyd, G. (2016) Contractile reserve expressed as systolic velocity does not predict response to CRT. *EP Europace* 18; suppl 2

Appendix D

6.1 Abstract

CRT improves symptoms of HF in the majority of patients. However 30% of patients do not feel any clinical benefit after CRT implantation. Previous research found a good relationship with exercise S' and prognosis. The aim of this study was to determine if exercise S' was able to predict a positive response to CRT. Thirty-four patients clinically selected for CRT were included. Response to CRT was determined using a reduction in ESV of at least 15%. All patients completed exercise echocardiography with simultaneous CPET, a 6-MWT, and completed QoL questionnaires prior and three months post CRT implantation. 68% patients of patients were classified as responders to CRT. Overall study population showed significant improvements in LVEF, NYHA, quality of life (QoL), S', end diastolic and systolic volumes, and 6-minute walk test (6-MWT) distance. No improvements were observed in either exercise S' or $\dot{V}O_{2\,peak}$ which may have been caused by the short follow-up time or the inclusion of patients unlikely to benefit from CRT. CRT response rate is highly dependent on criteria used to define response, and the criteria vary dramatically between clinical trials causing a large variety in results dependent which definition is chosen, which makes it difficult to compare studies. This study showed that exercise S' was not able to describe a group of patients more likely to respond to CRT therapy. Exercise S' is an excellent predictor for cardiac hospitalisation and mortality and should be continued to be used as a prognosticator for future events in patients with HF.

6.2 Introduction

CRT has revolutionised the treatment of advancing HF and has proven to be very effective in patients presenting with severe HF refractory to optimal medical treatment (Cleland *et al.*, 2005). Despite CRT treatment about 30% of eligible patients do not have a beneficial symptomatic response (Bristow *et al.*, 2004) and a significant number of patients do not show echocardiographic improvement in left ventricular dimensions and/or function (Yu *et al.*, 2003, 2004). The use of various echocardiographic parameters have been reported to predict a favourable response, especially left ventricular reverse remodelling and improvement of systolic function (Bax *et al.*, 2004; Pitzalis *et al.*, 2002). However, the PROSPECT trial concluded that no resting echocardiography parameter proved useful in identifying patients more likely to benefit from CRT (Chung *et al.*, 2008). Among various echocardiographic methods, TVI has been most recently examined, as it can describe regional myocardial function and timing of activation with a high temporal resolution (Penicka *et al.*, 2004; Søgaard *et al.*, 2002; Yu *et al.*, 2004). It is increasingly understood that the extent of ventricular dyssynchrony is dynamic and changes between rest and exercise in a high proportion of HF patients, and this may be associated with a worse prognosis (Lafitte *et al.*, 2006; van Zalen *et al.*, 2015). Exercise S' and $\dot{V}O_{2\,peak}$ have been known to have a good relationship in a range of patients and healthy controls (McIntosh *et al.*, 2013). Patients with a reduced exercise S' during exercise are more likely to suffer from cardiac hospitalisation and mortality. The aim of this study was to establish whether exercise S' could predict a positive response to CRT. It was hypothesised that exercise S' would predict a positive response in patients clinically selected for CRT.

6.3 Methods

6.3.1 Patients

The study was approved by the National Ethics Committee (Appendix A) and all patients gave written informed consent before starting study procedures. Fifty-seven patients gave informed consent and completed the baseline visit. Inclusion criteria were a reduced LVEF below 35%, symptomatic HF despite optimal medical treatment, adequate echocardiographic windows and clinically selected for CRT according to contemporary guidelines (some patients with right bundle branch block and narrow QRS were included who would not be considered eligible currently). Nineteen patients were excluded for the following reasons: death before study finished (6 patients), cerebrovascular accident (1 patient), too unwell to continue to participate (1 patient), unable to cycle (1 patient), claustrophobic with the CPET mask (1 patient), withdrew (1 patient), LV lead displacement (2 patients), did not qualify for CRT - LVEF greater than 35% on study echo (6 patients). A total of 34 patients scheduled for CRT implantation completed baseline and 3 months testing. Indications for CRT implantation were according to the current guidelines at the time of inclusion. Exclusion criteria included unstable angina, percutaneous coronary intervention or coronary artery bypass grafting within last 6 months, cerebrovascular accident within 3 months, severe lung disease, or severe valvular disease.

6.3.2 Study protocol

Rest and exercise echocardiography in combination with CPET on a semi recumbent cycle ergometer (Ergoline; Schiller, Switzerland) was performed before and 3 months post CRT implantation. During both visits Quality of Life (QoL) was assessed using the Minnesota living with HF questionnaire (Rector *et al.*, 1987) and patients completed a 6-MWT.

6.3.3 Echocardiography

Echocardiography was performed using a GE Vivid 7 or 9 platforms (Vingmed-General Electric, Horten, Norway) equipped with a phased-array 3.5 MHz transducer. Two-

dimensional, Doppler, and TVI was obtained at rest and during exercise. LV volumes and LVEF were calculated using Simpson's biplane method in the apical four-chamber and two-chamber views. Transmitral Doppler was obtained by placing a PW Doppler sample volume at the top of the mitral valve leaflets. PW Doppler for $\dot{Q}$ assessment was taken in the five-chamber view 1 cm below the aortic valve. Spectral pulsed wave TVI was obtained for the six peri-annular sites of the mitral annulus (septal, lateral, inferior, anterior, posterior, and anteroseptal). Three cardiac cycles were obtained and averaged. Response to CRT was determined using a reduction in end- systolic volume of at least 15% (Pitzalis *et al.*, 2002; Yu *et al.*, 2003). Responders and non-responders were compared to determine differences in response to CRT.

6.3.4 Cardiopulmonary exercise test

A semi-recumbent cycle ergometer (ERG 911 S/L, Schiller, Baar, Switzerland) was used in combination with a breath-by-breath analyser (Schiller Powercube AT-104 PC, Ganzhorn, Baar, Switzerland or the Cosmed, Quark CPET, Rome, Italy). $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ were continuously measured. Blood pressure, oxygen saturation and ECG were monitored throughout. Patients were asked to continue their medication as normal. After obtaining resting echocardiographic parameters, a 3 minute static rest period was included followed by a 3 minute unloaded warm up. Work rate then increased by 5, 10 or 15 W each minute individually determined based on patient's functional status and cadence was kept constant throughout. Patients were encouraged to continue cycling until voluntary exhaustion aiming to obtain between 8-12 minutes of exercise. Echocardiography measurements commenced when patients were close to finishing the test determined either by an RER > 0.95 and if patients were not taking beta-blockers in combination with a peak predicted HR > 85%. All measurements were taken within 90 seconds of completing exercise. Patients were verbally encouraged until maximal exertion. $\dot{V}O_{2\,peak}$ was calculated from the average 30 seconds during the final stage of the exercise test.

6.3.5 Statistical analyses

All data is presented as mean ± SD or percentage for continuous variables and categorical data is presented as absolute values and percentages. Paired student t-tests were used for parametric data and the Wilcoxon Signed Rank Test was used for non-parametric data to analyse improvements from baseline and after three months. Independent student t-tests and Mann Whitney U tests were used to determine differences between responders and non-responders. Correlation analyses was performed using either Pearson's (for parametric data) or Spearman's (for non-parametric data) correlation coefficient. Interobserver variability was undertaken from 10 randomly selected patients and intraclass ICC were calculated. All statistical analyses were carried out using the SPSS version 20.0; SPSS inc, Chicago, USA). A p-value of <0.05 was considered significant.

6.4 Results

Thirty-four patients completed baseline and follow-up testing. Baseline demographics for all patients are presented in Table 6.1. 68% of patients were classified as responders to CRT based on reduction in ESV of 15% or more. The majority of patients were male (61%), average age was 71 ± 8.7 years and the average QRS duration was 156 ± 23 ms. No differences between both responders and non-responders were observed pre-implant with respect to the major clinical characteristics (Table 6.1).

Table 6.1: Patient baseline demographics

	All patients (n= 34)	Non-responders (n=11)	Responders (n=23)
Male	22 (65%)	9	13
Age	71 ± 8.7	70.5 ± 8.0	73.4 ± 10.5
Height	169 ± 11	168 ± 9.8	172 ± 11.5
Weight	81.0 ± 19	81.8 ± 18.6	85.3 ± 19.1
QRS duration	156 ± 23	149 ± 32	160 ± 19.3
QRS >150 ms	25 (74%)	6 (54%)	19 (83%)
QRS < 120 ms	3 (8%)	3 (27%)	0 (0%)
NYHA 2/3	11 /23	3/8	8/15
IHD	21 (62%)	8	13
LBBB	25 (74%)	6	19
COPD	4(12%)	1	3
Diabetes	7 (21%)	1	6
Hypertension	15 (44%)	4	11
CABG	4 (12%)	2	2
PCI	5 (15%)	1	4
Smoking	5 (15%)	1	4

*IHD – ischaemic heart disease; LBBB – left bundle branch block; COPD – chronic obstructive pulmonary disease, CABG – coronary artery bypass graft; PCI – percutaneous coronary intervention

Baseline characteristics were similar for both responders and non-responders (Table 6.2). The primary end point of the study (S') did not differ between responders and non-responders at rest (5.1 ± 1.3 vs. 5.5 vs. 1.5 $cm \cdot s^{-1}$) or at exercise (6.4 ± 1.6 vs. 6.8 ± 2.2 $cm \cdot s^{-1}$; Figure 6.1; Table 6.2). No difference were found for resting S', exercise S', or delta S' between responders and non-responders (Figure 6.1).

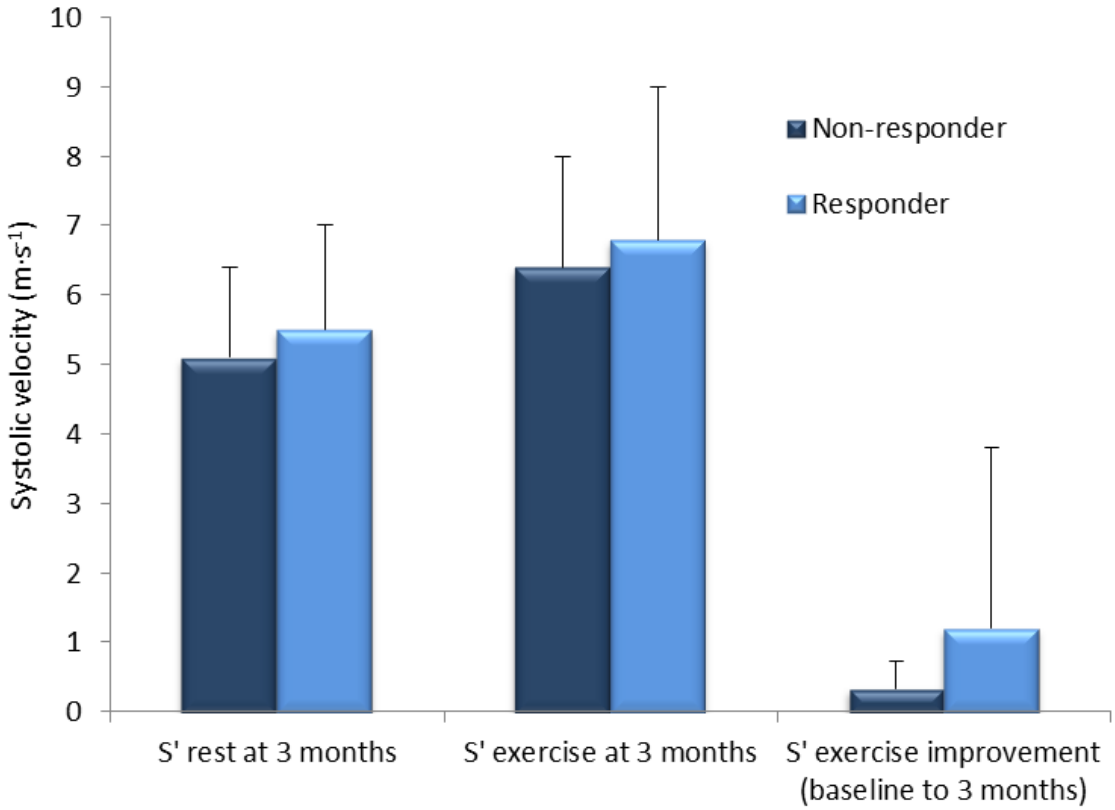


Figure 6.1: Systolic velocity (S') at rest and exercise differences between responders and non-responders

Responders showed improvements in NYHA class (-43%), QoL (-44%), LVEF (+68%), resting S' (+18%) and 6-MWT distance (31%), whereas non-responders only improved in NYHA (+35%), QoL (+47%), and LVEF (+32%) (Table 6.2, Figure 6.2). LVEF improved for all patients but responders showed a significant greater improvement in LVEF compared to non-responders (15.0 ± 6.7 vs. 8.0 ± 9.8%; p = 0.02). Responders showed a significant improvement in 6-MWT distance, however this improvement was not significantly different compared to non-responders (52.2 ± 98.3 vs. 12.3 ± 66.1 m; p=ns; Table 6.2).

If responder status was determined using a reduction in LVEF of more than 15% a significant difference was found between responders and non-responders for improvement in 6-MWT distance (49.8 ± 72.4 vs. 9.5 ± 31.6 m; p = 0.009). Furthermore when responder definition was defined by increase in LVEF over 5% and a reduction in NYHA class by more than 1, 6-MWT distance difference got worse for the non-responders.

Interobserver variability measured by ICC was strongest for exercise S'; ICC: 0.95; (95% CI: 0.81-0.99) compared to exercise LVEF; ICC; 0.57 (95% CI:-0.82-0.92). Similarly, for the intraobserver variability the ICC was strongest for exercise S'; ICC: 0.97; (95%CI: 0.89-0.99), compared to exercise LVEF; ICC: 0.57; (95% CI: -0.8-0.92).

Table 6.2: Parameters for all responders and non-responders; baseline vs. 3 months post CRT implantation

	Non-responder (n=11)		**Responder (n=23)**	
	Baseline	3 months	Baseline	3 months
Functional parameters				
NYHA	2.7 ± 0.5	1.8 ± 0.8*	2.7 ± 0.5	1.5 ± 0.6*
QoL	46.9 ± 21	27.1 ± 21*	52.4 ± 17.2	29.8 ± 18.3*
Echocardiographic parameters				
LVEF (%)	27.7 ± 6.8	35.7 ± 10.8§	26.7 ± 8.0	41.7 ± 6.6*
ESV (mL)	137 ± 65.3	141 ± 63.1	119 ± 35.2	68.3 ± 24.5
S' rest ($cm \cdot s^{-1}$)	4. 8 ± 2.1	5.1 ± 1.3	4.8 ± 1.3	5.5 ± 1.5§
S' exercise ($cm \cdot s^{-1}$)	6.0 ± 1.6	6.4 ± 1.6	6.4 ± 1.9	6.8 ± 2.2
LVOT VTI (cm^2)	15.1 ± 4.7	16.9 ± 5.5	17.6 ± 4.4	18.0 ± 2.4
Exercise parameters				
$\dot{V}O_{2\,peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	14.3 ± 5.7	14.0 ± 4.3	13.6 ± 3.8	13.5 ± 3.8
$\dot{V}O_2$ at the VT ($mL \cdot kg^{-1} \cdot min^{-1}$)	9.3 ± 2.6	10.2 ± 2.7	10.1 ± 2.0	10.0 ± 1.8
$\dot{V}_E / \dot{V}CO_2$ slope	32.3 ± 5.1	31.6 ± 2.1	31.6 ± 3.8	31.8 ± 3.0
OUES ($(mL \cdot min^{-1}) \cdot (L \cdot min^{-1})^{-1}$)	1454 ± 430	1440 ± 340	1428 ± 473	1450 ± 449
6-MWT (m)	331 ± 133	343 ± 146	278 ± 130	328 ± 137§

*Baseline vs. 3 months P<0.01; § Baseline vs. 3 months P<0.05

NYHA – New York Heart Association; QoL – quality of life; LVEF – Left ventricular ejection fraction; S' – Systolic velocity; LVOT VTI – left ventricular outflow tract velocity time integral; $\dot{V}O_{2peak}$ - peak oxygen uptake; VT – ventilatory threshold; OUES – oxygen uptake efficiency slope; 6-MWT – 6 minute walk test

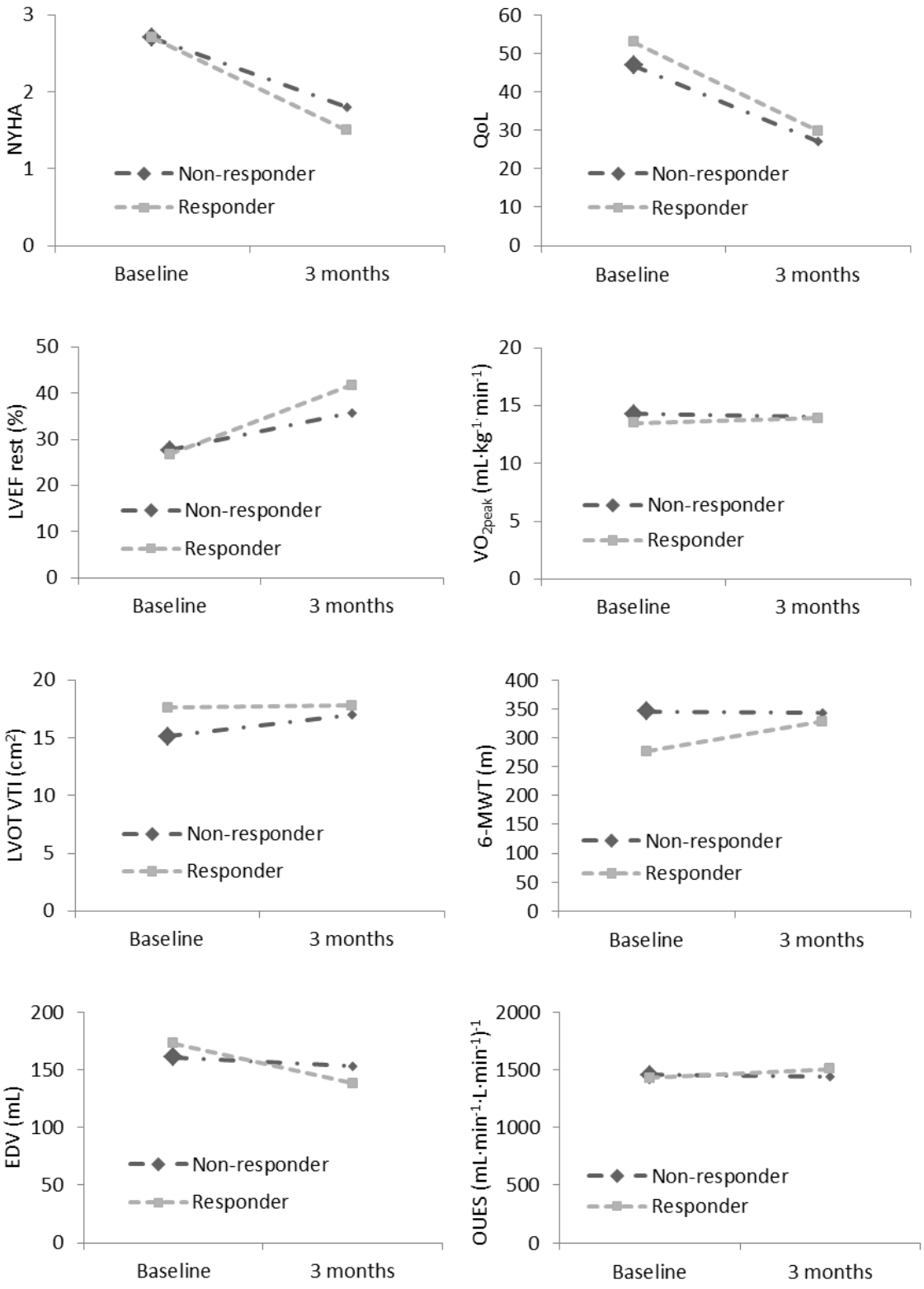


Figure 6.2: Secondary endpoints for responders and non-responders and change from baseline till 3 months. QoL – Quality of Life; LVEF – Left ventricular Ejection Fraction; $\dot{V}O_{2\,peak}$ – peak oxygen uptake; LVOT VTI – Left ventricular outflow tract velocity time integral; 6-MWT – 6 minute walk test; EDV – end diastolic volume; OUES – oxygen uptake efficiency slope

At three months following CRT implantation significant improvements were observed in many response parameters (NYHA class, QoL, LVEF, end diastolic and end systolic volumes, and S' at rest; Table 6.2). No improvements were observed in any CPET parameters, although there was an overall improvement in 6-MWT distance (Table 6.2).

Table 6.3: Parameters for all patients (n=34). Baseline and 3 months post CRT implantation

	Baseline	**3 months**
Functional parameters		
NYHA	2.7 ± 0.5	1.6 ± 0.7*
QoL	50.6 ± 18	28.9 ± 19.1*
Echocardiographic parameters		
LVEF (%)	27.0 ± 7.5	39.8 ± 8.5*
EDV (mL)	169 ± 55.5	145 ± 63.5*
ESV (mL)	125 ± 46.8	91.9 ± 53.0*
S' rest ($cm \cdot s^{-1}$)	4.8 ± 1.6	5.4 ± 1.4§
S' exercise ($cm \cdot s^{-1}$)	6.3 ± 2.1	6.7 ± 2.0
LVOT VTI (cm^2)	16.8 ± 4.6	17.7 ± 3.6
Exercise parameters		
$\dot{V}O_{2\,peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	13.8 ± 4.4	14.1 ± 3.4
$\dot{V}O_2$ at the VT ($mL \cdot kg^{-1} \cdot min^{-1}$)	9.8 ± 2.2	10.0 ± 2.1
$\dot{V}_E / \dot{V}CO_2$ slope	31.9 ± 5.6	31.7 ± 4.5
OUES ($(mL \cdot min^{-1}) \cdot (L \cdot min^{-1})^{-1}$)	1436 ± 453	1447 ± 412
6-MWT (m)	294 ± 131	333 ± 138§

*Baseline vs. 3 months P<0.01; § Baseline vs. 3 months P<0.05

NYHA – New York Heart Association; QoL – quality of life; LVEF – Left ventricular ejection fraction; S' – Systolic velocity; LVOT VTI – left ventricular outflow tract velocity time integral; $\dot{V}O_{2\,peak}$ - peak oxygen uptake; VT – ventilatory threshold; OUES – oxygen uptake efficiency slope; 6-MWT – 6 – minute walk test

6.5 Discussion

The main finding of the study was that exercise S' was unable to predict a positive response to CRT. This was in disagreement with the hypothesis set out at the start of this study. HF patients with a reduced exercise S' during exercise are more likely to suffer from cardiac hospitalisation and mortality (van Zalen *et al.,* 2015). However this relationship did not reflect response to CRT. Objective measures of exercise tolerance (including $\dot{V}O_{2\,peak}$) failed to improve 3 months after CRT implantation. $\dot{V}O_{2\,peak}$ has been known to have a strong relationship with exercise S' in a range of patients and healthy controls (McIntosh *et al.*, 2013). Therefore it is not surprising that neither variable were able to predict a response to CRT.

An explanation for the exercise parameters being unable to predict a positive response warrants further examination. A modest overall improvement was found for 6-MWT distance. It may that the relatively short follow-up time of 3 months did not allow for immediate changes in LV remodelling and $\dot{Q}$ to occur but the more subtle improvements in cardiometabolic function which depend heavily on peripheral muscle metabolic activity, which is down regulated in HF, takes longer to evolve. This is not the only study to show little or no effect of CRT implantation on $\dot{V}O_{2\,peak}$ (Beshai *et al.*, 2007; Abraham *et al.*, 2004). Currently there is no agreed optimal timeline to assess response. Exercise assessment stills play a significant role in determining response to CRT as objective assessment of a patients' exercise tolerance is vital to determine patients' well-being and is arguably the most important outcome variable.

The ultimate goal of CRT is symptomatic improvement and also improvements in cardiac function and outcomes. Major studies have demonstrated significant improvements in 6-MWT distance, $\dot{V}O_{2\,peak}$ and LVEF after CRT treatment (Cazeau *et al.*, 2001; Higgins *et al.*, 2003; Sutton *et al.*, 2003; Young *et al.*, 2003). CRT reduces mortality and morbidity and when compared to patients on medical therapy alone a significant event-free survival is observed (Lindenfeld *et al.*, 2007). It is vital to determine which patients will most likely benefit from CRT. Current guidelines state that patients should have a LVEF of less than 35%, NYHA class II - IV, and a QRS duration of at least 120 ms. CRT is not indicated in patients with a QRS duration less

than 120 ms. During recruitment for this current study patients were included who were clinically selected for CRT by a consultant cardiologist using current guidelines. However guidelines have undergone changes since recruitment of this study and patients with QRS duration of less than 120 ms do not qualify for CRT treatment anymore as guidelines actually advise against CRT in these patients (Brignole *et al.*, 2013). Three patients included in this study had a QRS duration below 120 ms. Not surprisingly, with knowledge of current research, these patient were classified as non-responders. Another criteria in the guidelines state that patients with non-LBBB QRS morphology should only be considered if QRS duration is more than 150 ms. This study had 4 patients included without LBBB and a QRS of less than 150 ms. Inclusion of these patients may have influenced outcome (Brignole *et al.*, 2013).

An overall improvement in NYHA class, QoL, LVEF, systolic and diastolic volumes, resting S', and 6-MWT distance were found for all patients. When patients were categorised in responder status based on a reduction in ESV of more than 15% post CRT, significant improvement in NYHA class, QoL and LVEF were found for responders and non-responders. However additional improvements in resting S' velocity and 6-MWT distance were found in the responder group. Defining responders status is done using either a clinical measurement assessment (NHYA, QoL, 6-MWT, $\dot{V}O_{2peak}$, or using LV reverse remodelling assessment (improvement in $\dot{Q}$, LVEF, reduction in LV ESV or EDV), or with the use of outcome measures (reduction in HF hospitalisation, morbidity and mortality) (Brignole *et al.*, 2013). Implementing the results of large clinical trials into daily clinical practice has proven problematic. Using different responder parameters may change the study outcome and without a prespecified chosen parameter and cut off it is difficult to reliably compare studies. CRT response is highly dependent on the criteria used to define CRT response. Studies have reported variation in response between 32 and 91% depending on which definition was chosen years (Bax *et al.*, 2003; Beshai *et al.*, 2007; Penicka *et al.*, 2004; Rocchi *et al.*, 2009). An additional problem is that symptomatic improvement does not always correlate with echocardiographic or functional assessment parameters, and vice versa.

A sub-analysis splitting our patients based on either an improvement in LVEF of more than 15% or changes in NYHA of more than 1 class in combination with an improvement in LVEF of more than 5% demonstrated on both occasions a significant greater 6-MWT distance for the responders which was not present in earlier analyses.

In addition a trend toward a higher exercise S' was found. This may suggest parameters obtained during exercise may play a role selecting patient for CRT but it also demonstrates the difficulty quantifying response to CRT and the large variety of results which become available dependent which definition is chosen.

Interobserver and intraobserver variability were excellent for S' at exercise unlike LVEF at exercise which was less reliable; this is in agreement with previous studies (McGowan and Cleland, 2003; Nikitin *et al.*, 2003; van Zalen *et al.*, 2015).

6.5.1 Study limitations

The sample size arguably was too small to accurately determine any significant changes between responders and non-responders. The sample size was too small to further subdivide the population without reducing the statistical power to an unacceptable level. Some included patients would not qualify for CRT using current guidelines and may have influenced the results. Furthermore the study was powered around the parameter of $\dot{V}O_{2\,peak}$ and in this population $\dot{V}O_{2\,peak}$ was not altered by CRT implantation.

6.6 Conclusion

An overall improvement was found in clinical measurements 3 months post CRT including QoL, and 6-MWT; in reverse remodelling measurements including LVEF, systolic and diastolic volumes and resting S'. However no improvements were observed in either exercise S' or $\dot{V}O_{2\,peak}$ which may have been caused by the short follow-up time or the inclusion or patients unlikely to benefit from CRT. CRT response rate is highly dependent on criteria used to define response, and the criteria vary dramatically between clinical trials causing a large variety in results dependent which definition is chosen. It also makes it difficult to compare studies. This study showed that exercise S' was not able to predict a group of patients more likely to respond to CRT therapy.

CHAPTER 7

ASYMPTOMATIC AORTIC STENOSIS: INSIGHTS FROM CARDIOPULMONARY EXERCISE TESTING COMBINED WITH ECHOCARDIOGRAPHY

Presented at the British Cardiac Society; 2017, Manchester

van Zalen, J., Badiani, S., Hart, L., Brickley, G., Beale, L., Marshall, A., Patel, N., Lloyd, G. (2017) The importance of contractile reserve when assessing asymptomatic patients with aortic stenosis. *Heart* 103; Suppl 5:A99

Appendix D

Under current review for publication in the International Journal of Cardiology

7.1 Abstract

Patients with asymptomatic severe AS still exhibit exercise limitation during objective exercise testing, but whether symptoms are due to the obstructiveness of the valve or underlying ventricular function remains poorly defined. While the aortic valve mean gradient is an easy parameter to measure, no consensus about the measurement of contractile reserve exists. Symptoms are difficult to obtain objectively due to aging of the population and multiple comorbidities. The aim of the study was to determine the level of reduced exercise tolerance, to establish the underlying determent of exercise ability, and any parameters predicting future events in patients with severe AS. Patients were followed up as part of an enhanced surveillance clinic which included CPET combined with exercise echocardiography and a measure of N-terminal pro-type natriuretic peptide (NT-ProBNP). Results revealed that a large proportion (41%) of supposedly asymptomatic patients had a lower than predicted % $\dot{V}O_{2\,peak}$ confirming that asymptomatic patients are more limited than they or their clinicians believe. Exercise ability in this population is poorly correlated to conventional measures of aortic valve severity but heavily dependent on the ability of the left ventricle to augment its longitudinal function during exercise (rho = 0.61; p<0.001). In multivariate analysis, exercise S' and age were the strongest independent predictors for $\dot{V}O_{2\,peak}$ with a R^2 for the model of 0.76. Exercise S' was independently correlated with NT-ProBNP which further confirms that the relationship to myocardial distress is stronger than conventional AS severity and LV remodelling parameters (r^2 =0.48). No patients died during follow up. However 9 patients required unplanned cardiac admission. Patients who required cardiac admission had a lower percentage predicted $\dot{V}O_2$ (77 ± 15.5 vs. 92% ± 18.0; p=0.03). A reduced exercise tolerance and more adverse ventricular remodelling predicted unplanned cardiac hospitalisation suggesting that where watchful waiting is an agreed strategy for patients with asymptomatic AS, a detailed assessment of a patient exercise tolerance using CPET should be undertaken. Combining CPET and exercise echocardiography and NT-ProBNP provides more insight into the subtle changes which occur when patients with severe AS begin to deteriorate. Overall focus should be more about the ventricle, especially under exercise conditions, and less about the valve.

7.2 Introduction

AS results in obstruction of blood flow through the aortic valve. The aetiologies of AS include, congenital, calcific (degenerative changes), and rheumatic. Degenerative AS is the leading indication for aortic valve intervention. AS is a common clinical condition in developed countries, and prevalence rises with aging of the population. Three to five percent of people aged 75 years or older suffer from AS which increases to around 4% in people over the age of 85 years (Nkomo *et al.*, 2006). Degenerative AS is a complex process of inflammation, fibrosis and calcification, which eventually leads to leaflet restriction and related haemodynamic consequences (Rajamannan *et al.*, 2011). The number of aortic valve replacements has doubled in recent years and is expected to continue to rise (Nkomo *et al.*, 2006). Echocardiography is used for the assessment of suspected or known valvular AS. The severity of AS and the LV response to chronic pressure afterload resulting in myocardial hypertrophy are evaluated at the same time (Otto, 2006). The ventricular response to chronic pressure overload and other consequences of AS such as subtle myocardial ischaemia (Otto, 2006) are also important to understand. Both processes combined, determine the rate when patients develop symptoms, adverse events, and the need of aortic valve intervention (Cioffi *et al.*, 2011; Pellikka *et al.*, 2005).

The natural history of AS is characterised by an extended latent period which can last between 10 – 20 years. While patients are asymptomatic during this period it is accepted that prognosis is excellent, however mortality rises dramatically from the onset of cardiac symptoms (breathlessness, syncope, angina)(Boasi *et al.*, 2012; Rosenhek *et al.*, 2010; Ross and Braunwald, 1968). Around two thirds of patients develop symptoms within five years from the diagnosis and around 75% of patients will have either died or received an aortic valve replacement (AVR) (Pellikka *et al.*, 2005). It is more challenging to establish symptoms in elderly patients who often have numerous co-morbidities and often suffer from reduced mobility, this makes the onset of symptoms related to the valve obstruction difficult to determine. Mortality risk in asymptomatic patients is associated with the severity of AS and its rate of progression (Otto, 1997; Pellikka *et al.*, 2005).

Current guidelines suggest that aortic valve intervention is indicated when patients become symptomatic or if there is echocardiographic evidence of imminent ventricular decompensation (Nishimura *et al.*, 2014). A delay to surgery may result in a decrease in myocardial performance, increasing myocardial fibrosis and remodelling which does not fully recover following surgery and this is associated with a significant increase in late morbidity and mortality (Treibel *et al.*, 2016, 2017). The timing to refer patients for aortic valve replacement is crucial and during assessment risks of valve replacement surgery are weighed up against the risk of adverse events without surgical intervention. Long-term durability and risks of a prosthetic valve should also be taken in consideration as well as the severity of the native valve stenosis which should be greater than the functional stenosis of the implanted prosthetic valve (Otto, 2006). Truly asymptomatic patients will not have any improvement in symptoms after aortic valve intervention and because there is such a low risk throughout the asymptomatic stage it is difficult to justify the risk of aortic valve intervention. But delaying surgery may result in a decrease in myocardial performance which might not fully recover following surgery. Determining why and when patients develop symptoms is not always straightforward especially in the elderly population. Around one third of 'asymptomatic patients' actually develop cardiac symptoms on exertion (Bhattacharyya *et al.*, 2013). Figure 7.1 summarises the reasons to consider either a watchful waiting strategy or consideration of an aortic valve intervention.

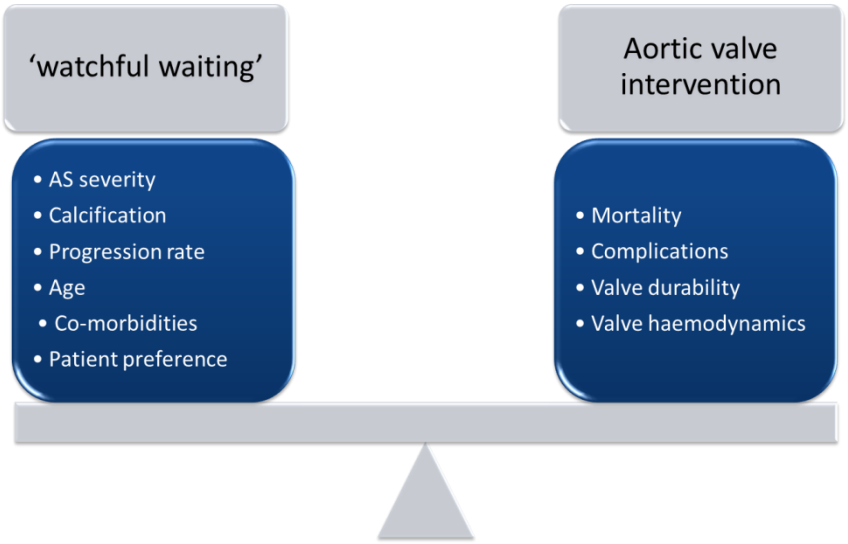


Figure 7.1: Reasons to consider for periodic monitoring vs. aortic valve intervention in patients with severe AS (Rashedi and Otto, 2015)

CPET is an objective assessment of patients' exercise tolerance and therefore can assist in unmasking any symptoms in AS (American Thoracic Society, 2003; Balady *et al.*, 2010). Studies have previously reported that over half of the included patients with 'asymptomatic' severe AS actually have a reduced $\dot{V}O_{2peak}$ (compared to the normal values) implying that a large proportion of self-reported asymptomatic patients are potentially actually limited by symptoms (Domanski *et al.*, 2017; Dulgheru *et al.*, 2013). CPET exercise echocardiography may provide additional information including the haemodynamic changes that occur during exercise. An increase in mean aortic pressure gradient of 18 mmHg or more during exercise is an independent predictor for death and hospital admissions (Lancellotti *et al.*, 2005). A recent review (Badiani *et al.*, 2016) from our institution, outlined the importance of managing AS as a left ventricular disease instead of focussing upon the severity of the valve stenosis. NT-ProBNP is a biomarker which is released in response to changes in stretch inside the LV. It has an established role in the diagnosis of HF especially when diagnosis HF in the acute setting. NT-ProBNP has good predictability in long-term morbidity and mortality (Januzzi *et al.*, 2006; McDonagh *et al.*, 2004). ESC guidelines have included NT-ProBNP in the diagnosing of HF (Ponikowski *et al.*, 2016). Using NT-proBNP may assist in the clinical management of asymptomatic patients with severe AS could cause LV pressure overload due to an adaptive process in order to maintain myocardial wall stress which may result in LV decompensation. Studies have demonstrated the usefulness NT-ProBNP may have to detect LV decompensation in patients with asymptomatic severe AS (Bergler-Klein *et al.*, 2004; Katz *et al.*, 2012; Orlowska-Baranowska *et al.*, 2008), however current guidelines have not yet included the routine measurement of NT-ProBNP.

Previous assumptions that AS progresses from normal systolic function and high gradients through to impaired function and low flow, hence low gradient is an oversimplification and at worst inaccurate as progression of these eventually severe AS phenotypes seem to follow different pathological pathways (Rassi *et al.*, 2014). AS is highly dependent on the responses of the myocardium and vasculature (Chin *et al.*, 2014; Dweck *et al.*, 2012). The aim of the present study was firstly to confirm the high level of reduced exercise tolerance in a cohort of patients with severe 'asymptomatic'

AS and secondly to determine if exercise ability in these symptom free patients was defined by obstruction to the aortic valve, ventricular remodelling or left ventricular contractile reserve. Thirdly, the study aimed to describe which parameter best predicted future events during clinical follow up. It was hypothesised that patients with AS would have reduced $\dot{V}O_{2\,peak}$ values and that exercise S' would show a relationship with $\dot{V}O_{2\,peak}$ and NT-ProBNP.

7.3 Methods

This was a retrospective longitudinal study of 32 patients with severe AS. The study was approved by the local audit committee from Eastbourne District General Hospital. For inclusion all patients were required to have either a calculated aortic valve area (AVA) of less than 1.0 cm^2, a peak aortic velocity (Vmax) of more than 4.0 $m{\cdot}sec^{-1}$ or a mean pressure gradient (mean PG) greater than 40 mmHg. All patients had a LVEF above 55%. Patients were followed up as part of an enhanced surveillance clinic which includes CPET combined with exercise echocardiography and NT-ProBNP measurements. All asymptomatic patients at Eastbourne District General Hospital with severe valvular lesions were referred to this clinic under supervision of consultant cardiologist. Patients' results were fed back to their referring cardiologist who made the clinical decision whether to refer for surgical intervention or continue watchful waiting. Exclusion criteria included self-reported symptoms associated with AS including dizziness, breathlessness, syncope, co-morbidities affecting symptoms, a positive test for reversible ischaemia, unable to exercise or poor echocardiographic windows.

7.3.1 Echocardiography

Echocardiography was performed using a GE Vivid 9 platform (Vingmed-General Electric, Horten, Norway) equipped with a phased-array 3.5 MHz transducer. All measurements were made according to the guidelines set by the British Society of Echocardiography (Rana *et al.*, 2012). At rest the LVOT diameter and ventricular internal dimensions were measured in zoom mode from the parasternal long axis view, measurements were taken immediately below the aortic valve hinge point. A protocol

was created and the following views were obtained both at rest and at peak exercise. The 2D apical views (4-chamber, 2-chamber, and apical long axis view), a 4-chamber view with colour TVI turned on in the background for retrospective analyses using colour TVI (Figure 2.17), CW and PW Doppler through the aortic valve (Figure 3.12), and 2D parasternal views (parasternal long axis, parasternal short axis at the papillary level). The mean trans-aortic gradient was measured using the modified Bernouilli equation. AVA was calculated using the continuity equation. LV volumes and LVEF were calculated using Simpson's biplane method in the apical four-chamber and two-chamber views (general methods section 3.4). Q-analysis was used retrospectively to determine rest and exercise S' (defined as the highest velocity during systole after the end of isovolumetric contraction) and was obtained from the lateral and septal wall and averaged at rest and exercise. Two-dimensional images of the three apical windows were obtained to determine if any wall motion abnormalities were present. The relative wall thickness (RWT) was calculated by multiplying the posterior wall thickness by two and dividing this by the LV end diastolic diameter. A value greater than 0.42 is suggestive of concentric hypertrophy and a value below 0.42 of eccentric hypertrophy (Lang *et al.*, 2005). Images were obtained in real time and analysed after each study. Images were stored offline.

7.3.2 Cardiopulmonary exercise test

A semi-recumbent tilting cycle ergometer (ERG 911 S/L, Schiller, Baar, Switzerland) was used. At the start of the test a 1 minute rest period was included followed by a 3 minutes unloaded warm up period. Exercise protocols were individually determined based on the patient functional status. Work rate (10-20 W) increased every minute until voluntary exhaustion aiming for 8-10 minutes of exercise. Patients were asked to continue to take their medication as usual. HR, blood pressure and oxygen saturation were monitored throughout. $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ were continuously measured and derived using a calibrated breath-by-breath analyser (Quark, Cosmed, Italy). Echocardiography measurements commenced when patients were close to finishing the test when the RER was exceeding 0.95 and if patients were not taking beta blockers in combination with a HR above 85% of predicted maximum. All

measurements were taken within 90 seconds of finishing exercise. Patients were verbally encouraged to exercise until maximal exertion. $\dot{V}O_{2\,peak}$ was expressed as the highest value from an average of 30s during the final stage of the exercise test. A predicted $\dot{V}O_2$ of less than 84% was considered to be reduced (American Thoracic Society, 2003). The $\dot{V}_E/\dot{V}CO_2$ slope was measured using the whole slope as a marker of the effectiveness of ventilation- perfusion matching.

7.3.3 NT-ProBNP

Venous blood sampling was performed at rest prior to the appointment. Venous blood samples (5 ml) were taken from the ante-cubital vein. The Roche Elecsys NTproBNP assay was used on a Roche Modular E170 immunoassay platform. Serum was collected using standard sampling tubes containing separating gel. Samples are centrifuged and the serum is stable for 3 days at 20-25 ^{o}C, 6 days at 2-8 ^{o}C or 24 months at -20 ^{o}C. NT-proBNP measurements were carried out using an ELISA technique using two monoclonal antibodies in a sandwich technique and streptavidin coated micropartices. Results were determined via a calibration curve which is instrument specifically generated by 2 point calibration and a master curve provided by the reagent barcode. Measuring range is 5-35000 pg·mL^{-1}. lower detection limit is 5 pg·mL^{-1}. There is no high dose hook effects at levels up to 300,000 pg·mL^{-1}. Repeatability has a coefficient of variation (CV) of between 1.2 and 1.9% and intermediate precision has a CV of between 1.7 and 3.1%.

7.3.4 Follow up

CPET combined with exercise echocardiography and the NT-ProBNP measurements were performed during all visits. Follow-up appointments occurred at 3, 6, 9 or 12 months. A consultant cardiologist specialist in cardiac imaging and valve disease determined if the patients should be considered for aortic valve intervention or if the patient should remain under follow up. Data used for the exercise predictive model was the last visit prior to aortic valve intervention or the last available follow-up appointment. Data used for cardiac events modelling was taken from the first test after referral to the clinic. Cardiac admissions (unplanned inpatient cardiac admission

lasting more than 24 hours) and aortic valve replacement were based on detailed analysis of hospital case notes and electronic records.

7.3.5 Statistical analyses

Normality of data was tested with the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± SD or as a median (interquartile range (IQR)). Categorical data is presented as absolute values and percentages. Pearson correlation coefficients or Spearman coefficients were used to determine correlations between $\dot{V}O_{2peak}$ or NT-ProBNP and clinical, demographic, and echocardiographic parameter. Potential predictors for $\dot{V}O_{2peak}$ or NT-ProBNP and clinical, demographic, and echocardiographic were entered in a multivariate linear regression model using stepwise selection. Student t-tests were used to determine differences between patients who were hospitalised vs. those that were not. Event rates were estimated using Kaplan-Meier curves and compared using a log-rank test. A p-value of less than 0.05 was considered significant. All statistical analyses were carried out using SPSS version 20.0; SPSS inc, Chicago, USA.

7.4 Results

A total of 32 patients were included. The average follow-up time was 23 ± 15 months, ranging from 1 up to 64 months over a total of 57 visits. Sixteen patients were referred for aortic valve intervention with an average time to referral of 14 ± 8.8 months, ranging from 0 up to 32 months. Three quarter of the patients were male. All patients had a LVEF within normal range. All demographics, exercise parameters and NT-ProBNP values are in Table 7.1. No patients died during follow-up. Median NT-proBNP was 301 (IQR 106 to 497) $pg \cdot mL^{-1}$. Average age at the latest visit was 74 (IQR 19) years.

Average $\dot{V}O_{2peak}$ was 18.7 (IQR 4.2) $mL \cdot kg^{1} \cdot min^{1}$. Almost half of the patients (41%) had a reduced exercise tolerance based on a predicted $\dot{V}O_{2peak}$ below 84%. Average OUES was 1993 ± 636 $(mL \cdot min^{1}) \cdot (L \cdot min^{1})^{-1}$, according to this parameter 7 patients (22%) revealed a predicted OUES below 84%. In contrast to conventional exercise parameters, no patient had a drop in blood pressure during exercise although three patients failed to augment their blood pressure. Four patients were short of breath disproportionate to the level of exercise. No patients suffered from chest pain or syncope during or post exercise.

Table 7.1: Demographics for all patients (n=32)

Parameter	**First visit**	**Latest visit**
Age (years)	68.5 ± 15.9	68.8 ± 15.7
Weight (kg)	78.8 ± 12.4	79.3 ± 12.5
Height (m)	1.72 ± 0.08	1.72 ± 0.08
BSA (m^2)	1.91 ± 0.2	1.92 ± 0.2
Males (%)	24 (75%)	24 (75%)
NT-proBNP ($pg \cdot mL^{-1}$)	256 (IQR 464)	301 (IQR 466)
Log NT-proBNP ($pg \cdot mL^{-1}$)	2.4 ± 0.48	2.4 ± 0.45
Rest LVEF (%)	62.2 ± 5.3	62.8 ± 5.4
RWT	0.44 ± 0.1	0.43 ± 0.1
Rest S' ($cm \cdot s^{-1}$)	5.6 ± 1.4	5.5 ± 1.14
Rest Vmax ($cm \cdot s^{-1}$)	3.9 ± 0.45	4.00 ± 0.5
Rest mean PG (mmHg)	34.7 ± 8.6	36.8 ± 9.4
SV rest (mL)	77.8 ± 18.0	75.7 ± 17.0
Rest AVA (cm^2)	0.90 ± 0.1	0.88 ± 0.2
Rest AVAi ($cm \cdot m^{-2}$)	0.46 ± 0.1	0.47 ± 0.1
$\dot{V}O_{2\,peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	19.5 ± 5.9	18.7 (IQR 4.2)
Patients below 84% predicted (%)	13 (41%)	13 (41%)
OUES ($(mL \cdot min^{-1}) \cdot (L \cdot min^{-1})^{-1}$)	1966 ± 518	1993 ± 636
HR peak ($beats \cdot min^{-1}$)	131 ± 22	133 ± 26.5
Peak WR (W)	106 ± 54.6	105 ± 56.5
Peak RER	1.09 ± 0.12	1.07 ± 0.1
$\dot{V}_E$ /$\dot{V}CO_2$ slope	31.3 ± 5.6	32.3 ± 5.3
Exercise S' ($cm \cdot s^{-1}$)	7.5 ± 2.1	7.4 ± 1.8
Exercise Vmax ($cm \cdot s^{-1}$)	4.5 ± 0.5	4.6 ± 0.5
Exercise mean PG (mmHg)	47.9 ± 12.6	50.4 ± 13.6
SV exercise (mL)	80.8 ± 18.2	80.5 ± 18.0
Exercise AVA (cm^2)	0.98 ± 0.2	0.95 ± 0.2
ΔS' from rest to exercise	1.85 ± 1.6	1.84 ± 1.6
Δmean PG from rest to exercise	13.4 ± 9.3	14.7 ± 10.0

BSA – body surface area; NT-ProBNP – Brain natriuretic peptide; LVEF – Left Ventricular Ejection Fraction; RWT – Relative wall thickness; S' – Systolic longitudinal velocity measured by Tissue Velocity Imaging; Vmax – peak velocity through the aortic valve; mean PG – mean pressure gradient; AVA- aortic valve area, AVAi – aortic valve area indexed; $\dot{V}O_{2\,peak}$ – peak oxygen consumption; OUES – oxygen uptake efficiency slope; HR – heart rate; WR – work rate; RER – respiratory exchange ratio; $\dot{V}_E$ /$\dot{V}CO_2$ slope – ventilatory efficiency slope; SV – stroke volume; Δ - difference

Table 7.2: Correlation (Spearman's rho) between $\dot{V}O_{2peak}$ and echocardiographic parameters at rest and exercise (latest visit)

Demographics	
Age (years)	-0.76*
Weight (kg)	0.19
Height (m)	0.45*
Resting parameters	
S' rest ($cm \cdot s^{-1}$)	0.16
LVEF rest (%)	-0.17
RWT	-0.21
Rest max V ($cm \cdot s^{-1}$)	0.42§
Rest mean PG (mmHg)	0.40§
Rest SV (mL)	0.26
Rest AVA (cm^2)	0.21
Rest AVAi ($cm^2 \cdot m^{-2}$)	-0.19
Dimensionless index	-0.14
Exercise parameters	
S' exercise ($cm \cdot s^{-1}$)	0.61*
LVEF exercise (%)	0.25
Exercise max V ($cm \cdot s^{-1}$)	0.43§
Exercise mean PG (mmHg)	0.43§
SV exercise (mL)	0.25
Exercise AVA (cm^2)	0.28
ΔS' from rest to exercise	0.44§
Δ mean PG from rest to exercise	0.16
Δ SV from rest to exercise	-0.05

*correlation with $\dot{V}O_{2peak}$ P<0.01; § correlation with $\dot{V}O_{2peak}$ P<0.05
LVEF – Left Ventricular Ejection Fraction; RWT – Relative wall thickness; S' – Systolic longitudinal velocity measured by Tissue Velocity Imaging; Vmax – peak velocity through the aortic valve; mean PG – mean pressure gradient; AVA- aortic valve area, AVAi – aortic valve area indexed; $\dot{V}O_{2peak}$ – peak oxygen consumption; SV – stroke volume; Δ - difference

Regarding the prediction of exercise performance, S' obtained at peak exercise had the strongest correlation with $\dot{V}O_{2\,peak}$ (rho = 0.61; p<0.001) while augmentation of LVEF did not (Table 7.2). A relationship was observed between conventional markers of AS obstruction and $\dot{V}O_{2\,peak}$; Vmax and mean PG at rest showed correlations of (rho=0.42; p=0.17) and rho=0.40; p=0.02) respectively (Figure 7.2; Table 7.2). No relationship was found with SV, AVA or dimensionless velocity index. Resting parameters for systolic function (LVEF or S' likewise did not correlate with $\dot{V}O_{2\,peak}$). A strong correlation was found with $\dot{V}O_{2\,peak}$ and age (rho=-0.76; p<0.0001 and height (rho=0.45; p=0.009) as expected. During exercise a similar weak association was found with the measures of aortic valve obstruction, Vmax (rho=0.43, 0.02) and mean PG (rho=0.43, 0.02) (Table 7.2) but again no significant correlation was observed for LVEF, SV or AVA during exercise and $\dot{V}O_{2\,peak}$. In multivariate analysis, exercise S' and age were the strongest independent predictors for $\dot{V}O_{2\,peak}$ with a R^2 for the model of 0.76 (Table 7.3).

Table 7.3: Multivariate regression analyses with $\dot{V}O_{2\,peak}$ as the dependent variable ($R^2 = 0.76$)

Variable	**B-coefficient**	**95% CI**	**P value**
S' exercise ($cm \cdot s^{-1}$)	1.004	0.03 – 1.98	0.04
Age (years)	-0.29	-0.41 - -0.18	<0.0001

Potential predictors for $\dot{V}O_{2\,peak}$ on bivariate analyses (age, height, rest Vmax, rest mean PG, exercise max V, exercise mean PG, exercise S')
S' – systolic longitudinal velocity; $\dot{V}O_{2\,peak}$ - peak oxygen uptake

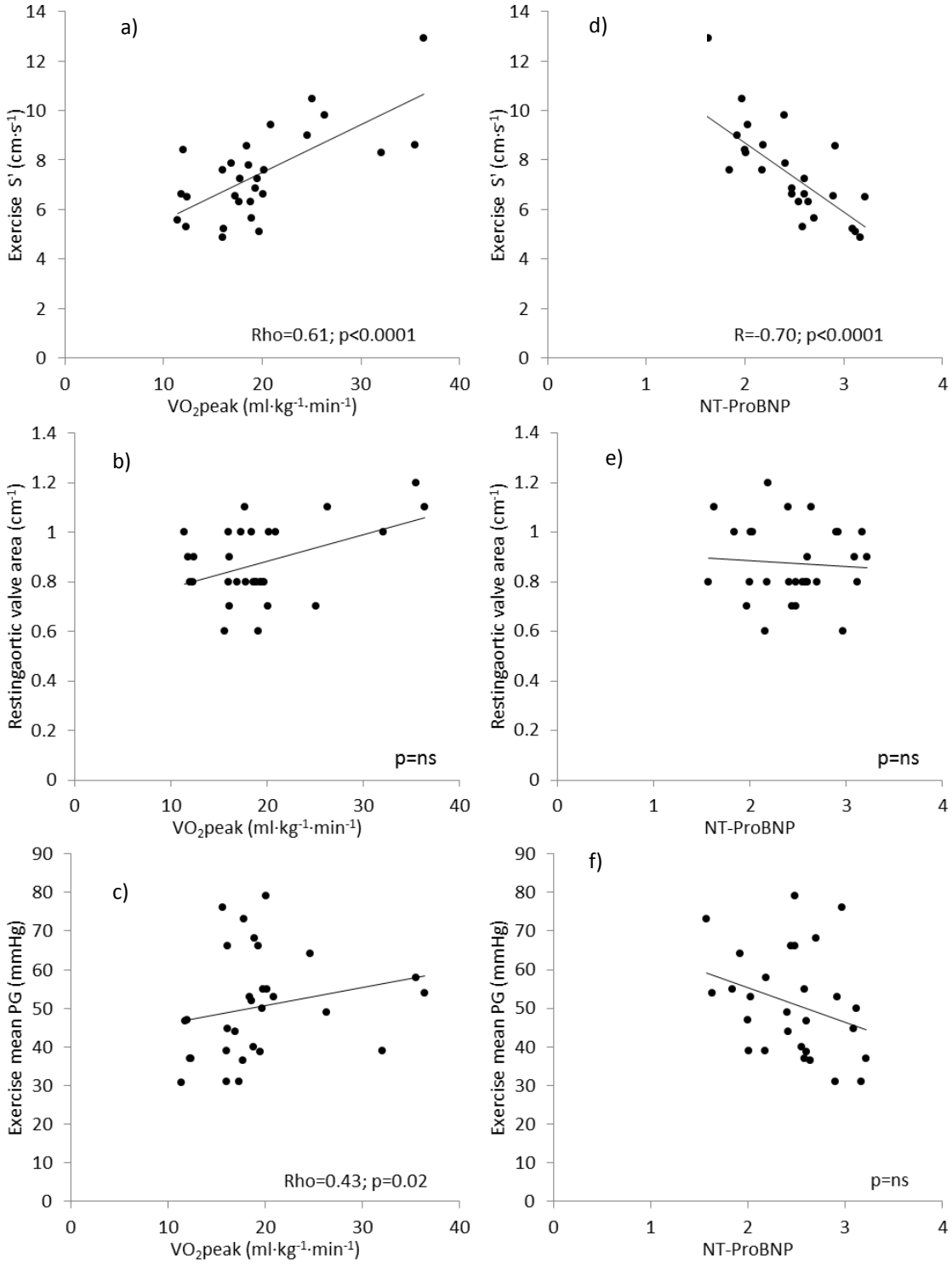


Figure 7.2: Regression analyses for a) $\dot{V}O_{2\,peak}$ and exercise S'; b) $\dot{V}O_{2\,peak}$ and AVA; c) $\dot{V}O_{2\,peak}$ and exercise mean PG; d) log NT-ProBNP and Exercise S'; e) log NT-ProBNP and AVA; f) log NT-ProBNP and exercise mean PG

Table 7.4: Correlation (Spearman's rho) between NT-ProBNP and echocardiographic parameters at rest and exercise (latest visit)

Demographics	
Age (years)	0.55*
Weight (kg)	0.23
Height (m)	-0.31
Resting parameters	
S' rest ($cm \cdot s^{-1}$)	-0.30
LVEF rest (%)	-0.06
RWT	-0.01
Rest max V ($cm \cdot s^{-1}$)	-0.23
Rest mean PG (mmHg)	0.28
Rest SV (mL)	-0.06
Rest AVA (cm^2)	-0.01
Rest AVAi ($cm^2 \cdot m^{-2}$)	0.14
Dimensionless index	0.02
Exercise echocardiography parameters	
S' exercise ($cm \cdot s^{-1}$)	-0.75*
LVEF exercise (%)	-0.46
Exercise max V ($cm \cdot s^{-1}$)	-0.32
Exercise mean PG (mmHg)	-0.35
Exercise SV (mL)	-0.44§
Exercise AVA (cm^2)	-0.31
ΔS' from rest to exercise	-0.58*
Δ mean PG from rest to exercise	0.22
Δ SV from rest to exercise	-0.33
CPET parameters	
$\dot{V}O_{2\,peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	-0.51*
OUES ($(mL \cdot min^{-1}) \cdot (L \cdot min^{-1})^{-1}$)	-0.46§
$\dot{V}_E / \dot{V}CO_2$ slope	0.34

*correlation with $\dot{V}O_{2\,peak}$ P<0.01; § correlation with $\dot{V}O_{2\,peak}$ P<0.05

BSA – body surface area; NT-ProBNP – Brain natriuretic peptide; LVEF – Left Ventricular Ejection Fraction; RWT – Relative wall thickness; S' – Systolic longitudinal velocity measured by Tissue Velocity Imaging; Vmax – peak velocity through the aortic valve; mean PG – mean pressure gradient; AVA- aortic valve area, AVAi – aortic valve area indexed; $\dot{V}O_{2\,peak}$ – peak oxygen consumption; OUES – oxygen uptake efficiency slope; Δ - difference

A further predictive model for the log NT-ProBNP demonstrated a good relationship with exercise S' (r = 0.75), but no relationship was observed for Vmax, mean PG or the AVA (Table 7.4). Multivariate analyses demonstrated that exercise S' was the strongest predictor for NT-ProBNP with an R^2 of 0.48 (Table 7.5).

Table 7.5: Multivariate regression analyses with NT-ProBNP as the dependent variable (R^2 = 0.48)

Variable	**B-coefficient**	**95% CI**	**P value**
S' exercise ($cm \cdot s^{-1}$)	-0.24	-0.37 - -0.10	0.001

Potential predictors for NT-ProBNP on bivariate analyses (age, $\dot{V}O_{2peak}$, exercise S', SV during exercise, OUES, $\dot{V}_E/\dot{V}CO_2$ slope)

$\dot{V}O_{2peak}$ - peak oxygen uptake; S' – longitudinal velocity; SV – stroke volume; $\dot{V}_E/\dot{V}CO_2$ slope – ventilatory efficiency slope; OUES – oxygen uptake efficiency slope;

No patients died during follow up. However 9 patients required unplanned cardiac admission. Patients who required cardiac admission had a lower percentage predicted $\dot{V}O_{2\,peak}$ (77 ± 15.5 vs. 92% ± 18.0; p=0.03) and a greater relative wall thickness (0.49 ± 0.11 vs. 0.40 ± 0.08 vs.; p=0.02) (Table 7.6). $\dot{V}O_{2\,peak}$ below 84% was a strong predictor for cardiac hospitalisation (Figure 7.3). A total of 16 patients were referred for aortic valve intervention during follow up. The only difference between those who were referred for surgery and those who continued with watchful waiting was a higher mean PG at rest (33.0 ± 7.2 vs. 39.7 ± 10.3 mmHg, p=0.049).

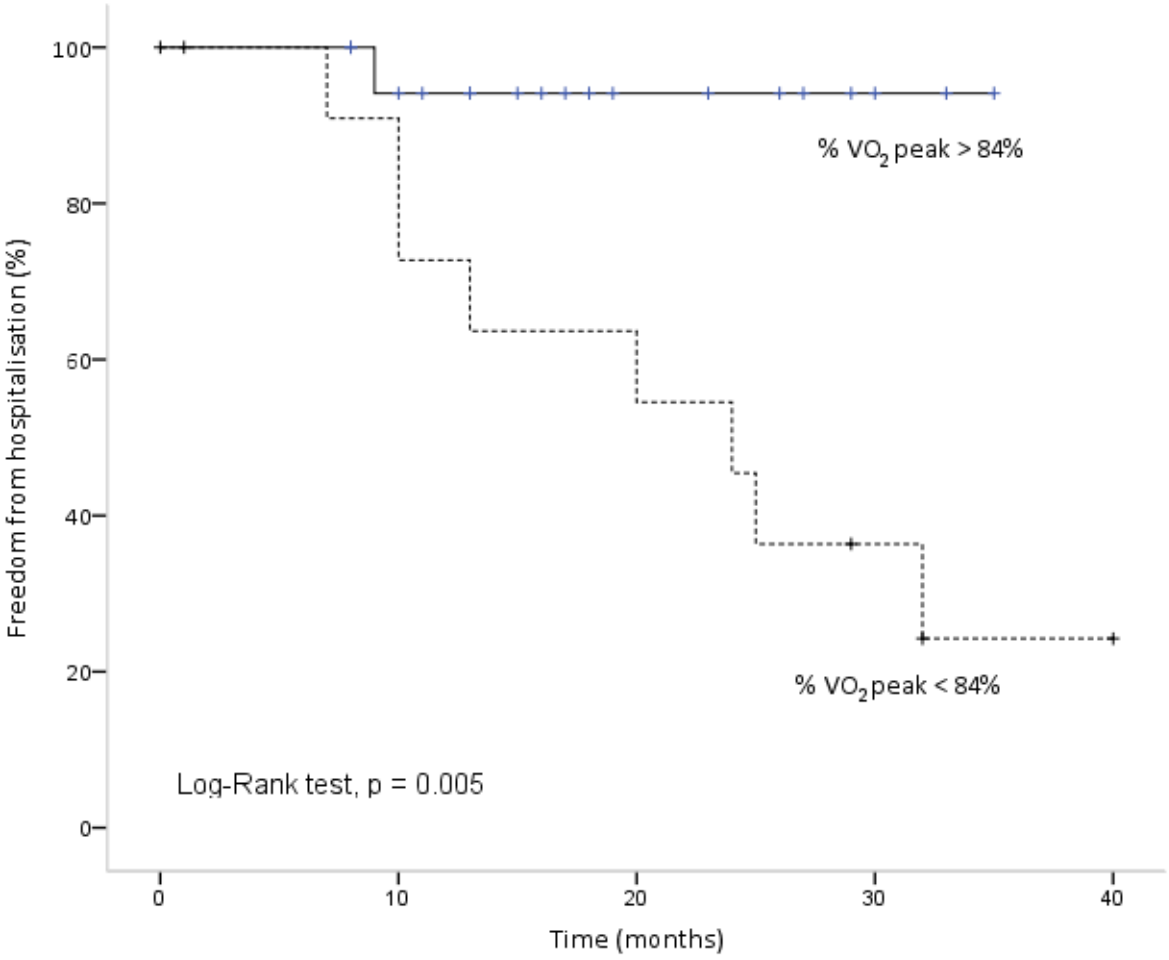


Figure 7.3: Hospitalisation survival curve for patients with a $\dot{V}O_{2\,peak}$ above and below 84% at the first visit to the clinic

Table 7.6: Differences in patients requiring cardiac admission vs. those who did not require any admission during follow up

	No cardiac admission (n=23)	**Cardiac admission (n=9)**
Age (years)	69.6 ± 14.9	65.8. ± 18.8
Weight (kg)	78.3 ± 13.5	80.2 ± 9.8
Height (m)	1.71 ± 0.08	1.75 ± 0.06
BSA (m^2)	1.9 ± 0.2	2.0 ± 0.1
Males (%)	10 (63%)	6 (38%)
Echocardiographic parameters		
Rest LVEF (%)	62.4 ± 5.5	61.8 ± 6.0
RWT	0.41 ± 0.08	0.51 ± 0.09*
Rest S' ($cm \cdot s^{-1}$)	5.2 ± 1.2	6.6 ± 1.31*
Rest Vmax ($cm \cdot s^{-1}$)	4.0 ± 0.49	3.8 ± 0.29
Rest mean PG (mmHg)	35.5 ± 8.7	32.6 ± 8.1
Rest SV (mL)	77 ± 16.5	66 ± 18.3
Rest AVA (cm^2)	0.91 ± 0.14	0.89 ± 0.11
Rest AVAi ($cm \cdot m^{-2}$)	0.46 ± 0.14	0.45 ± 0.05
Exercise S' ($cm \cdot s^{-1}$)	7.1 ± 1.8	8.4 ± 2.6
Exercise Vmax ($cm \cdot s^{-1}$)	4.5 ± 0.5	4.5 ± 0.4
Exercise mean PG (mmHg)	48.6 ± 13.7	46.2 ± 9.7
Δ S' from rest to exercise	1.9 ± 1.5	1.8 ± 2.0
Δ mean PG from rest to exercise	13.3 ± 10.6	13.6 ± 5.4
n (mean PG > 18 mmHg with exercise)	7 (30%)	2 (22%)

	No cardiac admission (n=23)	Cardiac admission (n=9)
CPET parameters		
$\dot{V}O_{2\,peak}$ (mL·kg^{-1}·min^{-1})	20.1 ± 5.8	18.0 ± 6.2
$\dot{V}O_{2\,peak}$ (% predicted)	92.7 ± 18.1	75.3 ± 14.3*
Patients below 84% predicted (%)	1 (4%)	8 (89%)*
OUES ((mL·min^{-1})·(L·min^{-1})$^{-1}$)	2006 ± 505	1820 ± 587
HR peak (beats · min^{-1})	132 ± 21.5	129 ± 24.5
Peak WR (W)	111 ± 55	91 ± 50
Peak RER	1.09 ± 0.13	1.09 ± 0.11
$\dot{V}_E/\dot{V}CO_2$ slope	30.6 ± 4.5	33.0 ± 7.9

*P<0.05

BSA – body surface area; NT-ProBNP – Brain natriuretic peptide; LVEF – Left Ventricular Ejection Fraction; RWT – Relative wall thickness; S' – Systolic longitudinal velocity measured by Tissue Velocity Imaging; Vmax – peak velocity through the aortic valve; mean PG – mean pressure gradient; AVA- aortic valve area, AVAi – aortic valve area indexed; $\dot{V}O_{2\,peak}$ – peak oxygen consumption; OUES – oxygen uptake efficiency slope; HR – heart rate; WR – work rate; RER – respiratory exchange ratio; $\dot{V}_E/\dot{V}CO_2$ slope – ventilatory efficiency slope; Δ - difference

7.5 Discussion

This study demonstrated that a large proportion of supposedly asymptomatic patients had a lower than predicted % $\dot{V}O_{2\,peak}$ confirming that asymptomatic patients are more limited than they or their clinicians believe. This is what was expected as set out in the first part of the hypotheses. It is also in agreement with previous reports in the literature (Domanski *et al.*, 2017; Dulgheru *et al.*, 2013). In this study the CPET evaluation identified a much higher proportion of symptomatic individuals than would have been identified if traditional parameters currently recommended in guidelines documents (including symptoms and fall in blood pressure) (Vahanian *et al.*, 2012). Furthermore a reduced exercise tolerance and more adverse ventricular remodelling, rather than aortic valve obstruction, predicted unplanned hospitalisation whereas the only difference between those who went for surgery was a higher mean PG, suggesting that clinicians may be more influenced by conventional measures of aortic obstruction. This supports the part of the hypothesis that exercise S' was related to $\dot{V}O_{2\,peak}$ and therefore ventricular response is at least as important as valvular obstruction. Exercise ability in this population was poorly correlated with conventional clinical measures of aortic valve severity, even under circumstances of flow augmentation, but was heavily dependent on the ability of the left ventricle to augment longitudinal function during exercise. Furthermore a similar inverse relationship with NT-ProBNP was observed for exercise S' whereas other parameters of LV function or valve obstruction were not related.

The severity of AS and the LV response to chronic pressure afterload resulting in myocardial hypertrophy contribute to the progression to the point where patients develop symptoms, adverse events occur, and therefore require surgery (Cioffi *et al.*, 2011; Otto, 2006; Pellikka *et al.*, 2005). Increased hypertrophy leads to impaired LV relaxation, reduced LV compliance, and greater metabolic demands (Lancellotti *et al.*, 2010c) and this has been associated with the progression of HF (Levy *et al.*, 1990). However the extent of LV hypertrophy only weakly correlates with the severity of AS (Dweck *et al.*, 2012; Kupari *et al.*, 2005; Salcedo *et al.*, 1989). Focal scar burden within the myocardium is strongly correlated with outcome following AVR and

prognosis (Barone-Rochette *et al.*, 2014; Dweck *et al.*, 2012), suggesting that ventricular response to afterload results in irreversible cellular myocardial changes which modulate outcome. LVEF is the standard parameter used for assessing global systolic dysfunction and a current indicator for aortic valve intervention (Nishimura *et al.*, 2014; Vahanian *et al.*, 2012). LVEF reduction, used in isolation, is unsatisfactory as in this circumstance reduction is a late manifestation of ventricular decompensation and myocardial fibrosis (Chin *et al.*, 2015; Lancellotti *et al.*, 2010a). Furthermore, in AS, it is common to overestimate systolic function for simple geometric reasons, as ventricular volumes are reduced due to concentric hypertrophy (Lancellotti *et al.*, 2010b) leading to a small SV for a given LVEF. The described model in this study of systolic function is clearly incomplete, more subtle and predictive parameters to describe ventricular performance are required.

Longitudinal systolic function is more sensitive in detecting early myocardial dysfunction (Pibarot and Dumesnil, 2012). When assessed by strain rate imaging (Kearney *et al.*, 2012; Lancellotti *et al.*, 2010; Yingchoncharoen *et al.*, 2012) it predicts adverse events more accurately than LVEF in AS patients (Nagata *et al.*, 2015). Lancellotti *et al*. (2010b) included 126 asymptomatic patients with severe AS and found that patients with impaired longitudinal function have a greater risk of developing cardiac events (Lancellotti *et al.*, 2010b). Annular or myocardial longitudinal velocity are an alternative, well established method of quantifying longitudinal systolic function (Nikitin *et al.*, 2004; Yu *et al.*, 2007). Although unlike 2D strain imaging, TVI is angle dependent, it has the advantage of being much less dependent on overall 2D image quality making it useful in most patients and during stress echocardiography. Alternative means of estimating LV dysfunction is the use of systemic biomarkers. Significant associations have been found between NT-proBNP and myocardial longitudinal contractility and the degree of symptoms in asymptomatic patients with severe AS (Lancellotti *et al.*, 2005; Poulsen *et al.*, 2007). Rajani *et al*. (2010) included 38 patients with moderate and severe AS and found that blood BNP levels strongly predicted patients who became symptomatic during exercise. NT-ProBNP is able to unmask early ventricular decompensation however the influence of age and sex and the threshold used to determine adverse events differ greatly

between studies. Guidelines including reference values should be established to implement the use of NT-ProBNP in a clinical setting in patients with severe AS.

In this study, confirming the results of many others, the standard clinical markers of AS severity correlate very poorly with predicted exercise limitation or outcomes. The only resting parameter which was associated with exercise ability was the mean pressure gradient however this was only a weak relationship. The poor correlation between resting echo findings and objective exercise limitation has been previously demonstrated in the literature (Domanski *et al.*, 2017; Dulgheru *et al.*, 2013). Exercise parameters, which do seem to predict prognosis in some studies have not previously predicted exercise ability (Domanski *et al.*, 2017). As far as we are aware no previous evaluations to date have investigated longitudinal velocity in relation to CPET at exercise.

This study clearly demonstrates a relationship between longitudinal velocity and $\dot{V}O_{2\,peak}$, not explained by other clinical parameters. The results are considerably more plausible because of the co-existing inverse, and this is amongst other measured parameters a unique relationship with log NT-ProBNP, thus suggesting that patients with lower longitudinal systolic reserve have on average, higher intracardiac pressures. We have previously documented the importance of systolic velocity reserve in a variety of different clinical conditions (McIntosh *et al.*, 2013; van Zalen *et al.*, 2015) and its importance seems to be confirmed here in patients with AS.

Both stress echocardiography and CPET have been used to establish the likelihood of future cardiac events. Exercise echocardiography provides additional information including the haemodynamic changes that occur during exercise. An increase in mean aortic pressure gradient of 18 mmHg or more on exercise is an independent predictor for death and hospital admissions (Lancellotti *et al.*, 2005). A study by Maréchaux *et al.*, (2010), included 186 asymptomatic patients with at least moderate AS (mean PG >35 mmHg) and preserved LV function (Maréchaux *et al.*, 2010). A 9-fold increase in event rate (AVR or death) was found in patients with an increase in mean gradient of more than 20 mmHg on exercise; the increase in gradient could not be predicted from resting clinical or echocardiographic data. In our cohort 8 patients demonstrated an

increase in mean PG of more than 20 mmHg. Three of these eight patients were referred for AVR. This was not associated with cardiac hospitalisation or referral for AVR and is probably due to the small numbers with a high gradient on exercise. Resting mean PG was higher for patients referred for AVR compared to those who were not suggesting that clinicians are more influenced by conventional measures of aortic valve obstruction. Our study suggests that exercise performance from CPET is the strongest predictor of cardiac hospitalisation. A recent study by Domanski *et al.*, (2017) found that a $\dot{V}O_{2peak}$ of less than 85% predicted was associated with lower event free survival in 51 asymptomatic patients with severe AS (Domanski *et al.*, 2017). Our data agrees with this finding. In the Domanski paper no parameters obtained during stress echocardiography were able to predict events concluding that CPET should be incorporated when patients are placed in the watchful waiting category. The authors did not include any parameters describing longitudinal function during exercise in the analyses. Longitudinal function has previously shown good prognostic power for future events (van Zalen *et al.*, 2015).

7.5.1 Study limitations

The study was retrospective and based around protocol clinical evaluation. Strain analysis either by TVI or by speckle tracking was not used in this study and this might have provided further insights into global and regional deformation. However the major benefit of obtained S' using TVI is the simplicity and high reproducibility. Furthermore, a semi-recumbent cycle ergometer was used instead of the traditional upright cycle ergometer. The use of the semi-recumbent cycle ergometer is necessary in order to obtain exercise echocardiographic parameters of good quality. Section 3.4.2 is a small validity analysis between the upright and the semi-recumbent cycle ergometer. Results show a good relationship and reasonable agreement between the upright and the semi-recumbent cycle ergometers. Finally the clinical decision to refer to surgery was carried out by a consultant cardiologist who had all information available (stress echocardiographic, CPET and NT-ProBNP parameters) but might have been biased; we were unable to determine which parameter was used in the decision to refer patients for surgical intervention.

7.6 Conclusion

A high percentage of patients with apparent asymptomatic severe AS with normal LVEF have a lower than predicted $\dot{V}O_{2\,peak}$. This is more dependent upon the ability of the left ventricle to augment longitudinal function on exercise rather than the obstructiveness of the aortic valve (either at rest or with augmented flow) or the resting structural remodelling of the left ventricle. Exercise S' was independently associated with NT-ProBNP which further confirms that the relationship to myocardial distress is stronger than conventional AS severity and LV remodelling parameters. The burden of unplanned hospitalisation was high (28%) and this was predictable using CPET. Furthermore more patients were unmasked as having abnormal exercise performance using CPET than conventional exercise parameters. This suggests that where watchful waiting is an agreed strategy for patients with asymptomatic AS, a detailed assessment of a patient exercise tolerance using CPET should be undertaken. Combining CPET and exercise echocardiography and NT-ProBNP provides more insight into the subtle changes which occur when patients with severe AS begin to deteriorate. This combined technique provides a more enhanced follow up and can help in the clinical decision making about the optimal timing of surgical aortic valve intervention. Overall focus should be more about the ventricle, especially under exercise conditions, and less about the valve.

CHAPTER 8

THE RELATIONSHIP BETWEEN OXYGEN UPTAKE AND THE RATE OF MYOCARDIAL DEFORMATION AS CHARACTERISED BY LONGITUDINAL SYSTOLIC VELOCITY DURING EXERCISE IN HEALTHY INDIVIDUALS

Presented at the European Society of Cardiology 2018, Munich, Germany

van Zalen, J., D'silva, A., Badiani′ S.,, Bhuva, A., Jones, S.,Torlasco, C., Hughes, A.D., Manisty, C., Sharma, S., Moon, J.C., Lloyd, G. (2018) Linking myocardial mechanical function to exercise performance: a cardiopulmonary stress echo study in first time London marathon participants. *In press*

Appendix D

8.1 Abstract

Patients' symptoms are most commonly assessed at rest, although many patients experience no symptoms at rest, but can become limited when exercising. CPET objectively describes exercise tolerance and is essential for the assessment of functional impairment and prognosis. The powerful relationship between exercise S', $\dot{V}O_{2\,peak}$ and prognosis is important to evaluate in greater detail. The augmentation of these parameters during exercise is still poorly understood. The overall aim of this study was to develop a mechanistic insight into the relation between various aspects of systolic function and the incremental rise in $\dot{V}O_2$, and the increase in a variety of left ventricular and haemodynamic parameters, with special focus on S'. Fifty-seven participants were included and all completed a CPET exercise echocardiogram prior running the London marathon. Echocardiographic images were obtained at set timings to obtain multiple measurements during exercise. Against relative $\dot{V}O_2$ a simple regression model was observed for both septal S' (R^2=0.59; P<0.0001) and for lateral S' (R^2=0.47; p< 0.0001). In multivariate testing S' showed a stronger relationship with $\dot{V}O_2$ than any other facet of systolic function and although LVEF also increased the strength, this relationship was less strong. Mean S' (β = 0.59, p<0.001) and LVEF (β = 0.25, p = 0.001 were the only echo predictors $\dot{V}O_2$ (R^2 = 0.66, p<0.0001). S' at RER > 1 was a stronger predictor of $\dot{V}O_2$ than GLS (R^2 = 0.67, β = 0.84; p<0.0001). The septal S'/ relative $\dot{V}O_2$ slope and relative $\dot{V}O_{2\,peak}$ (r = 0.62; p<0.0001) and lateral S'/relative $\dot{V}O_2$ slope and relative $\dot{V}O_{2\,peak}$ (r =0.44; p<0.0001). The S' / $\dot{V}O_2$ slope is able to predict $\dot{V}O_{2\,peak}$, and OUES, and this strongly suggests that the $\dot{V}O_2$ / S' relationship is about contractile performance coupling rather than describing two co linear variables that increase with exercise. It also represents a novel mean for evaluating cardiac performance which may be important in other disease states when participants are not able to exercise to exhaustion, as valuable information can be obtained from submaximal data. More research is needed to investigate the S' / $\dot{V}O_2$ relationship in diseased myocardium. The slope function between S' and $\dot{V}O_2$ represents a new and unique means of describing contraction and performance coupling which predicts maximum cardiopulmonary performance.

8.2 Introduction

Previous chapters in this thesis have demonstrated that while patients symptoms are most commonly assessed at rest, many patients experience no symptoms at rest, but can become limited when exercising. Exercise is the ideal physiological condition to monitor cardiac function and symptoms simultaneously and evaluating patients during exercise provides a more complete and objective assessment of patients symptoms. CPET objectively describes exercise tolerance and is essential for the assessment of functional impairment and prognosis (Guazzi *et al.*, 2012). Semi-supine exercise is often the preferred method of choice allowing image acquisition to occur at different exercise intensities and allowing the evaluation of the dynamic myocardial response to exercise. The powerful relationship between some parameters (exercise S' and prognosis, (McIntosh *et al.*, 2013; van Zalen *et al.*, 2015)) have been established previously, others such a LVEF have failed to show a relationship with $\dot{V}O_{2\,peak}$. Exercise S' has shown a linear relation with peak exercise tolerance across a range of different cardiac diseases and healthy individuals (McIntosh *et al.*, 2013).

The various aspects of LV systolic function (preload, afterload, SV, LVEF, S') are all modulated by exercise to some extent. But the augmentation of these parameters and their relationship to maximum cardiopulmonary performance remains poorly understood. In particular what remains unclear is whether this relationship is an epiphenomenon (i.e. the sicker you are, the less exercise you can do and consequently you have a lower $\dot{V}O_{2\,peak}$ and S') or whether patients with a depressed myocardium are less able to augment a velocity response and consequently have a lower $\dot{V}O_{2\,peak}$.

The overall aim of this study was to develop a mechanistic insight into the relation between different aspects of systolic function and the incremental rise in $\dot{V}O_2$ and the increase in left ventricular and haemodynamic parameters, with special focus on systolic longitudinal function, in normal participants undertaking the London marathon for the first time. By examining the incremental augmentation slopes the aim is to establish the left ventricular myocardial contribution to changing incremental effort exercise.

Therefore the following aims were tested:

1) The relationship between various systolic parameters and $\dot{V}O_2$ during exercise
2) To create a multivariate model of factors which independently describe the $\dot{V}O_2$ response
3) To determine whether the regressive slope relationship between $\dot{V}O_2$ / S' could predict peak $\dot{V}O_2$ to develop a new parameter incorporating both cardiopulmonary exercise and exercise echocardiography parameters that could be applied at a submaximal level.

The first hypotheses set out for this study included that exercise S' and $\dot{V}O_2$ would have a linear relationship up to about 60% of exercise intensity where S' will plateau, which is a similar trajectory as SV. The second hypotheses was exercise S' was able to predict $\dot{V}O_2$ and thirdly the $\dot{V}O_2$ / S slope is able to predict $\dot{V}O_{2\,peak}$ values.

8.3 Methods

This study included 68 healthy participants. Inclusion criteria were successful inclusion into the London marathon in October 2015. This study is a sub-study from a British Heart Foundation funded study investigating if marathon training causes increased left ventricular trabeculation with Professor Sanjay Sharma as principal investigator. The study was approved by the London ethics committee (Appendix A). A full medical history and written inform consent were obtained prior to inclusion. Participants had no prior significant medical history. All participants completed a CPET exercise echocardiogram on a semi-recumbent cycle ergometer (detailed described in general methods).

8.3.1 Echocardiography

Echocardiography was performed using a GE Vivid 9 platform (Vingmed-General Electric, Horten, Norway) equipped with a phased-array 3.5 MHz transducer. Images were obtained at rest and every 1 minute and 15 seconds. Three apical 4-chamber view (with and without TVI) was recorded and was termed the abbreviated protocol. A more enhanced protocol was collected at rest, at 5 minutes into exercise (excluding

the 3-minute warm-up period), and when the RER was above 1.0 (Figure 8.1). This included the images already obtained for the abbreviated protocol and in addition the apical two-chamber, apical long axis view, parasternal short axis view at the base and apical level, and a PW at the level of the LVOT (one centimetre below the aortic valve) were collected.

All analyses were carried out online using GE Echopac software. S' was derived from colour derived TVI images where the sample volume was placed at the annulus of the septal and lateral wall. S' was defined as the highest velocity during systole after the end of isovolumetric contraction. At least three cardiac cycles were obtained and S' was averaged for each time point. During the full protocol; Simpson's biplane was measured (in the apical 4-and 2-chamber view), global longitudinal strain (GLS) in the three apical views and the LVOT VTI. Images were obtained in real time and analysed after each study. Images were stored offline. Speckle-tracking strain analysis was accepted when the software and visual inspection indicated adequate tracking. If tracking was inadequate, manual adjustments were made or the analysis was excluded from overall analyses. GLS was obtained from the apical 4-chamber view (basal septum, mid septum, apical septum, basal lateral, mid lateral, and apical lateral), the apical 2-chamber view (basal inferior, mid inferior, apical inferior, basal anterior, mid anterior, apical anterior) and the apical long axis view (basal posterior, mid posterior, basal anteroseptal, mid anteroseptal). If data was of insufficient quality it was excluded from analyses. Insufficient quality data included poor TVI tracing, exclusion of the mitral valve annulus (for colour TVI measurements), poor endocardial border definition (for biplane), and poor frame rate (for speckle tracking strain analyses).

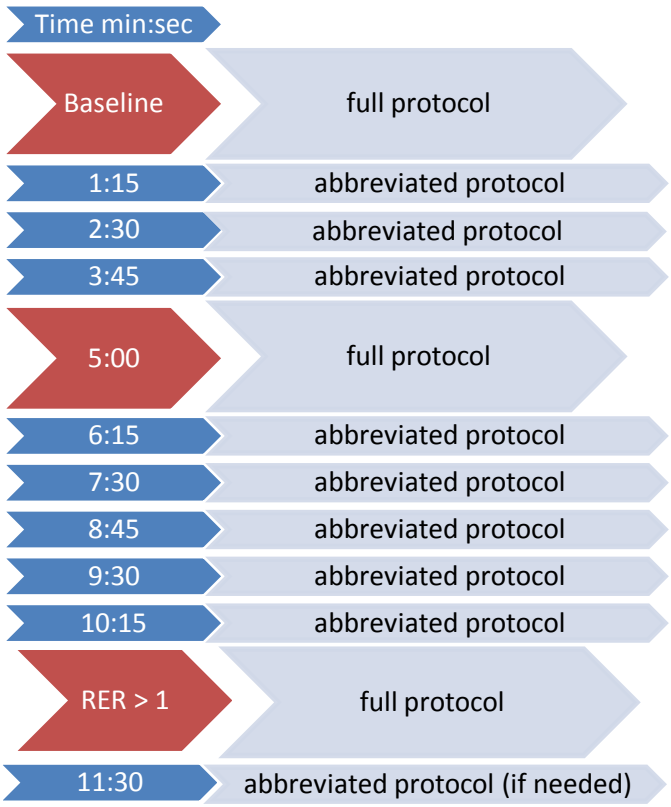


Figure 8.1: Schematic protocol when obtaining echocardiographic images

8.3.2 Cardiopulmonary exercise testing

A semi-recumbent cycle ergometer (ERG 911 S/L, Schiller, Baar, Switzerland) was used. At the start of the test a 3 minute rest period was included followed by a 3 minutes warm up period. Exercise protocols were individually determined based on functional status and physical appearance. Work rate (15, 20, 25 or 30 W) increased every minute until voluntary exhaustion aiming for 8-10 minutes of exercise. HR, blood pressure and oxygen saturation were monitored throughout. $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ were continuously measured and derived using a calibrated breath-by-breath analyser (Cosmed Quark CPET, Rome, Italy). Patients were verbally encouraged to exercise until maximal exertion. $\dot{V}O_{2\,peak}$ was expressed as the highest value from an average of 30s during the final stage of the exercise test. The OUES is the slope of $\dot{V}O_2$ against the logarithm of $\dot{V}_E$ ($\log\dot{V}_E$) (Baba *et al.*, 1996) and is used to estimate maximal exercise tolerance from a submaximal test. The VT was determined using the V-slope method where the $\dot{V}CO_2$ is plotted as a function of $\dot{V}O_2$ and can identified as the $\dot{V}O_2$ at which the change in slope of the relationship of $\dot{V}CO_2$ to $\dot{V}O_2$ occurs. To confirm this breakpoint the dual criteria

was used looking at the relationship between the ventilatory equivalents and $\dot{V}O_2$, the VT is the point where O_2 reached the minimum value and begins to rise with no associated increase in the $\dot{V}_E/CO_2$.

8.3.3 Statistical analyses

Data was tested for normality using the Kolmogorov-Smirnov statistical test. Spearman's correlations were calculated for S' and $\dot{V}O_2$ potential relationships. $\dot{V}O_2$ was averaged over 10 seconds and were linked with corresponding S' values. Relationships between $\dot{V}O_2$ and S' were investigated and regression models were computed. All data points for $\dot{V}O_2$ and S' were not normally distributed and therefore the residuals of the data were tested to see if linear regression was appropriate. The residuals used for the linear regression (S' and $\dot{V}O_2$) were tested for normality and were normally distributed. The residual plots and assumptions were met including good homoscedasticity of the data. (Appendix C). A scatter plot with 95% confidence interval was plotted and a linear regression model was built to describe the relationship. The augmentation curve was) investigated in more detail (LVEF, systolic and diastolic volumes, LVOT VTI and GLS and correlated with corresponding $\dot{V}O_{2\,peak}$ values. All significant correlations were entered into a multivariate regression model to determine the strongest predictor for $\dot{V}O_2$. For each individual the S' and $\dot{V}O_2$ was determined and averaged for all patients. This average slope function was correlated with $\dot{V}O_{2\,peak}$. Inter- and intraobserver variability was undertaken for $\dot{V}O_{2\,peak}$, OUES and the VT from 15 randomly selected participants and ICC were calculated.

8.4 Results

Sixty-eight participants were recruited for this study. Eleven participants were excluded from data analyses due to insufficient quality of data. The remaining 57 patients were included in the final analyses. Thirty-two males and twenty-five females with an average age of 29.2 ± 3.3 years, a mean weight of 71.5 ± 13.1 kg and a mean height of 175 ± 10.3 cm. Table 8.1 describes the haemodynamic and echocardiographic responses to exercise at baseline, 5 minutes into exercise and when the RER was consistently over 1. All parameters except EDV significantly increased during exercise from rest (at 5 minutes and when the RER was over 1.0). CPET variables are described in table 8.2.

Table 8.1: Haemodynamic and echocardiographic responses at baseline and exercise

	Rest	5 minutes	RER > 1.0
HR (beats ·min^{-1})	68.6 ± 10.6	129.4 ± 14.6*	151.8 ± 14.3§
Septal S' (cm ·s^{-1})	7.2 ± 1.4	10.3 ± 1.7*	13.8 ± 1.5§
Lateral S' (cm ·s^{-1})	8.4 ± 1.6	12.5 ± 1.5*	14.4 ± 1.2§
LVEF (%)	61.0 ± 2.8	68.9 ± 3.6*	69.8 ± 3.9§
EDV (mL)	119.8 ± 30.2	117.5 ± 31.2	113.8 ± 28.9
ESV (mL)	46.9 ± 13.3	36.9 ± 11.5*	35.5 ± 12.7§
SV (mL)	34.9 ± 14.9	48.8 ± 14.9*	55.0 ± 19.4§
GLS (%)	-18.0 ± 2.4	-21.5 ± 3.1*	-21.7 ± 2.7§

* Baseline vs. 5 minutes; $p < 0.05$; §; Baseline vs. RER > 1.0; $p < 0.05$

HR – heart rate; S' – systolic velocity; LVEF – left ventricular ejection fraction; EDV – end diastolic volume; ESV- end systolic volume; GLS – global longitudinal strain; SV – Stroke volume

Table 8.2: Exercise peak parameters for all participants (n=57)

	All participants
Absolute $\dot{V}O_{2\,peak}$ ($mL \cdot min^{-1}$)	2.8 ± 0.7
Relative $\dot{V}O_{2\,peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	38.7 ± 6.5
Predicted $\dot{V}O_2$ (%)	107 ± 17.0
WR peak (W)	226 ± 55
HR peak (beats · min^{-1})	168 ± 17.5

$\dot{V}O_{2\,peak}$ – peak oxygen uptake; WR – work rate; HR – heart rate

8.4.1 Longitudinal contractile reserve

All available S' (septal and lateral) were linked with the corresponding $\dot{V}O_2$. Table 8.3 demonstrated a good correlation between absolute and relative $\dot{V}O_2$ and lateral and septal S'.

Table 8.3: Spearman's correlation between septal S', lateral S' and $\dot{V}O_2$ using all available S' and corresponding $\dot{V}O_2$ for all participants (n=57)

	Relative $\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	Absolute $\dot{V}O_2$ ($mL \cdot min^{-1}$)
Septal S' ($cm \cdot s^{-1}$)	0.78 (p <0.0001)	0.83 (p <0.0001)
Lateral S' ($cm \cdot s^{-1}$)	0.73 (p <0.0001)	0.75 (p <0.0001)

S' – systolic longitudinal velocity; $\dot{V}O_2$ – oxygen uptake

All available data points for each individual were entered into a simple regression model. $\dot{V}O_2$ as the dependent variable and septal and lateral S' as the independent variable. This demonstrated linearity between variables. Against relative $\dot{V}O_2$ a simple regression model was observed for both septal S' (R^2=0.59; P<0.0001) and for lateral S' (R^2=0.47; p< 0.0001) (Figure 8.2). Against absolute $\dot{V}O_2$ a simple regression equation was observed for both septal S' (R^2=0.67; p<0.0001) and for lateral S' (R^2=0.49; p< 0.0001) (Figure 8.3). When septal and lateral S' were averaged and entered in the model to predict $\dot{V}O_2$, the model demonstrated significance for relative $\dot{V}O_2$ (R^2 = 0.58; P<0.0001) and absolute $\dot{V}O_2$ (R^2 = 0.66; P<0.0001) (Figure 8.4).

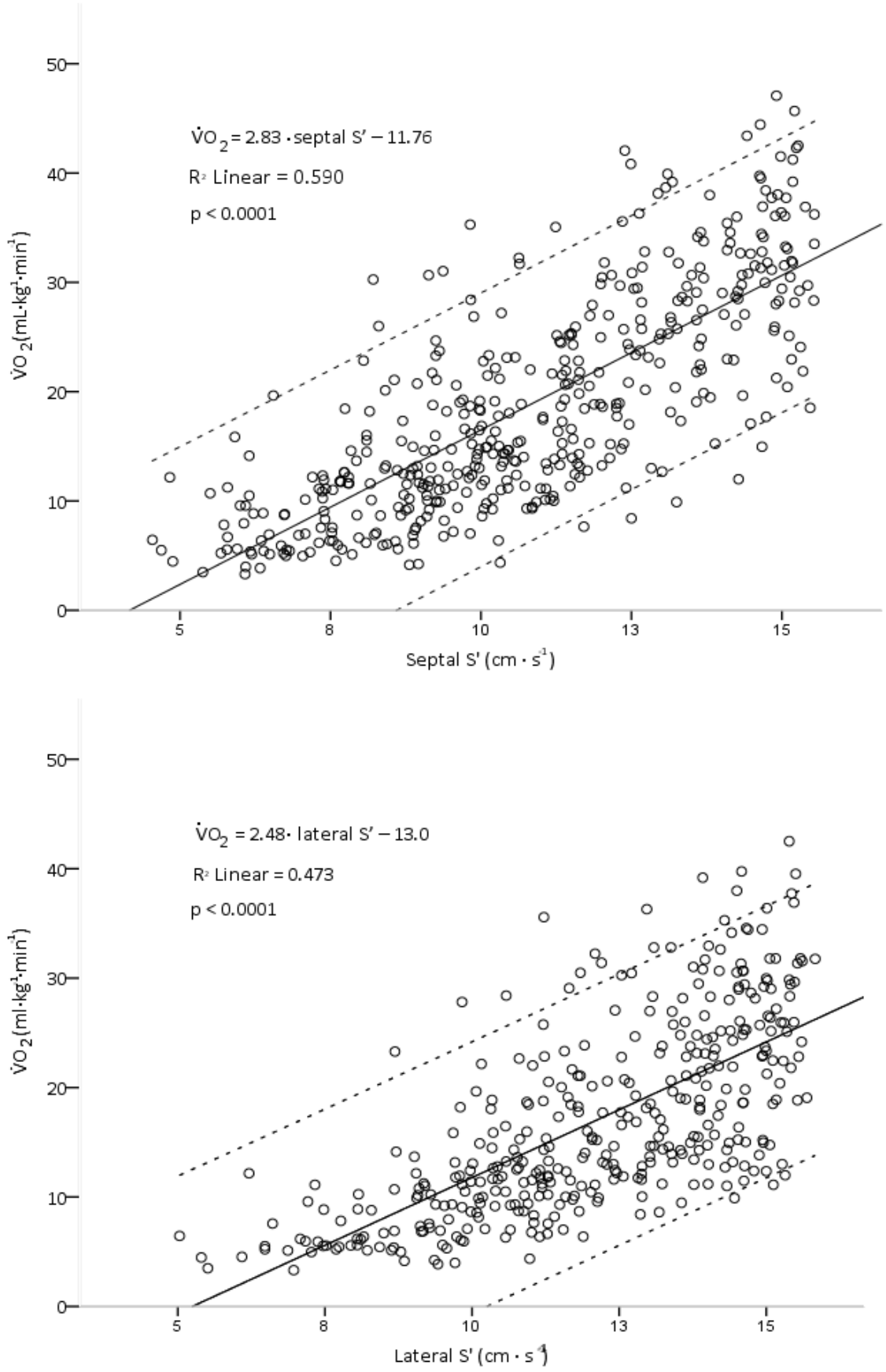
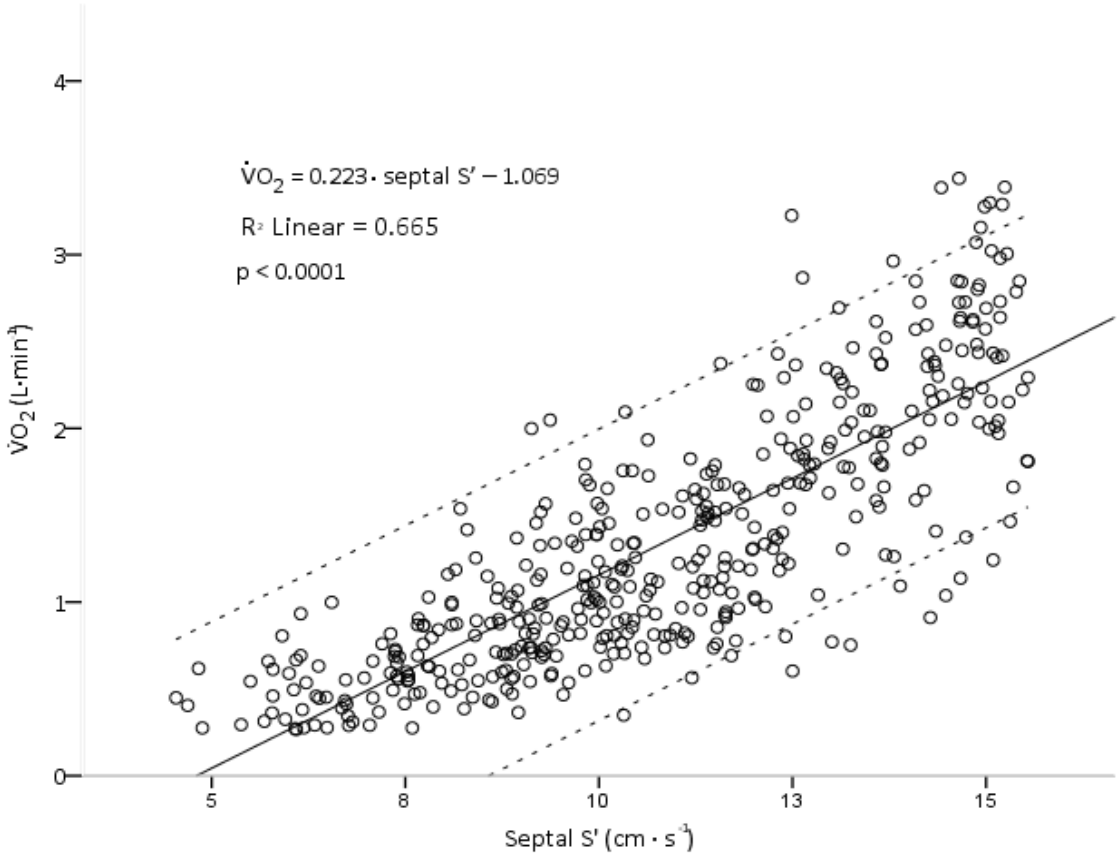


Figure 8.2: Scatterplots for all available data points for each individual for the relationship between relative $\dot{V}O_2$ and S'



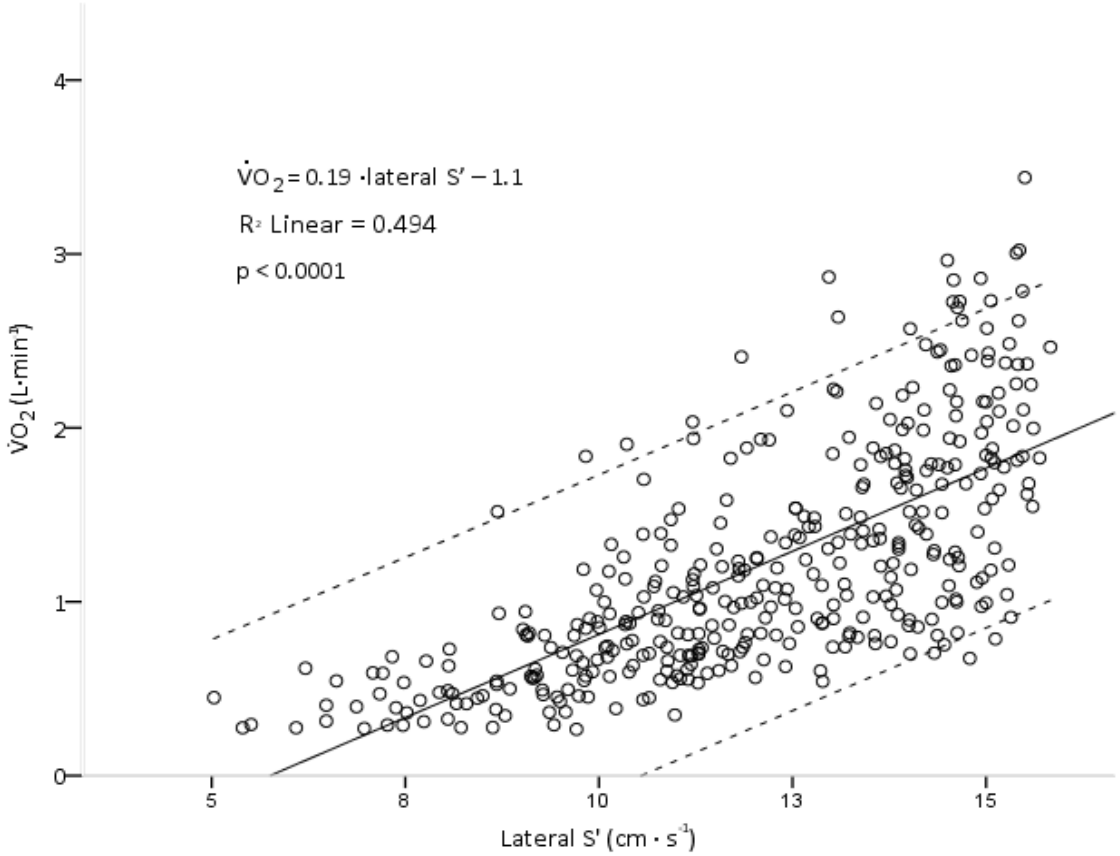


Figure 8.3: Scatterplots for all available data points for each individual for the relationship between absolute $\dot{V}O_2$ and S'

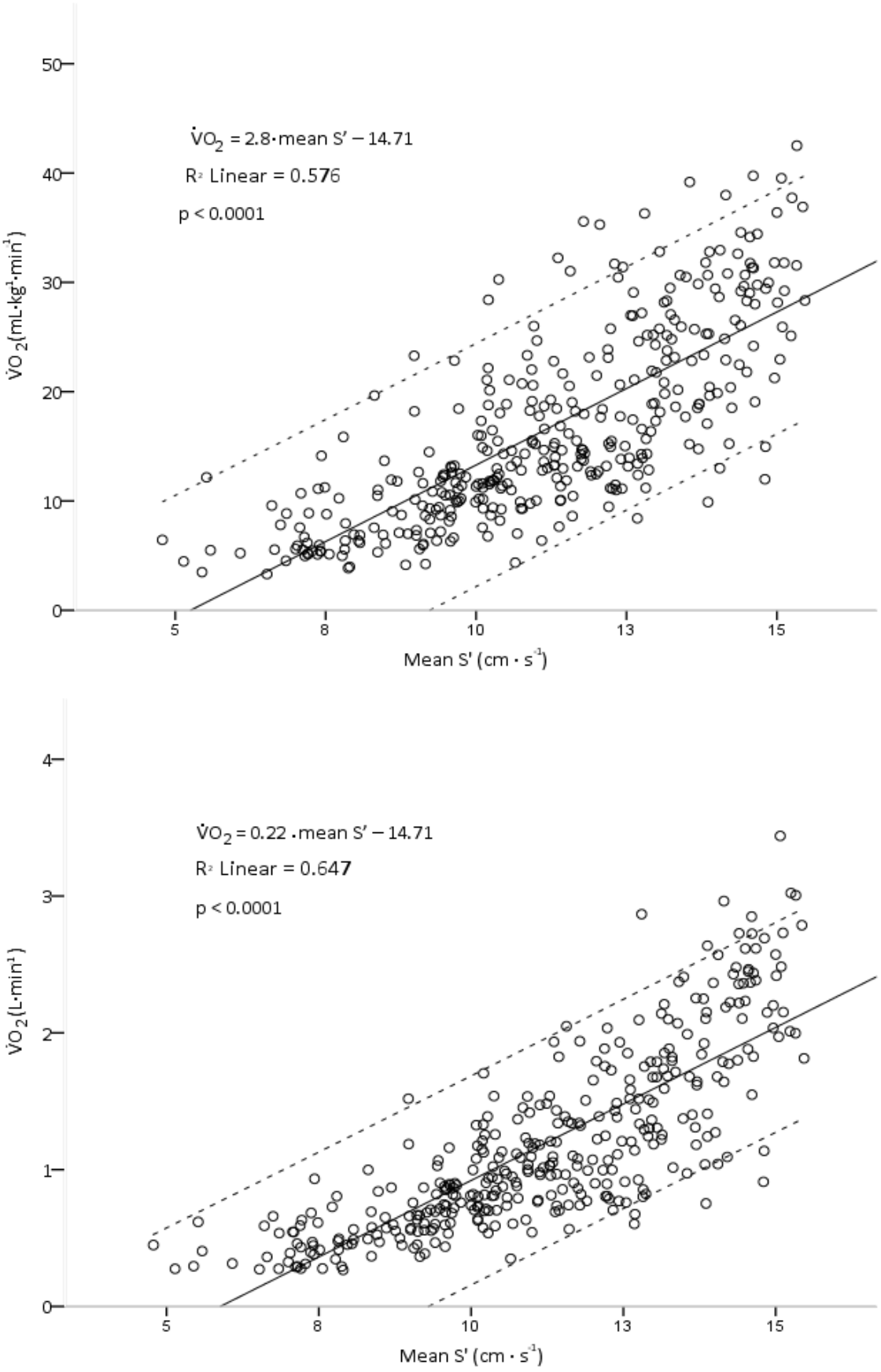


Figure 8.4: Scatterplots for all available data points for each individual for the relationship between relative and absolute $\dot{V}O_2$ and mean S'

8.4.2 Multi parametric modelling

A multivariate analysis was used to assess the relative importance of other parameters which describe systolic cardiac augmentation and the relationship with $\dot{V}O_2$. Data points available for these analyses were at rest, at 5 minutes and when the RER > 1. All echocardiography data were linked with their corresponding $\dot{V}O_2$ data at the matching time points.

Table 8.4: Spearman's rho correlation between LVEF, systolic volume, SV, CO and GLS and corresponding $\dot{V}O_2$ for all participants (n=57)

	Relative $\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	Absolute $\dot{V}O_2$ ($mL \cdot min^{-1}$)
Mean S' ($cm \cdot s^{-1}$)	0.79 (p<0.0001)	0.84 (p<0.0001)
LVEF (%)	0.70 (p<0.0001)	0.67 (p<0.0001)
ESV (mL)	-0.32 (p<0.0001)	-0.21 (0.01)
SV (mL)	0.38 (p<0.00001)	0.51 (p<0.0001)
GLS (%)	-0.51 (p<0.0001)	-0.46 (p<0.0001)

S' – Systolic longitudinal velocity; $\dot{V}O_2$ – oxygen uptake; LVEF – Left ventricular ejection fraction; ESV – end systolic volume; SV – stroke volume; GLS – global longitudinal strain

A multivariate regression model was established to determine which aspect of systolic augmentation was able to predict $\dot{V}O_2$. All available data point for each individual for LVEF (Figure 8.5), SV (Figure 8.6) and GLS (Figure 8.7) were plotted against corresponding $\dot{V}O_2$ values.

Multivariate regression predicted that mean S' ($\beta = 0.59$, $p<0.001$) and LVEF ($\beta = 0.25$, $p = 0.001$ were significant predictors for relative $\dot{V}O_2$. The overall model fit was $R^2 = 0.66$, $p<0.0001$. For absolute $\dot{V}O_2$ the significant predictors were mean S' ($\beta = 0.62$, $p<0.0001$) and LVEF ($\beta = 0.21$, $p <0.0001$). The overall model fit was $R^2 =0.71$, $p<0.0001$.

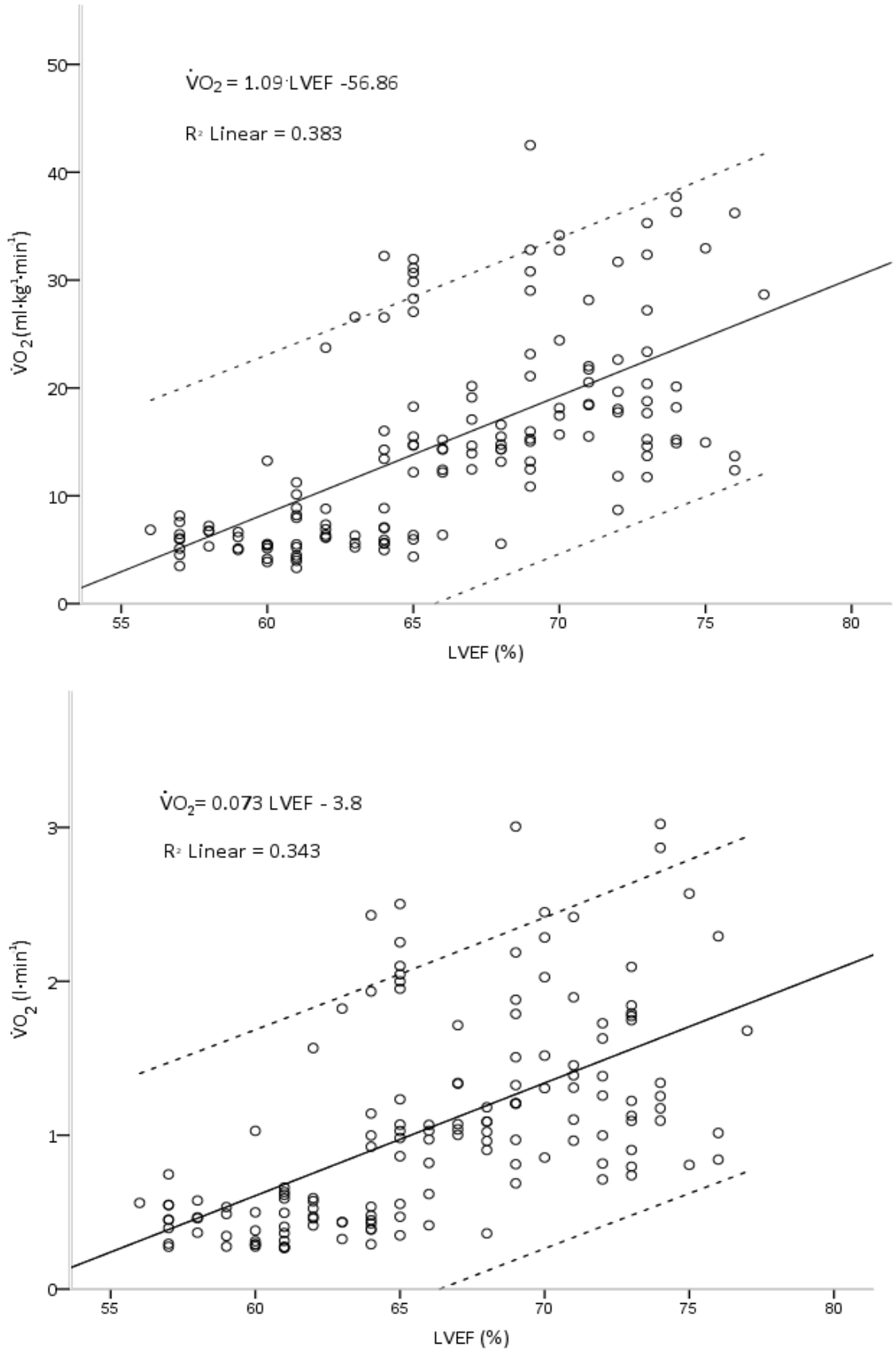


Figure 8.5: Scatterplots for all available data points for each individual for the relationship between LVEF and corresponding $\dot{V}O_2$ values (relative $\dot{V}O_2$ – top and absolute $\dot{V}O_2$ - bottom)

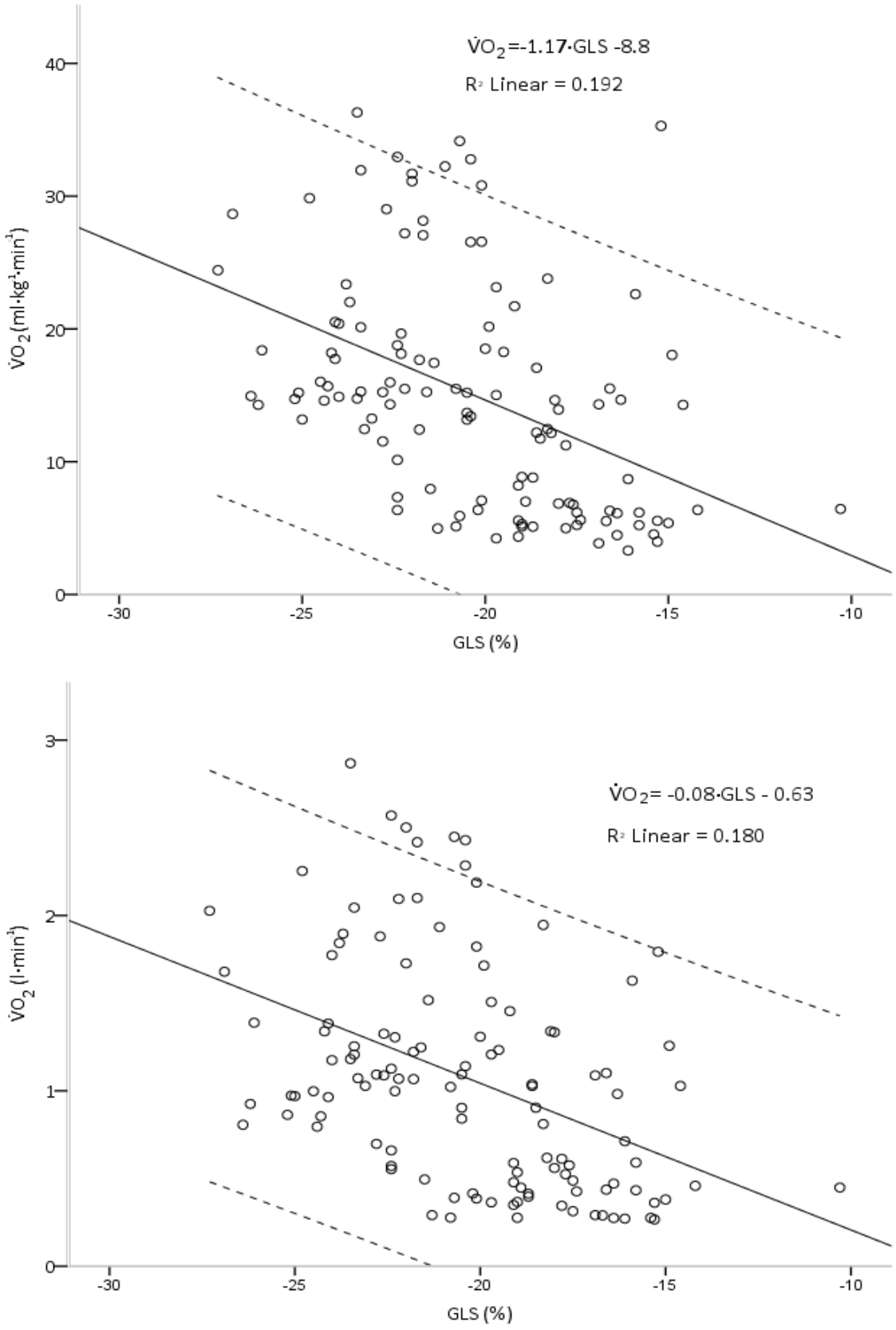


Figure 8.6: Scatterplots for all available data points for each individual for the relationship between GLS and corresponding $\dot{V}O_2$ values (relative $\dot{V}O_2$ – top and absolute $\dot{V}O_2$ - bottom)

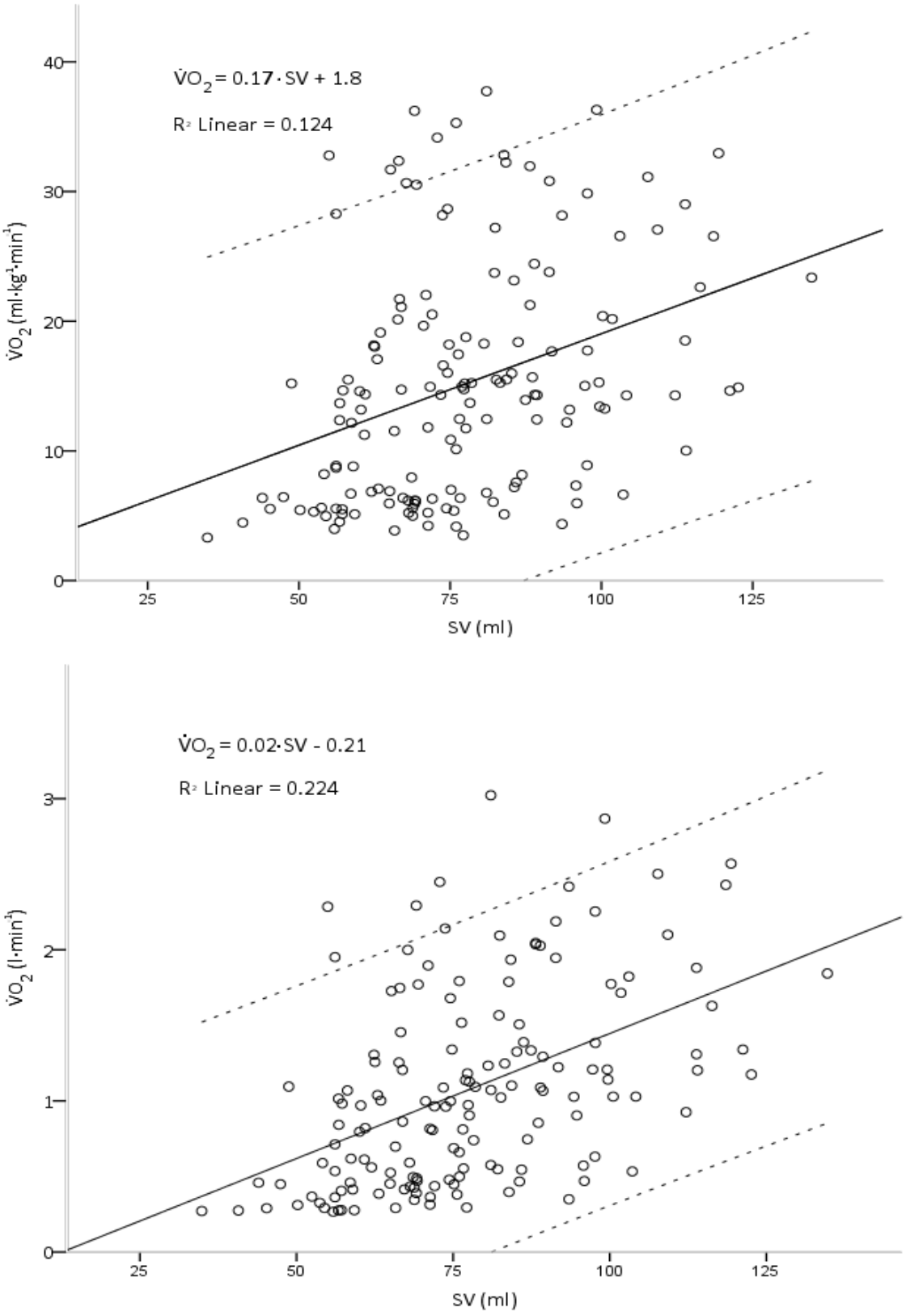


Figure 8.7: Scatterplots for all available data points for each individual for the relationship between SV and corresponding $\dot{V}O_2$ values (relative $\dot{V}O_2$ – top and absolute $\dot{V}O_2$ - bottom)

8.4.3 GLS and systolic longitudinal function

A sub analyses looked in more detail into the GLS and S' relationship. There was a significant relationship between mean S' and GLS (r = -0.56, p<0.0001). When performing the multivariate regression analysis S' was a stronger predictor for $\dot{V}O_2$ than GLS, for relative $\dot{V}O_2$ (R^2 = 0.61, β = 0.76; p<0.0001); and for absolute $\dot{V}O_2$ (R^2 = 0.67, β = 0.84; p<0.0001).

8.4.4 Systolic augmentation and $\dot{V}O_2$ relationship

The ratio of S' to $\dot{V}O_2$ was established in the form of the regression parameters of $\dot{V}O_2$ / S' slope calculated for each individual participant to establish whether the amount of $\dot{V}O_2$ increased for every incremental unit of systolic velocity could predict exercise tolerance. Figure 8.8 shows an example of an individual participant. The slope function was averaged for all participants (Table 8.5).

Table 8.5: Average slope functions

Slope	Mean ± SD
Sep S' / Relative $\dot{V}O_2$	4.2 ± 1.6
Lat S' / Relative $\dot{V}O_2$	4.5 ± 2.0
Sep S' / Absolute $\dot{V}O_2$	0.30 ± 0.12
Lat S' / Absolute $\dot{V}O_2$	0.33 ± 0.15
Sep S' / WR	33.1 ± 11.6
Lat S' / WR	36.7 ± 16.2
Sep S' / HR	13.8 ± 3.0
Lat S' HR	14.6 ± 3.6

Sep – septal; Lat – lateral; S' – systolic longitudinal velocity; $\dot{V}O_2$ – oxygen uptake; WR – work rate; HR – heart rate

This analysis demonstrated a significant regressive relationship between the septal S'/ relative $\dot{V}O_2$ slope and relative $\dot{V}O_{2peak}$ (r = 0.62; p<0.0001) and lateral S'/relative $\dot{V}O_2$ slope and relative $\dot{V}O_{2peak}$ (r =0.44; p<0.0001). The septal S'/absolute

$\dot{V}O_2$ slope and absolute $\dot{V}O_{2peak}$ showed a significant relationship ($r = 0.71$; $p<0.0001$) and lateral S' / absolute $\dot{V}O_2$ slope and absolute $\dot{V}O_{2peak}$ ($r = 0.61$; $p<0.0001$). The relationship was stronger for the septum than the lateral wall and for stronger for absolute as opposed to relative $\dot{V}O_{2peak}$. This data is suggestive that the slope is able to predict peak $\dot{V}O_2$ values.

8.4.5 Submaximal analysis

A significant relationship was found between the septal S'/ $\dot{V}O_2$ slope and the OUES ($r = 0.64$; $p<0.0001$) and lateral S' / $\dot{V}O_2$ and OUES ($r = 0.64$; $p<0.0001$) and for the septal S'/ $\dot{V}O_2$ slope and the $\dot{V}O_2$ at the VT ($r = 0.65$; $p<0.0001$) and lateral S' / $\dot{V}O_2$ and the VT ($r= 0.57$; $p<0.0001$). This data is suggestive that there is a relationship between submaximal variables and the S' / $\dot{V}O_2$ slope (Figure 8.9).

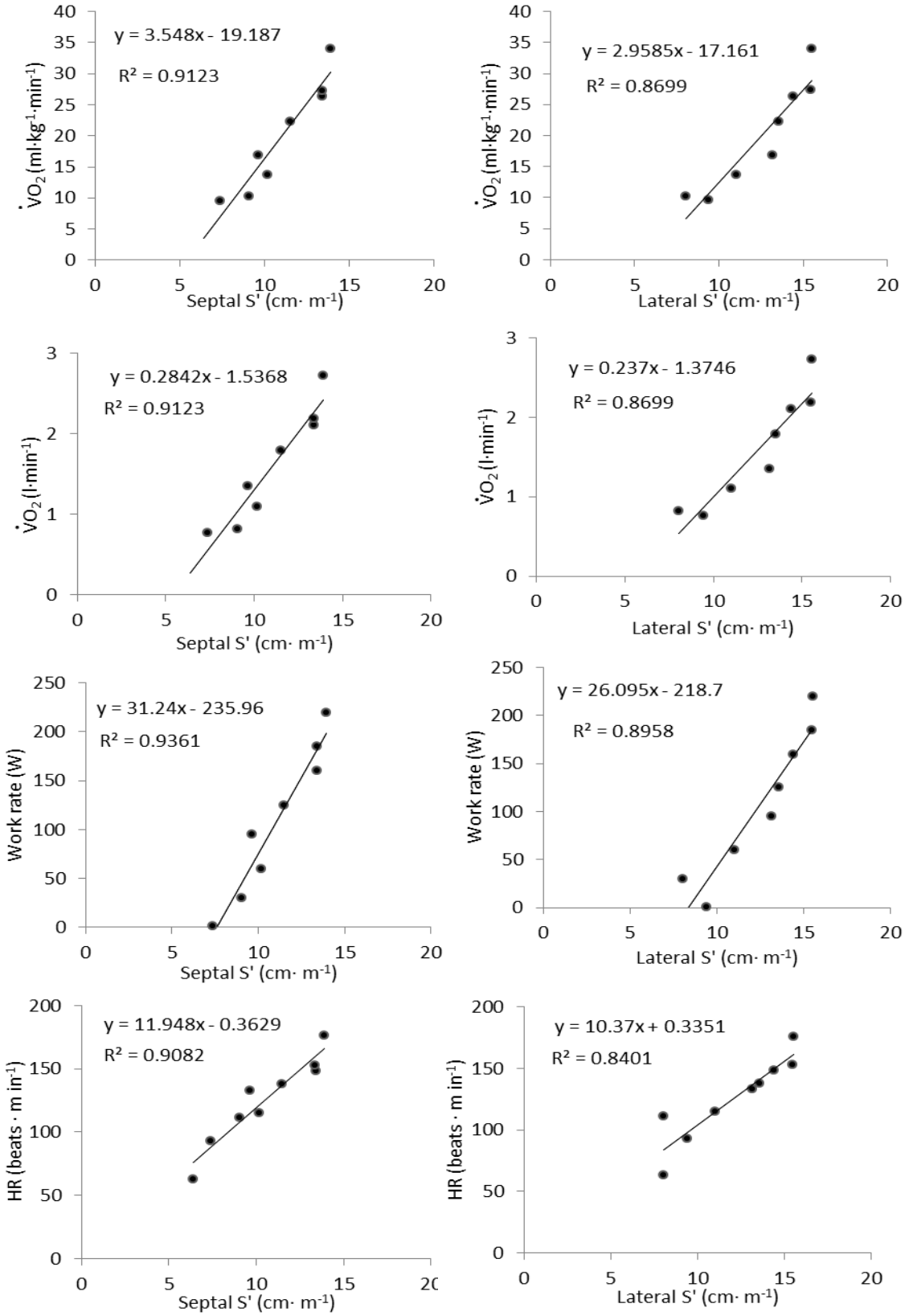


Figure 8.8: Individual slopes for 1 participant. $\dot{V}O_{2\,peak}$ – 3.1 L·min^{-1} / 38.8 mL·kg^{-1}·min^{-1}; peak HR – 175 beats·min^{-1} and peak work rate 265 W

$\dot{V}O_2$ – Oxygen uptake; S' – systolic longitudinal velocity; HR – heart rate

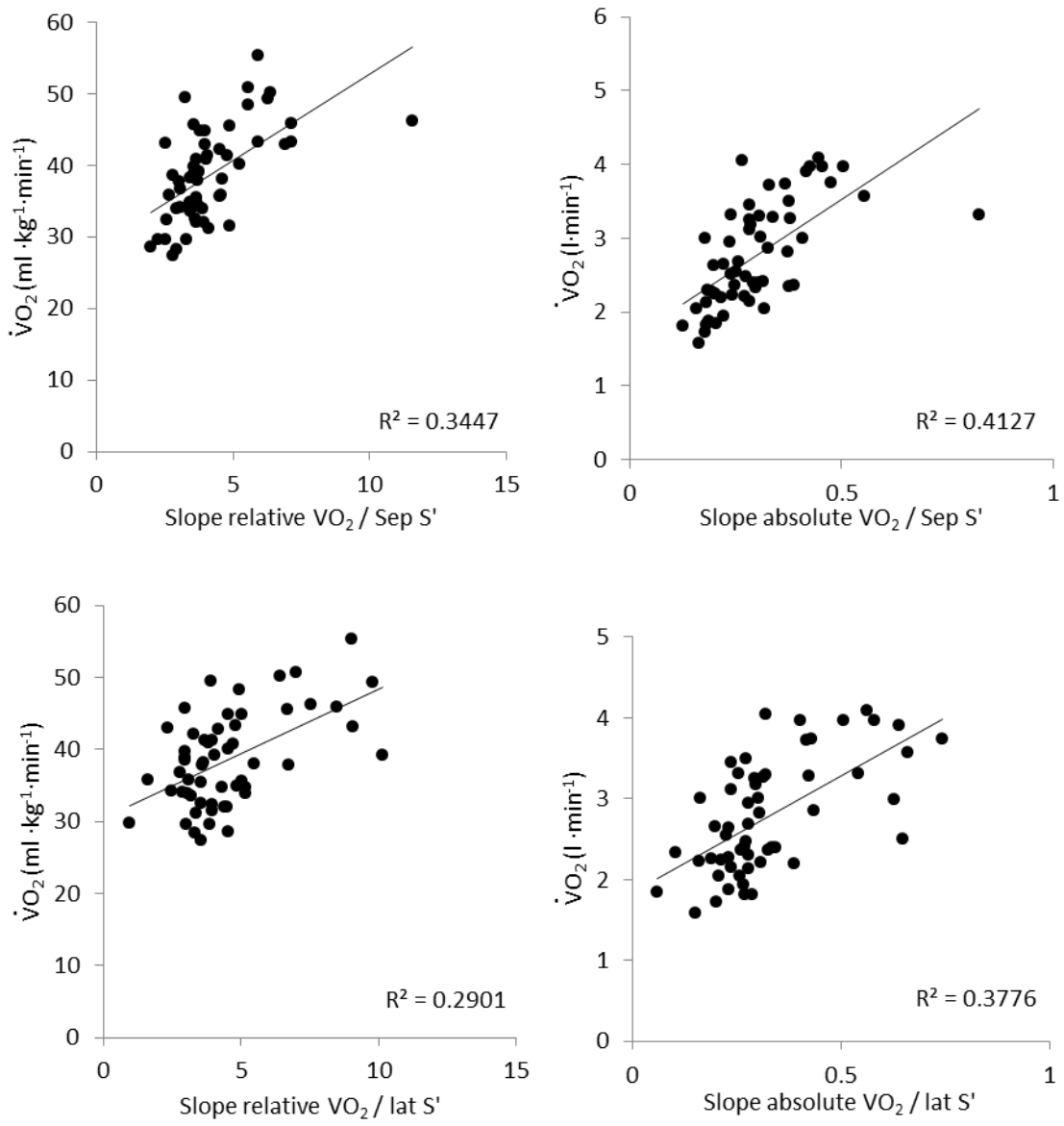


Figure 8.9: $\dot{V}O_2$ / S' slope vs. $\dot{V}O_{2\,peak}$ for absolute and relative $\dot{V}O_2$ and septal and lateral S' for all participants

$\dot{V}O_{2\,peak}$ – peak oxygen uptake; S' systolic longitudinal velocity; Sep -Septal; Lat – Lateral

8.4.6 Inter- and intraobserver variability

Interobserver variability measured by ICC was strong for $\dot{V}O_{2\,peak}$; ICC: 0.99; (95% CI: 0.98-1) and for OUES; ICC: 1; (95% CI: 0.99 – 1). $\dot{V}O_2$ at the VT was slightly weaker; ICC: 0.71 (95% CI: 0.344-0.89). The intraobserver variability was strong for $\dot{V}O_{2\,peak}$; ICC: 0.99; (95% CI: 0.97-1) and for OUES; ICC: 0.98; (95% CI: 0.94 – 0.99). $\dot{V}O_2$ at the VT was slightly weaker; ICC: 0.86 (95% CI: 0.64-0.95).

8.5 Discussion

This study assessed the normal systolic myocardial augmentation responses with corresponding $\dot{V}O_2$ to exercise in a cohort of healthy first time marathon runners. The increase in S' with increase in $\dot{V}O_2$ was found to have a linear relationship, which was not what was expected in the hypotheses. Increase in $\dot{V}O_2$ also demonstrated a linear relationship with work rate and HR. These findings can be used as reference values for normal augmentation responses to exercise. S' showed a stronger relationship than any other facet of systolic function and although LVEF also increased the strength, this relationship was less, this was in agreement with the second hypotheses. The S' / $\dot{V}O_2$ slope was able to predict $\dot{V}O_{2peak}$, and OUES, again agreeing with our hypotheses. This strongly suggesting that the $\dot{V}O_2$ / S' relationship is about contractile performance coupling rather than describing two co linear variables that increase with exercise. It also represents a novel means for evaluation of cardiac performance which may be important in other disease states when participants are not able to exercise to exhaustion, as valuable information can be obtained from submaximal data.

The strength of the current study is the simultaneous measurement of echocardiographic and CPET parameters at numerous stages during exercise which enhances our understanding of systolic myocardial augmentation and $\dot{V}O_2$, and has never been described previously. Some studies have used echocardiographic measurement to describe cardiac function but these studies only used echocardiography values obtained at rest and peak exercise or at a predetermined HR (Bandera *et al.*, 2017; Goebel *et al.*, 2007; Punn *et al.*, 2012) but fail to describe any submaximal values or compare these to $\dot{V}O_2$ values.

Combining exercise echocardiography and CPET adds a significant understanding of myocardial augmentation and exercise tolerance. Laufer-Perl *et al.*, (2017) combined exercise echocardiography with CPET in patients with MS. Measurements were obtained at rest, during unloaded cycling, at the VT and at peak exercise. Results showed that healthy participants had a greater increase in S', E', SV, LVEF compared to patients with MS. It is difficult to determine the augmentation of the slopes in this

study as time points were not obtained every minute but at different stages of exercise (during unloaded cycling, at the VT, and at peak exercise). The VT is an important measurement during a CPET as this is a submaximal measurement which often is the point patients start to feel breathless and some studies have found the VT to be superior than $\dot{V}O_{2\,peak}$ in prognostic value (Madonna *et al.*, 2012; Older *et al.*, 1993, 1999; Older, 2013). The VT occurs because there is an increased requirement of excess $\dot{V}CO_2$ and therefore a breakpoint in the $\dot{V}CO_2$ – $\dot{V}O_2$ graph appears. However, as this breakpoint is determined post exercise using the V-slope method, since all data is needed for accurate determination, it is unclear how the authors managed to obtain echocardiographic images at the VT. The VT in the present study showed a good relationship with the $\dot{V}O_2$ / S' slope suggesting that the relationship between exercise parameters and S' is linear and has prognostic value.

8.5.1 Augmentation during exercise

The trajectory for $\dot{V}O_2$ is well known. Typically, $\dot{V}O_2$ increases linearly with work rate until a plateau is reached. This plateau in combination with a peak RER > 1.1 and a HR within 10 beats·min^{-1} of age predicted maximum suggest that a $\dot{V}O_{2\,max}$ has been reached. The term was first introduced by Hill and Lupton in 1923 as the oxygen intake during an exercise intensity at which actual $\dot{V}O_2$ reaches a maximum beyond which no increase in effort can increase it (Hill and Lupton, 1923). However in the clinical setting these criteria are rarely met and therefore the term $\dot{V}O_{2\,peak}$ is used which describes the highest $\dot{V}O_2$ attained during a test. Previous research found a good relationship between peak S' and $\dot{V}O_{2\,peak}$ (McIntosh *et al.*, 2013). The trajectory of the S' slope has not yet been described in detail in adults. Cifra *et al.*, (2016) described the myocardial response to exercise in a paediatric cohort and its relation to HR. The study demonstrated high feasibility for TVI acquisition and excellent intra- and interobserver variability of TVI values, in at least 96% of participants TVI was successfully obtained. These parameters are excellent parameters to describe systolic myocardial function. The myocardial response to exercise was described for systolic and diastolic parameters and linear relationships were found for S', E', E/E', strain in relation to HR.

The authors concluded that colour TVI and GLS are robust methods when assessing myocardial response to exercise.

8.5.2 Contractile reserve

Contractile reserve is described using many different parameters. It is the evaluation in LV functional response under exercise stress. This can be measured using echocardiographic modalities. Echocardiography is a non-invasive and relatively easy way to obtain information regarding patients well-being. Failure to increase contractile reserve is associated with higher mortality, more events and hospitalisations (Pedone *et al.*, 2005). In patients with valvular heart disease, exercise echocardiography can be used to assess dynamic valve function by measuring changes in haemodynamic gradients or the severity of regurgitation during exercise (Bonow *et al.*, 2006; Vahanian *et al.*, 2012). The most common parameters are LVEF, volume change, S', GLS, and change in diastolic parameters.

8.5.2.1 LVEF

The most frequently used parameter to describe cardiac function is LVEF. However resting LVEF is not able to predict $\dot{V}O_{2peak}$ (Benge *et al.*, 1980; Carell *et al.*, 1994; Cohn *et al.*, 1993). Cohn *et al.*, (1993) included 763 men and found a large variety in resting LVEF and $\dot{V}O_{2peak}$. However obtaining LVEF during exercise does have incremental prognostic value. HF patients who were able to increase their LVEF 5% or more had a better prognosis than those we were unable to increase their LVEF (Bax *et al.*, 1999; Pedone *et al.*, 2005; Werner *et al.*, 1994). Lancellotti *et al.*, (2009) found that HF patients who were able to increase their LVEF were more likely to benefit from CRT, and vice versa. The inability to increase LVEF during stress echocardiography has been shown to be a strong predictor for mortality (Pedone *et al.*, 2005). A recently published meta-analysis by Waddingham *et al.*, (2017) included 9 studies which primarily used two different criteria for contractile reserve, wall motion score index and change in LVEF. Authors concluded that non-ischaemic patients with contractile reserve have lower mortality and fewer hospital admissions. However, as previously mentioned,

LVEF can be challenging to obtain reliably and has some major limitations including a lack of reproducibility, dependence on loading conditions and it only describes maximum displacement at the end of systole meaning the longitudinal component of systolic function is not completely described.

8.5.2.2 Systolic longitudinal velocity

Peak S' and $\dot{V}O_{2peak}$ show a good correlation in a range of cardiac patients and healthy individuals (Ciampi *et al.*, 2013; McIntosh *et al.*, 2013). A reduced peak exercise S' has shown to be impaired in patients with HF (van Zalen *et al.*, 2015), in patients with HCM (Ha *et al.*, 2006), and in patients with type II diabetes mellitus (Ha *et al.*, 2007). However S' augmentation during exercise is still poorly described. Cifra *et al.*, (2016) describes a linear relationship between S' and HR with exercise in a paediatric cohort and describes good reproducibility and less variability compared to GLS obtained during exercise. Our study is in agreement as a linear relationship was found between S' and HR.

8.5.2.3 Diastolic parameters

Diastolic function and exercise has been given substantial interest over the past few years, especially in patients with HF and preserved LVEF. Several studies found an independent relationship between left ventricular diastolic dysfunction and exercise tolerance (Grewal, 2009; Mogelvang *et al.*, 2009; Wang *et al.*, 2003, 2005). A study by Kasner *et al.*, (2015) included 52 patients with HFPEF and 26 control patients and found a failure in E' wave in 27 patients which correlated with a fall in SV suggesting that impaired diastolic reserve contributed to exercise intolerance in patients with HFPEF. Cifra *et al.*, (2016) found a linear relationship between E' and HR with exercise in healthy children. A study by Vinereanu *et al.*, (2002) investigated systolic and diastolic parameters at rest and during exercise in athletes and healthy controls. Exercise tolerance was best predicted from the E/A ratio at rest, EDV and diastolic longitudinal velocity during exercise. Authors concluded that $\dot{V}O_{2peak}$ was determined by diastolic loading and early relaxation rather than by systolic function. Although E'

and A' waves, have been shown to have prognostic value, the difficulty remains in measuring the separate E and A waves as fusion of these waves is often seen with exercise. Different criteria are used to differentiate these waves, making comparison between studies difficult and therefore obtaining diastolic parameters on exercise remains problematic. The main difficulty arises in how to determine the influence of diastolic function on exercise as there is a relatively close relationship between S' and E' making it difficult to determine which is more dominant. Diastolic function has a significant relationship with systolic function and may often not be fully valued. Early diastolic motion (caused by mitral annular descent) is one of the main determents for the release of energy stored during systole, and therefore, S' and other systolic measures also inevitably describe in part the behaviour of the myocardium during early diastole (Notomi *et al.*, 2006; Pacileo *et al.*, 2003).

8.5.2.4 Global longitudinal strain

Strain imaging is an alternative for describing myocardial longitudinal function (Dandel *et al.*, 2009). Two-dimensional strain speckle tracking has the clear advantage of being angle independent compared to TVI. Speckle tracking requires higher frame rates which may not be sufficient to properly track the increased HRs at exercise. This may result in under sampling, especially during exercise. Recent studies have suggested a potential benefit of speckle track derived GLS in detected reversible ischaemia during dobutamine stress echocardiography but routine use especially during exercise echocardiography is limited due to the limited range of HRs which can be sampled (Moonen *et al.*, 2009; Sicari *et al.*, 2008). Our study shows a linear relationship between GLS and $\dot{V}O_2$. Joyce *et al.*, (2015) found a reduced rest to peak GLS to be correlated with significant coronary artery disease and suggest that GLS is the optimal parameter for the detection of ischaemia. A sub-analysis in this study found that there was a strong relationship between S' and GLS but exercise S' was a stronger predictor for $\dot{V}O_2$ than GLS when entered in a multivariate model. Cifra *et al.*, (2016) also described GLS during exercise and a linear relationship with HR was found. The authors described GLS to be a measurement feasible to obtain during exercise but when compared to S' there was a larger variability noted.

This study shows that septal S' was a stronger predictor for $\dot{V}O_2$ than lateral S'. Potential explanation for this might be because TVI is angle dependent. The apical 4-chamber view was optimised for the septal wall which provides an optimal angle for the septal S'. However this often resulted in a worse alignment providing a lesser angle to obtain the lateral S', which may explain why the lateral s' was a less powerful predictor for $\dot{V}O_2$.

The slope of S' / $\dot{V}O_2$ was ascertained if submaximal S' had any valuable prognostic power. This is particularly important for patients who are not able to exercise until exhaustion due to musculoskeletal problems or other underlying conditions. Results showed that the ratio of S' to $\dot{V}O_2$ was able to predict $\dot{V}O_{2\,peak}$ values. The S' / $\dot{V}O_2$ slope was also determined for OUES and the VT with strong correlation found. This new and unique relationship should be investigated in more detailed especially in patients with diseased myocardium to determine if this may be a potential explanation for a reduction in exercise tolerance.

8.5.3 Limitations

Septal S' was a better predictor for $\dot{V}O_2$ than lateral S'. This is probably due to angle of TVI values obtained. The septum is often vertical with the TVI sample line but the lateral wall was often not optimised for the change and angle and this might have contributed to the changes in values.

No diastolic parameters were reported. The purpose of this study was to investigate the relationship between systolic parameters and $\dot{V}O_2$. The population also had no diastolic abnormalities and therefore obtaining these would not be relevant. Also as the population investigated is relatively young – high HR were obtained – no accurate diastolic parameters are obtainable at these HRs as it becomes too difficult to distinguish between E and A waves. Colour TVI aliasing velocity was set at 16 $cm \cdot s^{-1}$ which may have been because of technical limitations.

8.6 Conclusion

This study clearly describes the strong relationship between longitudinal function (as expressed by S') and $\dot{V}O_2$ through exercise. S' which represents early systolic function seems to be more important than other systolic parameters including GLS which also describes longitudinal function and is considered the 'gold standard'.

The S' / $\dot{V}O_2$ relationship shows that the augmentation is linked to $\dot{V}O_{2peak}$ which shows that the relationship is more than simply collinearity. It also offers a novel parameter to evaluate disease states where this relationship may be different.

A detailed understanding of contractile recruitment was established and this provides additional mechanistic information about changes in heart function. The relationship between the augmentation slope (S' / $\dot{V}O_2$) and $\dot{V}O_{2peak}$ may provide prognostic information for patients who are not able to exercise until maximal exhaustion. More research is needed to investigate the S' / $\dot{V}O_2$ relationship in diseased myocardium. Obtaining augmentation data during exercise can have clinical relevance as it provide valuable information on cardiac function which may be different than normal during exercise, implying underlying cardiac dysfunction that are not apparent at rest.

The examination of early systolic velocity and CPET not only provides a unique insight into myocardial function not available by other means but also strongly suggest that at least in normal individuals, systolic velocity and its augmentation is a key determinant of exercise ability.

CHAPTER 9

GENERAL DISCUSSION AND FUTURE RESEARCH

The main aim of the thesis was to describe the additional diagnostic benefit and mechanistic insights that could be gained by combining exercise echocardiography and CPET. This technique was applied in a variety of different situations to describe the extent of the relationship between exercise and myocardial function. A wide variety of patients with cardiac disease were recruited including; patients with AF, patients with HF, patients awaiting CRT implantation and patients with severe AS. A group of healthy participants was included to critically describe the normal augmentation curve using S' and its relationship to an increase in $\dot{V}O_2$ during incremental exercise. The main hypothesis was that exercise echocardiography can effectively be combined with CPET and valuable information is obtained for the patient, physiologist and consultant to better manage cardiac patients.

Integrating CPET and echocardiography connects two disciplines together; exercise physiology and cardiology. Prior to embarking on a PhD, a BSc. (Hons) in Sport and Exercise Science was followed by a MSc. in Applied Exercise Physiology. The MSc. dissertation compared exercise capacity in cardiac patients with AF and healthy controls. All patients underwent CPET testing at Eastbourne DGH. Alongside my present supervisors and cardiology staff a collaboration between the University and the hospital was initiated. Exercise science and cardiology became integral within the hospital setting which led me to a research physiologist position and an opportunity to start the PhD journey. CPET testing became the main responsibility and knowledge regarding clinical responses to exercise were obtained. Initially only research CPETs were performed, but a weekly clinical CPET service has now been established. All empirical studies have been presented at national or international conferences. The young investigator award by the British Society of Echocardiography (BSE) was awarded to me, for the study described in chapter 5. Full BSE accreditation in adult transthoracic echocardiography was achieved in 2015 and the Echo in Africa project was attended to develop key skills in echocardiography.

There were several challenges to overcome at the start of the thesis. Combining both tests required careful consideration into the technical, safety and feasibility aspects. The initial validation studies described in the methodology section demonstrated that integrating CPET with stress echocardiography was possible. No physiological response

differences in CPET were found between a semi-recumbent and the upright cycle ergometer. Stress echocardiography requires a semi-recumbent ergometer to obtain the best possible images during exercise. Adding the CPET equipment to patients was straightforward and patients tolerated the system and responded well. Integrating CPET with exercise echocardiography provides unique information regarding exercise responses. For example, CPET is able to demonstrate failure to increase oxygen pulse which is associated with a reduction in stroke volume and simultaneous echocardiography may be able to provide a possible explanation for this failure in contractile reserve.

The heart is typically imaged at rest to describe cardiac function both in heath and disease. However at rest, symptoms may not be present. Often symptoms do not appear until cardiac dysfunction is far advanced. Clinicians understandably prefer their own judgement and the most common method currently used to grade HF patients' symptoms is the NYHA classification (Table 2.5). Higher NYHA class has been associated with poorer outcomes in heart failure patients (Ahmed *et al.*, 2006; Scrutinio *et al.*, 1994). This traditional classification method is subjective and poorly reproducible. Raphael *et al.* (2007) investigated the usefulness of the NYHA classification system and found that there is poor concordance between cardiologists. Patients own judgement of their walk distance correlated poorly with actual exercise capacity measured by CPET, suggesting that there is no consistent method to assess NYHA class. However this classification system remains the base of functional assessment in clinical guidelines such as selection for CRT, mitral valve intervention (Nishimura *et al.*, 2014) and heart failure pharmacologic treatment (Ponikowski *et al.*, 2016). This subjective classification system may have major impact on deciding treatment strategies.

Guidelines primary emphasis is placed on LVEF including HF and CRT guidelines (Ponikowski *et al.*, 2016, Brignole *et al.*, 2013). The cardinal symptom for patients is exercise intolerance, but LVEF relates poorly to exercise tolerance (Carell *et al.*, 1994; Clark *et al.*, 1994; Rubis *et al.*, 2009; Witte *et al.*, 2004) and prognosis (Florea *et al.*, 2000; Grayburn *et al.*, 2005; Guazzi *et al.*, 2010b; Wang *et al.*, 2003, 2005). Exercise may cause symptoms to arise and evaluating patients during exercise may represent a

more complete evaluation of the patient. CPET is an objective measure to evaluate prognosis, risk stratification of disease progression, effect of treatments and it provides an objective assessment of a patient's exercise tolerance. Exercise can be incorporated when assessing patients and traditionally tests such as exercise tolerance tests and 6-MWTs are used. However these tests are dependent upon patients' motivation. CPET is able to objectively measure patients' exercise intolerance and is increasingly performed in everyday clinical practice. CPET may aid in the solution to these problems. This enhanced assessment unmasks symptoms which may not be apparent at rest. It is non-invasive, safe, and reproducible (American Thoracic Society, 2003; Skalski *et al.*, 2012). Most importantly it has been linked to evidence based hard end-points, including mortality and morbidity (Guazzi *et al.,* 2010; Kavanagh *et al.*, 2002, 2003; Vanhees *et al.*, 1994). While CPET provides an overall assessment of cardiopulmonary wellbeing and can differentiate cardiac from ventilatory and respiratory components, it lacks the ability to provide a detailed anatomical and pathological assessment of facets; fortunately it can be combined with echocardiography. Echocardiography is the most extensively used diagnostic test in cardiology. It is a powerful, non-invasive, and painless technique used for the diagnosis, management and follow-up in patients with cardiac disease. It provides valuable information about cardiac chambers, valves, myocardium, pericardium and the aorta. During exercise, echocardiography provides useful and valuable information regarding myocardial function and haemodynamic response and diagnostic and prognostic value.

The main aim of the thesis was to determine if stress echocardiography could be combined with CPET and to determine the benefits of this novel method of testing cardiac patients. In order to investigate parameters during exercise, an examination was carried out to determine whether resting echocardiography parameters had any ability to predict exercise tolerance in a very common representative cardiac condition: atrial fibrillation. Testing patients at rest does not provide the clinician with any insight into the likelihood of resultant symptoms. The absence of any relationship between resting echocardiographic parameters and exercise parameters justified a subsequent range of studies to examine different disease states under stress

conditions in order to establish a model to truly describe cardiac potential. Study 2 showed that S' was a highly reproducible and reliable parameter. Peak S' was able to predict prognosis to a greater extent than either diastolic parameters or LVEF. Lateral and septal S' were obtained in at least 98% of patients during exercise. Exercise S' showed the strongest association with clinical outcomes more so than traditional parameters such as LVEF. This study demonstrated that measuring S' during exercise echocardiography might have an important role in understanding the likelihood of adverse clinical outcomes in HF patients. Study three investigated whether exercise S' was able to predict a positive response to CRT. CRT has revolutionised the treatment of advancing HF, and has been shown to have impressive prognostic value (Cleland *et al.*, 2005). However there remains a group of eligible patients who do not have any beneficial symptomatic response (Bristow *et al.*, 2004) or improvements in left ventricular function (Yu *et al.*, 2003, 2004). Exercise S' and response to CRT had not previously been investigated. Results demonstrated that there was a 68% response rate to CRT and an overall improvement in functional, echocardiography, and exercise parameters. No differences were found in peak S' between responders and non-responders. Exercise S' was unable to predict a positive response to CRT and should be continued to be used as a prognosticator for future events. Study 4 included patients with severe AS. These patients are often asymptomatic for a number of years when prognosis is excellent. Mortality rises dramatically from the onset of any cardiac symptoms (breathlessness, syncope, and angina). Current guidelines suggest aortic valve replacement is indicated when patients become symptomatic or if there is echocardiographic evidence of imminent ventricular decompensation (Nishimura *et al.*, 2014). However evaluating patients at rest is challenging and not always straightforward especially in an elderly population. Around one third of 'asymptomatic patients' actually develop cardiac symptoms on exertion (Bhattacharyya *et al.*, 2013). Study four included 32 patients with severe AS over an average follow-up time of 23 months, sixteen patients were referred for aortic valve intervention. 41% of supposedly asymptomatic patients with normal LVEF had a reduced exercise tolerance and were therefore more functionally limited than they or their clinicians believe. $\dot{V}O_{2\,peak}$ was poorly correlated with conventional clinical measures of aortic valve severity, but was heavily dependent on the ability of the left ventricle to augment

longitudinal function during exercise. The burden of unplanned hospitalisation was high and this was due to more adverse ventricular remodelling, rather than valve obstruction. Combining CPET and exercise echocardiography provided a greater insight into the subtle changes which occur when patients with severe AS begin to deteriorate. The combined method provided an enhanced follow up and assisted in the clinical decision making when determining the optimal timing of aortic valve intervention. In the AS population emphasis should be more about the ventricle, under exercise conditions, and less about the valve.

The above studies highlighted the powerful relationship between systolic myocardial velocity, $\dot{V}O_{2\,peak.}$ as well as clinical outcomes. However the normal augmentation of cardiac function during exertion and its relationship to an increase in $\dot{V}O_2$ demand was still poorly described elsewhere. Previously focus had been placed on parameters obtained at peak exercise instead of the parameters obtained throughout exercise. In order to understand this relationship better, a detailed description of the relationship between S' and oxygen uptake during incremental exercise was required. Study five included 57 healthy, recreational marathon runners and investigated the relationship between $\dot{V}O_2$ and different augmentation curves including S' in much greater detail. The shape and extent of myocardial augmentation was determined. It also provided normative data and once more demonstrated the pivotal relationship between S' and $\dot{V}O_2$. The nagging doubt that this was just an epiphenomena was addressed by creating a unique joint parameter between S' and $\dot{V}O_2$. The slope of this relationship is an entirely new way of looking at the prediction of exercise performance and the change in unit velocity per unit $\dot{V}O_2$ in this study, enabled a strong prediction of $\dot{V}O_{2peak}$. The study demonstrated that both mechanistic and performance parameters used together can provide additional predictive accuracy.

9.1 Future research

The present thesis has critically determined the novel and exciting combination of exercise echocardiography and CPET, and the additional value when incorporated into daily clinical practice. It is relatively straightforward to combine a CPET with an exercise echocardiography protocol. The complex relationship between exercise echocardiography and CPET in a variety of different cardiac patients has been described and relationships between exercise parameters and myocardial function have been described in detail in healthy myocardium. Future work will incorporate a wider age range to understand the biological progression of these relationships as well as the effect of interventions such as training.

The direction of future research includes extending these findings to various cardiac patients. Studies extending and further developing the key findings are already underway these include a study of patients with severe AS. The study uses stress echocardiography and CPET and the use of a continuous implantable sensor to detect deterioration in patients with asymptomatic severe AS under a 'watchful waiting' programme. The thesis already highlights some of the limitations of current understanding of AS, consequently the study is being carried out in order to establish an enhanced understanding in patients with moderate AS and symptom progression, ventricular and vascular involvement, using the combination of CPET and exercise echocardiography, biomarker measurement and a non-invasive measurement of central blood pressure.

A second study again using concept from the present thesis will include patients with primary MR in order to determine the optimal time cut-off for intervention. MR, like AS is an area where there is significant confusion on the timing of the intervention. The study will include approximately 250 patients from Eastbourne DGH and St. Bartholomew Hospital. LV longitudinal and torsion deformation, 3D volumes parameters and their relationship to the severity of MR will be examined. Also in asymptomatic patients with moderate to severe primary MR, correlation between LV mechanics variables to exercise testing variables from CPET including $\dot{V}O_{2max}$ and OUES as well as follow up symptoms will be assessed.

A third proposed study will examine right and left ventricular mechanics during exercise stress in relation to functional capacity and recovery following surgery in patients with Tetralogy of Fallot and pulmonary regurgitation. Pulmonary regurgitation is a frequent adult complication following childhood repair of Tetralogy of Fallot. The condition may lead to progressive right ventricle dilation and right sided HF if not corrected. Although the stages of right ventricular dysfunction have been studied in detail, the pathophysiology of right ventricular dysfunction in late survivors remains poorly understood. The optimal timing of pulmonary valve replacement remains contentious, as the decision should be balanced between the risks of re-intervention and irreversible right ventricular failure. Correlation between $\dot{V}O_{2\,peak}$ and right ventricular function and whether right ventricular systolic and diastolic parameters can predict exercise capacity is still an area of controversy. The study intends to extend and further develop the findings from the thesis and apply them to the right ventricle, advancing the understanding of pathophysiology, treatment strategies and their relationship to exercise capacity in patients with repaired Tetralogy of Fallot.

A fourth proposed study plans to use the combination of exercise echocardiography and CPET in a cohort of patients with HCM. LVEF is often normal in these patients, but other major problems with myocardial function are present. The best method of assessing this subgroup of highly symptomatic patients with mid-cavity HCM is unknown, and as such this study will collect data on different symptoms and exercise performance assessments. As demonstrated there are numerous ways of taking forward the key concepts gained from the present PhD which will be valuable not only for research purposes but ultimately for diagnosis, treatment and ultimately for the benefit to the patient.

9.2 Conclusion

This thesis demonstrates a novel and exciting new way to describe myocardial function by fusing two well validated techniques. During exercise, symptoms are often exacerbated and therefore the logical condition to evaluate patients. CPET is a complete, objective and reproducible description of a patients exercise tolerance. It is able to provide unique and invaluable insights into disease status and disease mechanisms and is increasingly used in everyday clinical practice. CPET fills an important unmet clinical need. Echocardiography is a useful and non-invasive test which provides important information regarding cardiac function. Evaluation under exercise conditions is increasingly recognised as adding both diagnostic and prognostic information in non-ischaemic heart disease as it permits simultaneous assessment of myocardial function and haemodynamic response and its diagnostic and prognostic value. Traditional tools such as exercise tolerance tests and 6MWTs are so confounded by patients' motivation that clinicians understandably prefer their own judgement. In most major trials and guidelines, the NYHA classification remains the bedrock of functional assessment. Integrating CPET with exercise echocardiography provides unique and robust data that can provide new and valuable insights into disease processes. This thesis has demonstrated that this integrated test provides important prognostic data in heart failure patients and may be able to assist in timing for valve intervention in patients with severe AS. Not only this but it has also provided a deeper mechanistic insight into the relationship between heart function and exercise ability, especially systolic longitudinal velocity. This has been explored in a large homogenous cohort of healthy individuals where the augmentation of cardiac function in relation to increasing oxygen uptake was described for the first time. In summary this thesis demonstrated that contractile function and $\dot{V}O_2$ are heavily linked and examining them both simultaneously provides mechanistic and diagnostic insights not available by any other means.

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Yu, C.-M., Fung, W.-H., Lin, H., Zhang, Q., Sanderson, J. E., and Lau, C.-P. (2003) Predictors of left ventricular reverse remodeling after cardiac resynchronization therapy for heart failure secondary to idiopathic dilated or ischemic cardiomyopathy. *The American Journal of Cardiology* 91(6): 684–688.

Yu, C.-M., Sanderson, J. E., Marwick, T. H., and Oh, J. K. (2007) Tissue Doppler Imaging: A New Prognosticator for Cardiovascular Diseases. *Journal of the American College of Cardiology* 49(19): 1903–1914.

APPENDIX A: REC ETHICAL APPROVAL

Health Research Authority

NRES Committee South East Coast - Brighton and Sussex
Health Research Authority
Ground Floor, Skipton House
80 London Road
London
SE1 6LH
Tel: 02079722551

30 April 2013

Dr Guy Lloyd
Consultant Cardiologist
East Sussex Healthcare NHS Trust
Eastbourne District General Hospital
Kings Drive
Eastbourne
BN21 2UD

Dear Dr Lloyd

Study title:	**Can Exercise induced changes in cardiac Synchrony Predict response to CRT (EXERT)**
REC reference:	**09/H1107/95**
Amendment number:	**modified amendment dated 18/3/2013 (1-26/11/2012, 2-13/2/13)**
Amendment date:	**18 March 2013**
IRAS project ID:	**30456**

Thank you for submitting the above amendment, which was received on 08 April 2013. It is noted that this is a modification of an amendment previously rejected by the Committee (our letter of 26 February 2013 refers).

The modified amendment has been considered on behalf of the Committee by the Vice-Chair.

Ethical opinion

I am pleased to confirm that the Committee has given a favourable ethical opinion of the modified amendment on the basis described in the notice of amendment form and supporting documentation. The Vice-Chair suggested that a stamped addressed envelope accompany the letter of invitation.

Approved documents

The documents reviewed and approved are:

Document	Version	Date
Summary/Synopsis	Summary of changes to EXERT	07 November 2012
	protocol version 1	
Modified Amendment	modified amendment dated 18/3/2013 (1-26/11/2012, 2-13/2/13)	18 March 2013
Covering Letter	Amended letter versinon 3	19 March 2013
Letter of invitation to participant	2	19 March 2013
Participant Consent Form	4	19 March 2013
Participant Information Sheet	5	19 March 2013
Protocol	6	19 March 2013

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

09/H1107/95:	**Please quote this number on all correspondence**

Yours sincerely

p.p. C A Bruce

Dr Simon Walton
Chair

E-mail: NRESCommittee.SECoast-BrightonandSussex@nhs.net

Copy to: *Ms Mary Nagle, East Sussex Hospitals NHS Trust*

APPENDIX B: BRITISH SOCIETY OF ECHOCARDIOGRAPY ACCREDITATION

Accreditation Certificate

THIS IS TO CERTIFY THAT

Miss J.J. Van Zalen

IS ACCREDITED BY THE SOCIETY AT

PROFICIENCY LEVEL

IN ADULT TRANSTHORACIC ECHOCARDIOGRAPHY

President

Chair, Accreditation Committee

Date: 4th July 2015 Valid Until: 31st December 2020

British Society of Echocardiography
Affiliated to the British Cardiovascular Society

Association of Cardiothoracic Anaesthetists

intensive care society
care when it matters

APPENDIX C: ADDITIONAL STATISTICAL MEASUREMENTS CHAPTER 8

Linear regression assumptions were determined as follows. A linear relationship was determined. The residuals of the regression (errors between observed and predicted values) had to be normally distributed. The Predicted Probability plot shows that the residuals are normally distributed for all models (Figure A1).

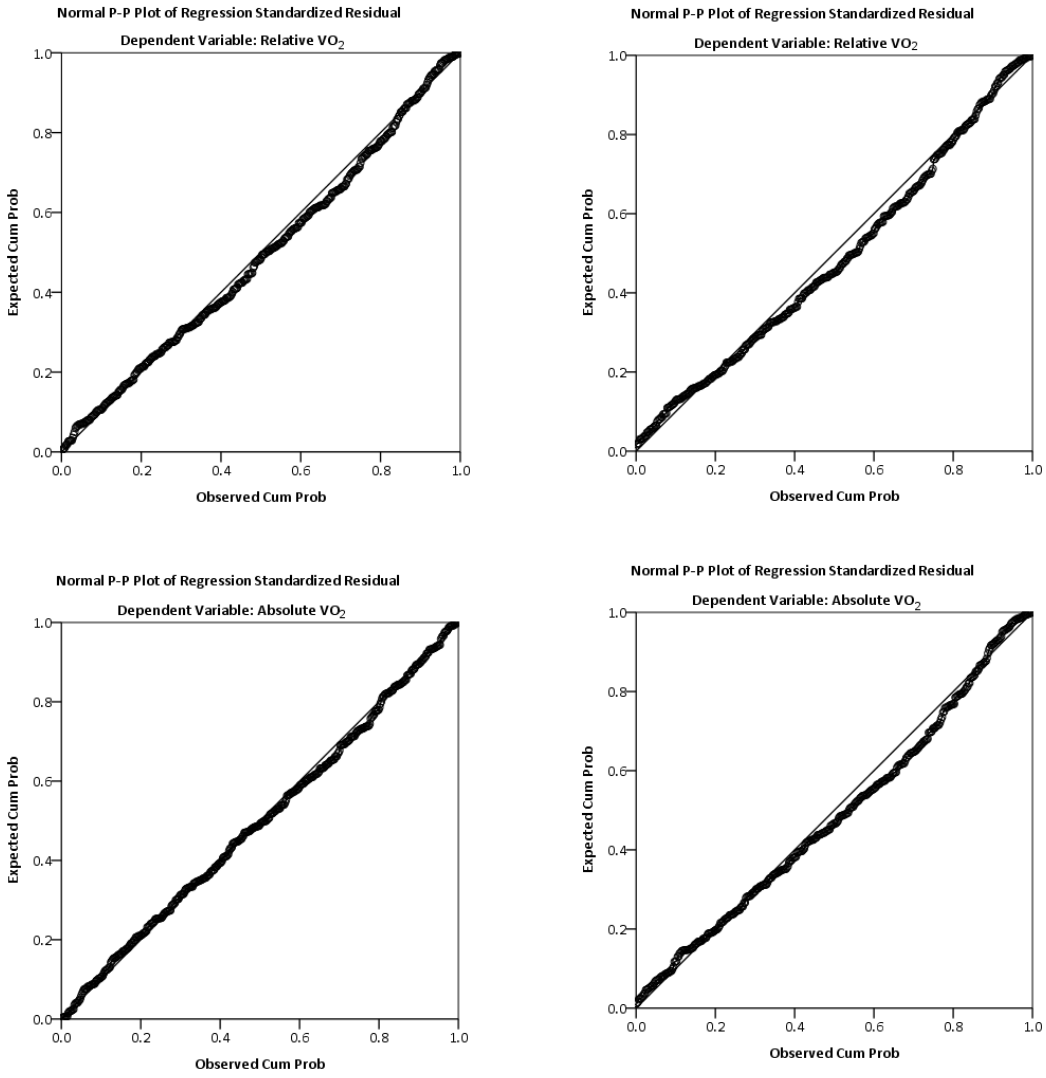


Figure A1: P-Plots for linear regression model for a) relative $\dot{V}O_2$ and septal S' (top left); b) relative $\dot{V}O_2$ and lateral S'(top right); c) absolute $\dot{V}O_2$ and septal S' (bottom left); and d) absolute $\dot{V}O_2$ and lateral S' (bottom right)

Further analyses showed good homoscedasticity observed for the data for both septal S' vs. relative $\dot{V}O_2$ and lateral S' vs. relative $\dot{V}O_2$ (graph 7.1). There is no obvious pattern observed and points are equally distributed above and below zero on the X- axis confirming linearity for our data.

Figure A2 below demonstrates the residual plot for septal S' as independent variable and relative $\dot{V}O_2$ as dependent variable (Figure A2) and the residual plot for lateral S' as independent variable and relative $\dot{V}O_2$ as dependent variable (Figure A3).

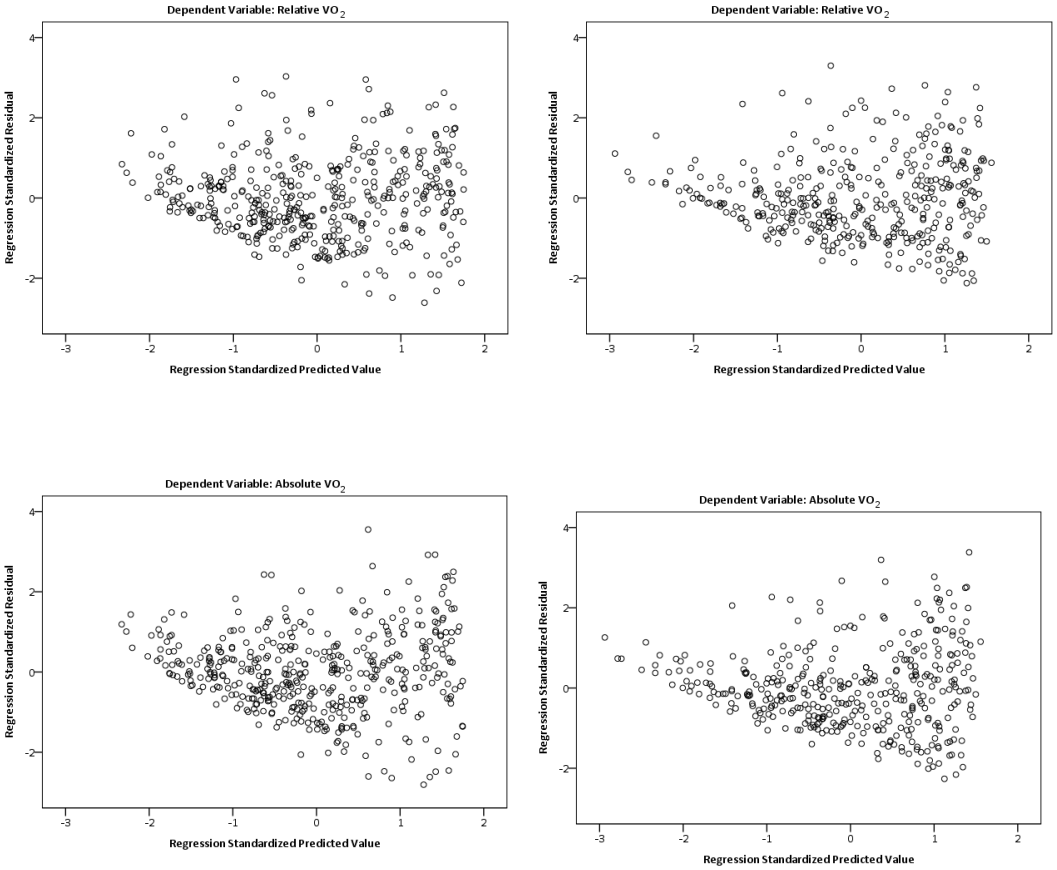


Figure A2: Residuals plot for relative $\dot{V}O_2$ (left) and absolute $\dot{V}O_2$ (right)

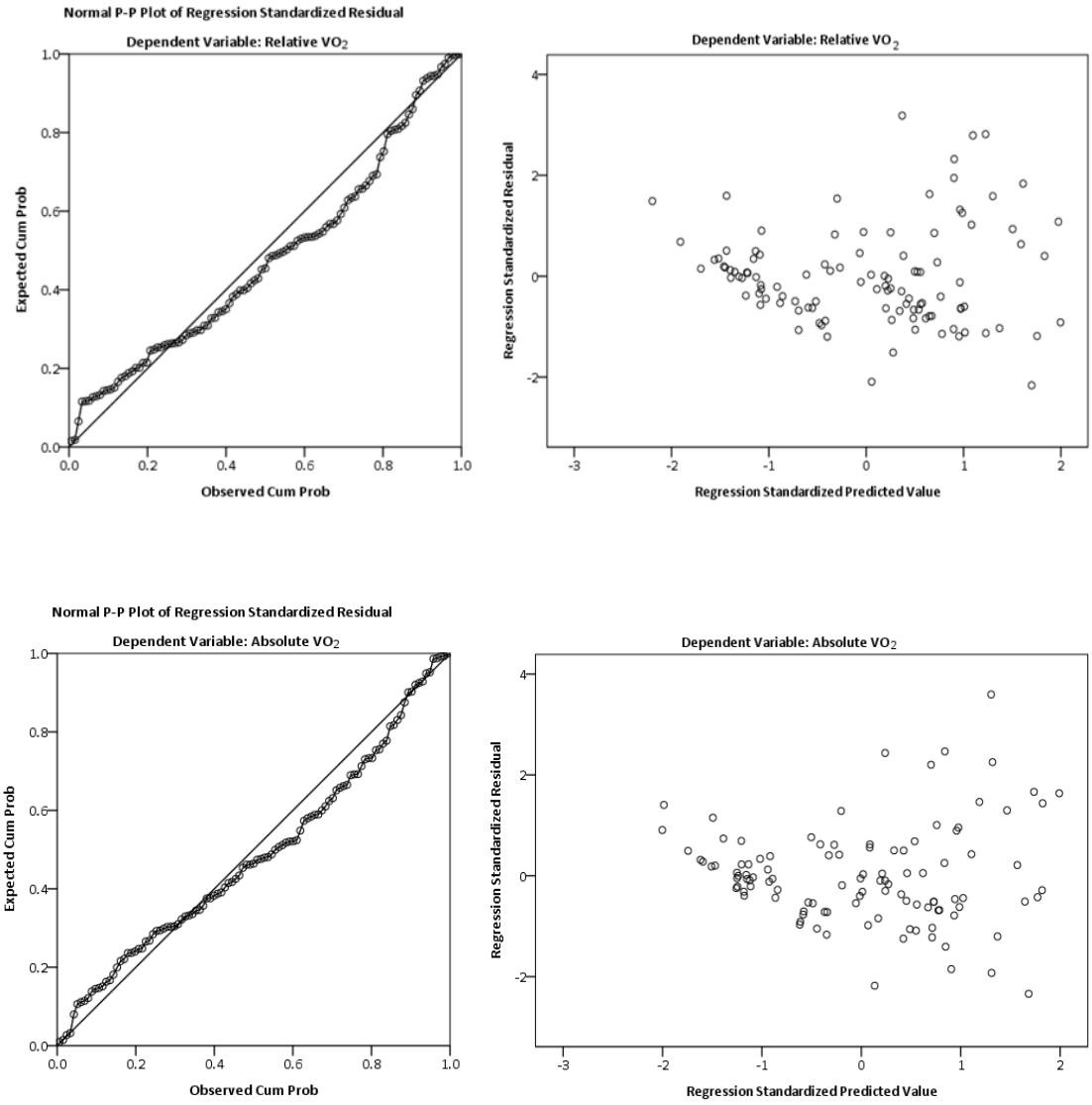


Figure A3: Multivariate analysis residuals plots for relative and absolute $\dot{V}O_2$

APPENDIX D: CONFERENCE POSTER PUBLICATIONS

East Sussex Healthcare NHS
NHS Trust

THE RELATIONSHIP BETWEEN RESTING TRANSTHORACIC ECHOCARDIOGRAPHY AND EXERCISE CAPACITY IN PATIENTS WITH PAROXYSMAL ATRIAL FIBRILLATION

Jet van Zalen[1], Conn Sugihara[1], Neil Sulke[1], Nik Patel[1], Guy Lloyd[2]

1) Eastbourne District General Hospital, Eastbourne, UK 2) St. Bartholomew's Hospital; Barts Health centre, London, UK

Background:

Resting transthoracic echocardiography (TTE) is routinely performed in the assessment of patients with atrial fibrillation (AF). Main echo findings are left atrium dilatation and left ventricular diastolic dysfunction and these may be important in relation to symptoms. Cardiopulmonary exercise testing (CPET) offers the best tool to assess the overall physiological effect of cardiac dysfunction. CPET data have been robustly linked to hard clinical end-points such as hospitalisation and death, regardless of age.

Aim:

To date, there are no published data assessing the link between resting TTE indices and objectively assessed exercise capacity in patients with AF.

Methods:

Standard TTEs and CPETs were performed in 69 patients scheduled for AF ablation. Data was prospectively grouped into four classes (LV systolic function; LV diastolic function; function; and LA size).

Results:

There were no significant univariate correlations between resting TTE parameters and peak exercise capacity. A multivariate model confirmed that after demographic factors were controlled for no resting TTE data had any significant association with exercise capacity. There was no significant relationship seen between LV diastolic function and LA size in absolute terms or indexed for BSA (LAVI), nor if diastolic function was alternatively defined as mean E/E'. Similarly, there was no significant linear relationship observed between LV diastolic function and LA functional parameters (fig 1). LV diastolic function did not correlate with LA size (r=-0.18, p=NS) or LA function (r=-0.21, p=NS), but did correlate with LV systolic function (r=0.41, p<0.001).

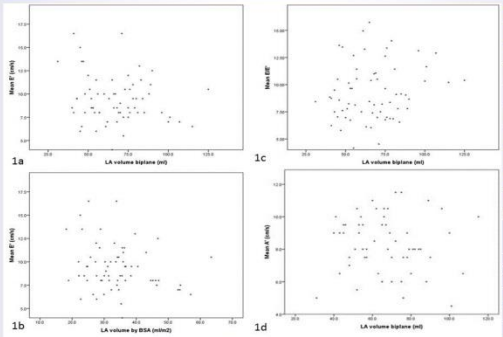


Fig 1: Graphs of TTE measures of left ventricular diastolic function and left atrial function against left atrial size. 1a: Mean E' versus LA volume, 1b: Mean E' versus LA volume by BSA, 1c: Mean E/E' versus LA volume, 1d: Mean A' versus LA volume

Age (years)	64.3 (SD 9.6)	**Prior MI**	3 (4%)
Height (cm)	171 (IQR 164 to 181)	**Prior CVA or TIA**	6 (9%)
Weight (kg)	84.2 (SD 16.1)	**Asthma**	4 (6%)
Body Mass Index (kg/m^2)	27 (IQR 24 to 31)	**COPD**	2 (3%)
Female	38 (55%)	**Prior Cancer**	6 (9%)
Atrial fibrillation	69 (100%)	**% pred VO_2 peak**	99.7% (IQR 87.7% - 113.0%)
Hypertension	34 (49%)	**VO_2 peak (l/min)**	1.66 (IQR 1.33 to 2.15)
Hyperlipidaemia	19 (28%)	**% predicted VT**	59.4% (SD 9.9%)
Diabetes	7 (10%)	**VO_2 at VT (l/min)**	1.03 (IQR 0.76 to 1.24)
CAD	11 (16%)	**VE/VCO_2 at VT**	28.0 (SD 4.1)

	LA volume	Mean A'	Mean E'	Mean S'
% pred VO_2peak	rho 0.05 (p=NS)	rho 0.01 (p=NS)	rho 0.01 (p=NS)	rho 0.09 (p=NS)
Mean S'	r -0.08 (p=NS)	r 0.29 (p=0.027)	r 0.41 (p<0.001)	
Mean E'	r -0.18 (p=NS)	r -0.21 (p=NS)		
Mean A'	r -0.06 (p=NS)			

Conclusion:

In patients with paroxysmal AF, conventional resting TTE data had no relationship with objectively assessed exercise capacity. Furthermore, there were no associations seen between LA size, LA function and LV diastolic function in this population. The role of resting TTE in patients with AF should be best reserved for the exclusion of underlying structural heart disease.

No conflict of interest

IMPAIRED CONTRACTILE RESERVE DEFINED BY SYSTOLIC LONGITUDINAL VELOCITY DURING EXERCISE, PREDICTS ADVERSE PROGNOSIS MORE STRONGLY THAN EITHER EXERCISE EJECTION FRACTION OR DIASTOLIC RESERVE

JJ. Van Zalen[1], R. Mcintosh[1], P. Raju[1], L. Beale[2], G. Brickley[2], S. Podd[1], N. Patel[1], GW. Lloyd[1]
[1]Eastbourne DGH, Eastbourne, United Kingdom, [2]University of Brighton; Chelsea School, Eastbourne, United Kingdom

Introduction:
Resting echocardiography measurements are poor predictors of exercise ability and prognosis in heart failure. The objective was to investigate the relationship between systolic velocity (S'), diastolic reserve (E/E') and ejection fraction (LVEF) obtained during stress echocardiography and clinical outcome.

Results:
80 patients were followed up for a median of 24 (3-8 month months). 11 patients died and 22 required hospitalisation. LVEF, E/E' and S' during exercise, as well as VO_2peak, were all predictors for mortality. A correlation was found between S' and VO_2peak. Exercise S', and exercise E/E' were associated with a higher risk of hospitalisation. ROC analysis identified S' as the strongest factor with an optimal sensitivity and specificity of 5.3 cm/sec for mortality and 5.7 cm/sec for hospitalisation. These figures were associated with a relative risk of 8.0 and 4.9 respectively, superior to both E/E' and LVEF.

Methods:
Patients with stable systolic heart failure underwent exercise stress echocardiography and simultaneous cardiopulmonary exercise testing. Volumetric and spectral tissue Doppler measurements were obtained, as was VO_2 peak. The end point was death or cardiac hospitalisation.

Parameter	Rest	Exercise
LVEF	0.35†	0.45*
S'	0.49*	0.66*
E'	0.26†	0.43*
E/E'	-0.46*	-0.34*
CO	0.07	0.41*

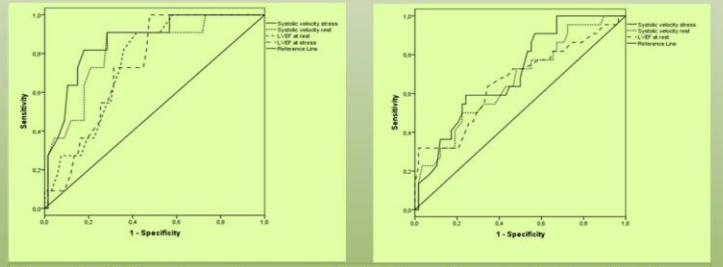


Figure 1: ROC analyses for mortality (left) and hospitalisation (right)

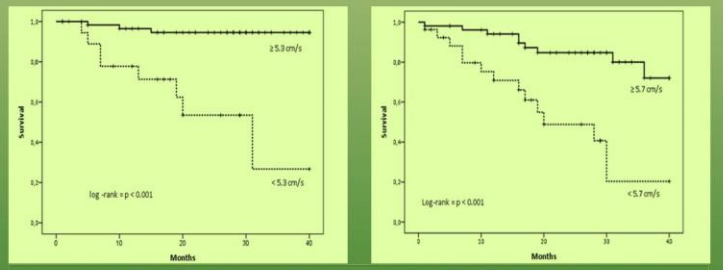


Figure 2: Kaplan Meyer curves for mortality (top) and hospitalisation (below) using the threshold obtained from the ROC analyses

Conclusion:
Heart failure prognosis is best determined using systolic velocity rather than diastolic reserve or LVEF during stress echocardiography. Obtaining S' is a simple and reproducible method which is widely available and if routinely implemented could provide valuable additional prognostic data to clinicians.

No conflict of interest declared

University of Brighton

East Sussex Healthcare NHS Trust

Contractile reserve measured by systolic velocity does not predict response to CRT

Jet van Zalen[1], Nik Patel[1], Prashanth Raju[1], Louisa Beale[2], Gary Brickley[2], Guy Lloyd[3]

1) Eastbourne District General Hospital, Eastbourne, UK 2) University of Brighton; Centre for Sport and Exercise Science and Medicine (SESAME) , Eastbourne, UK 3) St. Bartholomew's Hospital; St. Bartholomew Hospital; Barts Heart centre, London, UK

Background

Cardiac resynchronisation therapy (CRT) improves symptoms of heart failure (HF) in the majority of patients. Longitudinal systolic function (S') by Tissue Velocity Imaging measured during exercise has previously been shown to have a good relationship with peak exercise uptake (VO_2peak).

Aim

The aim of this study was to determine if exercise S' was able to predict a positive response to CRT.

Methods

34 patients clinically selected for CRT were included. All patients underwent CPET stress echocardiography and parameters were obtained at rest and at exercise. Response to CRT was determined using a reduction in end-systolic volume of at least 15%. 68% of patients were classified as responders to CRT. Responders and non-responders were compared to determine differences in response to CRT.

Results

The overall population showed significant improvements in NYHA class, QoL, end diastolic and systolic volumes, and in 6-MWT distance after 3 months of implant. Baseline characteristics were similar for both responders as non-responders. No difference were found for resting S', exercise S', or delta S' between responders and non-responders. Exercise S' was unable to predict a positive response to CRT for responders and non-responders respectively.

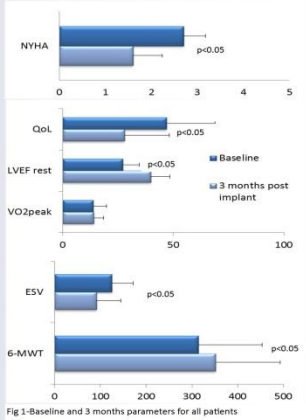
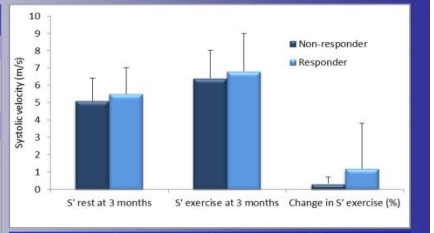


Fig 1-Baseline and 3 months parameters for all patients

	Non-responder (n=11)	Responder (n=23)	P value
Functional parameters at 3 months			
NYHA	1.8 ± 0.8	1.5 ± 0.6	ns
QoL	27.1 ± 21.4	29.8 ± 18.3	ns
Echocardiographic parameters at 3 months			
LVEF rest (%)	35.7 ± 10.8	41.7 ± 6.6	ns
S' rest (m/s)	5.1 ± 1.3	5.4 ± 1.5	ns
S' stress (m/s)	6.4 ± 1.6	6.8 ± 2.2	ns
Change in exercise S'	0.33 ± 1.1	0.39 ± 2.6	ns
Change in exercise S'(%)	12.2 ± 26.1	15.2 ± 46.2	ns
LVOT VTI rest (cm2)	17.0 ± 5.2	17.8 ± 2.5	ns
E/E' rest	13.3 ± 6.7	14.5 ± 5.9	ns
Exercise parameters at 3 months			
VO_2peak (ml/kg/min)	14.0 ± 4.3	13.5 ± 3.8	ns
OUES (ml/min/l/min)	1440 ± 339	1428 ± 473	ns
6-MWT (m)	343 ± 136	328 ± 130	ns



	All patients (n= 34)	Non responders (n=11)	Responders (n=23)
Male	23 (61%)	9	13
Age	71 ± 8.7	70.5 ± 8.0	73.4 ± 10.5
Height	169 ± 11	168 ± 9.8	172 ± 11.5
Weight	81.0 ± 19	81.8 ± 18.6	85.3 ± 19.1
IHD	23 (61%)	8	13
Smoking	6 (15.8%)	1	4
CABG	4 (11%)	2	2
LBBB	28 (74%)	6	19
QRS duration	156 ± 23	149 ± 32	160 ± 19.3
COPD	5 (13%)	1	3
Diabetes	8 (21%)	1	6
Hypertension	16 42%)	4	11
PCI	7 (18%)	1	4

Conclusion

Exercise S' should be continued to be used as a prognosticator for future events but is not useful in predicting response to CRT.

No conflict of interest

East Sussex Healthcare NHS Trust | Barts Heart Centre | University of Brighton

The importance of contractile reserve when assessing asymptomatic patients with aortic stenosis

Jet van Zalen[1,3], Sveeta Badiani[1,3], Lesley Hart[1], Louisa Beale[2], Gary Brickley[2], Andrew Marshall[1], Nik Patel[1], Guy Lloyd[3]

1) Eastbourne District General Hospital, Eastbourne, UK 2) University of Brighton; Centre for Sport and Exercise Science and Medicine (SESAME) , Eastbourne, UK 3) St. Bartholomew's Hospital; St. Bartholomew Hospital; Barts Heart centre, London, UK

Background

Asymptomatic patients may exhibit symptoms during objective exercise testing, but whether symptoms are due to the obstructivity of the valve or underlying ventricular function remains unknown. While the mean gradient is an easy parameter to measure, no consensus about the measurement of contractile reserve exists. Longitudinal abnormalities may occur in the presence of a normal ejection fraction and the augmentation of these parameters is poorly described.

Aim

The aim of this study was to examine the echocardiographic predictors of exercise ability during cardiopulmonary exercise testing combined with stress echocardiography.

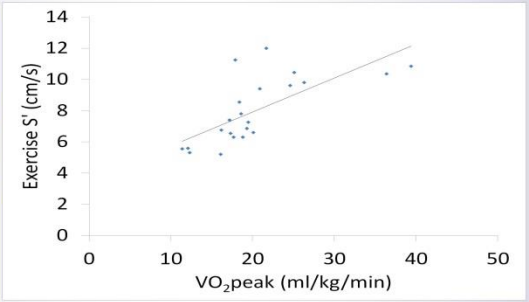
Methods

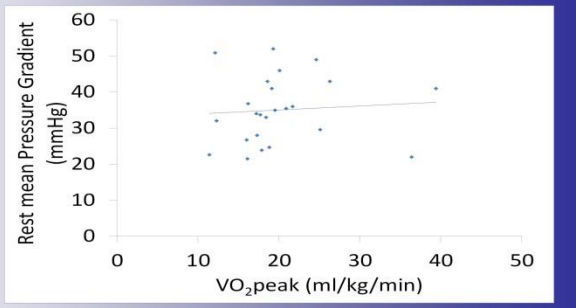
24 asymptomatic patients with moderate to severe or severe aortic stenosis and preserved ejection fraction (LVEF>55%) underwent stress echocardiography with simultaneous cardiopulmonary exercise testing. The primary assessment of exercise ability was VO_2peak. Echocardiography was measured at rest and during peak exercise as defined as RER > 1.

Results

VO_2peak showed a poor relationship with conventional resting parameters of severity including peak velocity (r=0.07;p=ns) and mean gradient (r=0.3;p=ns), AVA (r=0.4;p=ns) and dimensionless index (rho=0.05;p=ns), resting systolic function (by EF (r=-0.18;p=ns) and TDI (r=0.39;p=ns) . During exercise systolic augmentation had a good relationship with exercise ability (r=0.71;p<0.0001) but the exercise mean gradient was weaker (rho=0.57,p=0.005) and there was no relationship with exercise LVEF (rho=0.18;p=ns).

Age (years)	68 ± 17.4
Weight (kg)	82.2 ± 15.4
VO_2peak (ml/kg/min)	20.1 ± 6.6
VO_2peak (%)	90.4 ± 17.3
VO_2peak < 84%	7
OUES (ml/min/l/min)	2049 ± 603A
S' exercise (cm/s)	8.0 ± 2.1
S' rest (cm/s)	5.7 ± 1.4
Rest max V (m/s)	3.9 ± 0.4
Rest mean PG (mmHg)	34.5 ± 9.2
Exercise max V (m/s)	4.5 ± 0.5
Exercise mean PG (mmHg)	49 ± 13
Rest AVA (cm^2)	0.9 ± 0.15
Dimensionless index	0.29 ± 0.06
LVEF rest (%)	61.4 ± 5.8
LVEF exercise (%)	65.1 ± 5.9





Conclusion

Longitudinal systolic function and particularly systolic augmentation is the strongest predictor of exercise ability when compared to conventional measures of severity.

No conflict of interest

Linking myocardial mechanical function to exercise performance: a cardiopulmonary stress echo study in first time London marathon participants

J. Van Zalen[1], A. D'silva[2], S. Badiani[3,5], A. Bhuva[4], S. Jones[4], C. Torlasco[3], A D. Hughes[4], C. Manisty[3], S. Sharma[2], J C. Moon[4], G. Lloyd[3,5]

(1) Eastbourne District General Hospital, Eastbourne, UK (2) St Georges Hospital, London, UK (3) Barts Health NHS Trust, London, UK (4) University College London, London, UK, (5) William Harvey Institute QMUL, London, UK

Background

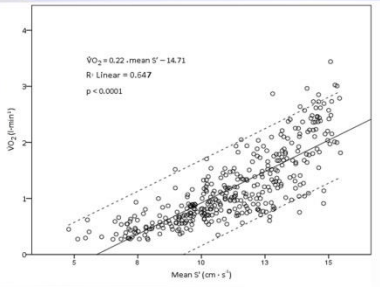
The cardiac determinants of exercise performance are poorly described and limited by the technical challenges of making direct measurements during exercise. Echocardiography linked to cardiopulmonary stress testing (CPET) was used to develop a greater mechanistic insight into the relation between systolic function and oxygen consumption (VO_{2peak}), (with special focus on systolic longitudinal function), in a group of healthy participants undertaking the London marathon for the first time.

Methods

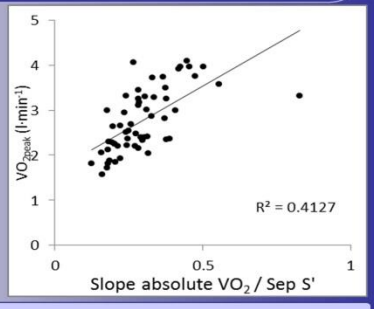
57 novice marathon runners (21-35 years) underwent echocardiography at rest and during incremental exercise on a semi recumbent cycle ergometer. Full echo datasets: systolic velocity (S'), ejection fraction (EF), end systolic volume, stroke volume, global longitudinal strain (GLS) were recorded at baseline, low intensity exercise and at a respiratory exchange ratio (RER) of 1.0. Colour Tissue Doppler was recorded every minute. Echo parameters were linked by time to CPET parameters. All subjects were exercised to maximum voluntary effort.

Results

Average VO_{2peak} was 2.8±0.7 $L{\cdot}min^{-1}$; 38.7±6.5 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$. Peak work rate was 226±55 Watt. VO_{2peak} was strongly positively associated with peak exercise average S' (Rho = 0.84; p<0.0001). S' at RER>1 was a stronger predictor of VO_{2peak} than GLS although the two parameters showed a modest correlation (r=-0.56, p<0.01). Multivariate regression predicted that mean S' (β=0.62, p<0.0001) and LVEF (β= 0.21, p<0.0001) were the only significant predictors for VO_2. The overall model fit was R^2=0.71, p<0.0001). The septal S'/VO_2 slope showed a significant relationship to VO_{2peak} (r=0.71; p<0.0001) this was slightly lower for the lateral S'/VO_2 slope and (r=0.61; p<0.0001).



	Rest	5 minutes	RER > 1.0
HR (beats ·min⁻¹)	68.6 ± 10.6	129.4 ± 14.6*	151.8 ± 14.3§
Septal S' (cm ·s⁻¹)	7.2 ± 1.4	10.3 ± 1.7*	13.8 ± 1.5§
Lateral S' (cm ·s⁻¹)	8.4 ± 1.6	12.5 ± 1.5*	14.4 ± 1.2§
LVEF (%)	61.0 ± 2.8	68.9 ± 3.6*	69.8 ± 3.9§
EDV (ml)	119.8 ± 30.2	117.5 ± 31.2	113.8 ± 28.9
ESV (ml)	46.9 ± 13.3	36.9 ± 11.5*	35.5 ± 12.7§
SV (ml)	34.9 ± 14.9	48.8 ± 14.9*	55.0 ± 19.4§
GLS (%)	-18.0 ± 2.4	-21.5 ± 3.1*	-21.7 ± 2.7§



Conclusion

This study cements the central role of longitudinal function and particularly S', in determining maximum exercise performance in normal subjects. Velocity was more predictive than longitudinal strain (currently considered gold standard). The slope function between S' and VO_2 represents a new, unique means of describing contraction/performance coupling which predicts maximum cardiopulmonary performance.

No conflict of interest

APPENDIX E: PUBLISHED PAPERS

van Zalen, J., Patel, N. R., Podd, S. J., Raju, P., McIntosh, R., Brickley, G., Beale, L., Sturridge, L. P., Lloyd, G. W. L. (2015) Prognostic importance of tissue velocity imaging during exercise echocardiography in patients with systolic heart failure. *Echo Research and Practice* 2(1): 19–27.

van Zalen, J., Sugihara, C., Sulke, N., Patel, N., Brickley, G., Beale, L., Lloyd, G. (2017) Pitfalls in the interpretation of cardiopulmonary exercise testing data. *The British Journal of Cardiology* 24: 98–99.

ID: 14-0074; June 2015
DOI: 10.1530/ERP-14-0074

RESEARCH

Prognostic importance of tissue velocity imaging during exercise echocardiography in patients with systolic heart failure

Jet van Zalen MSc, Nikhil R Patel MBBS FRCP, Steven J Podd MBBS MRCP, Prashanth Raju MBBS MRCP, Rob McIntosh MBBS MRCP, Gary Brickley PhD[1], Louisa Beale PhD[1], Lydia P Sturridge MBBS MRCP and Guy W L Lloyd MD FRCP

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Email
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Abstract

Resting echocardiography measurements are poor predictors of exercise capacity and symptoms in patients with heart failure (HF). Stress echocardiography may provide additional information and can be expressed using left ventricular ejection fraction (LVEF), or diastolic parameters (E/E′), but LVEF has some major limitations. Systolic annular velocity (S′) provides a measure of longitudinal systolic function, which is relatively easy to obtain and shows a good relationship with exercise capacity. The objective of this study was to investigate the relationship among S′, E/E′ and LVEF obtained during stress echocardiography and both mortality and hospitalisation. A secondary objective was to compare S′ measured using a simplified two-wall model. A total of 80 patients with stable HF underwent exercise stress echocardiography and simultaneous cardiopulmonary exercise testing. Volumetric and tissue velocity imaging (TVI) measurements were obtained, as was peak oxygen uptake (VO_2 peak). Of the total number of patients, 11 died and 22 required cardiac hospitalisation. S′ at peak exertion was a powerful predictor for death and hospitalisation. Cut-off points of 5.3 cm/s for death and 5.7 cm/s for hospitalisation provided optimum sensitivity and specificity. This study suggests that, in patients with systolic HF, S′ at peak exertion calculated from the averaged spectral TVI systolic velocity of six myocardial segments, or using a simplified measure of two myocardial segments, is a powerful predictor of future events and stronger than LVEF, diastolic velocities at rest or exercise and VO_2 peak. Results indicate that measuring S′ during exercise echocardiography might play an important role in understanding the likelihood of adverse clinical outcomes in patients with HF.

Key Words
- stress echocardiography
- tissue Doppler imaging
- left ventricular ejection fraction

Introduction

Systolic heart failure (HF) is a major cause of mortality and morbidity, and its prevalence is increasing due to the ageing population (1). It is conventionally defined by demonstrating typical clinical symptoms and signs associated with compatible findings on a resting echocardiogram (2). Patients with systolic dysfunction respond to a range of physical and medical therapies, but nonetheless have a poor prognosis (3). Resting echocardiography and particularly left ventricular ejection fraction (LVEF) has been shown to be a poor predictor of

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exercise capacity (4, 5). Several studies have suggested the additional value that stress echocardiography has on exercise capacity and symptoms (5, 6, 7) and prognosis (8, 9, 10, 11).

Stress echocardiography adds prognostic value in patients with myocardial ischaemia secondary to coronary artery disease (12, 13). Furthermore, echocardiographic data during exercise provide additional information regarding patients' overall exercise ability (14). Patients with HF demonstrating an increase in LVEF of 5% (in absolute terms) or more during stress echocardiography have a better prognosis (15, 16, 17). However, LVEF can be challenging to obtain reliably and has some major limitations including a lack of reproducibility, dependence on loading conditions and it only describes maximum displacement at the end of systole meaning the longitudinal component of systolic function is not completely described. Systolic annular velocities obtained during stress echocardiography show a strong relationship with exercise tolerance (6, 18) and the change in early diastolic velocity has also proven predictive (19). The relationship between both systolic and diastolic velocities and prognosis, however, remains undetermined. Therefore, the objective of this study was to investigate whether systolic velocity (S′), diastolic reserve (E/E′) and LVEF, all of which describe different aspects of cardiac function, would relate to mortality and cardiac hospitalisation in an established cohort of patients with systolic HF who had undergone stress echocardiography and cardiopulmonary exercise testing as part of a research study.

Methods

This was a retrospective longitudinal study of 80 patients with systolic HF participating in cohort studies undertaken at our institution using the same echocardiography and cardiopulmonary exercise test (CPET) protocols (20) (explained in more detail below). All patients were medically treated for systolic HF and had been stable on medical therapy for at least 1 month before study inclusion. The definition of systolic HF was made by the combination of appropriate symptoms and a depressed LV on echocardiography. Exclusion criteria included unstable angina, symptomatic angina, evidence of reversible ischaemia, PCI (percutaneous coronary intervention) or coronary artery bypass graft (CABG) within the last 6 months, severe lung disease or poor echocardiographic windows. Informed written consent was obtained and all studies were approved by the local ethical committee.

Echocardiography

Echocardiography was performed using a GE Vivid 7 platform (Vingmed-General Electric, Horten, Norway) equipped with a phased-array 3.5 MHz transducer. Two-dimensional, spectral Doppler and tissue velocity imaging (TVI) were obtained at rest and during exercise. LV volumes and LVEF were calculated using Simpson's biplane method in the apical four-chamber and two-chamber views. Transmitral Doppler was obtained by placing a pulsed wave Doppler sample volume at the tips of the mitral leaflets. Pulsed wave Doppler for cardiac output assessment was taken in the five-chamber view 1 cm below the aortic valve. TVI was performed with the sample volume placed at mitral annulus in the three-apical views. Exercise S′ (defined as the highest velocity during systole after the end of isovolumetric contraction) was obtained from six peri-annular sites of the mitral annulus (septal, lateral, inferior, anterior, posterior and anteroseptal). At least three cardiac cycles were obtained and S′ was averaged for each segment and all available S′ were averaged. At instances where a reproducible TVI recording was not achieved, all available recordings were used to calculate the average. Myocardial velocity during early diastole (E′) was measured on the lateral wall because this was laid down in one of the study protocols (because of the inclusion of a proportion of patients who had undergone previous cardiac surgery, in whom septal diastolic velocity might not have been representative). Images were obtained in real time and analysed after each study. Images were stored offline.

Cardiopulmonary exercise test

A recumbent cycle ergometer (ERG 911 S/L, Schiller, Baar, Switzerland) was used. Peak oxygen uptake (VO_2 peak) was used as the main outcome variable as it has been previously shown to be a strong predictor of mortality in patients with systolic HF (21, 22). Patients were asked to continue to take their medication as usual. At the start of the test a 3-min rest period was included followed by a 3 min of warm-up period. Exercise protocols were individually determined based on functional status. Work rate (5, 10, 15 or 20 W) increased every minute until voluntary exhaustion aiming for 6–10 min of exercise. Heart rate, blood pressure and oxygen saturation were monitored throughout. Oxygen uptake, carbon dioxide production and ventilation were continuously measured and derived using a calibrated breath-by-breath analyser (Schiller Powercube AT-104 PC, Ganzhorn, Baar, Switzerland).

A respiratory exchange ratio >1 was used to indicate good effort (7). Echocardiography measurements commenced when patients were close to finishing the test when the RER was exceeding 0.95 and if patients were not taking β-blockers in combination with a peak predicted HR >85%. All measurements were taken within 90 s of finishing exercise. Patients were verbally encouraged to exercise until maximal exertion. All tests were performed according to the exercise testing guidelines (23). VO_2 peak was expressed as the highest value from an average of 30 s during the final stage of the exercise test.

Follow-up

All-cause mortality and cardiac hospitalisation end points were evaluated by cross-referencing with the hospital information system (which is linked to the UK registry of death), the clinical case notes, contacting the primary care physician and, where necessary, contacting the patient by telephone. No patient was lost to follow-up. Where hospitalisations had occurred, all best endeavours to evaluate the notes were made to ensure that the hospitalisation was HF related. Data on re-admission were based on the primary diagnosis at discharge.

Statistical analyses

All data are expressed as mean±S.D. or percentage for continuous variables and categorical data are expressed as absolute values and percentages. Pearson's correlation coefficients or Spearman's coefficients were used to determine relationship between echocardiographic variables and exercise tolerance. Differences between groups were investigated using the Student's *t*-test for continuous data and the χ^2 test for categorical data. All variables were assessed for univariate statistical significance using Cox's proportional hazard regression model for mortality and hospitalisation. All significant predictors of outcome were entered into multivariate Cox's proportional model (forward selection) to identify the strongest predictors of mortality or cardiac hospitalisation. Another Cox's regression analysis was performed interchanging the average systolic velocities for the average of the septal and lateral walls. Data from Cox's regression analysis are expressed as hazard ratios (HRs) with 95% CI. Receiver operating characteristics (ROC) curves were used to determine the optimal prognostic threshold value (highest combination of sensitivity/specificity) for mortality and hospitalisation. Interobserver variability was undertaken from 12 randomly selected subjects and intraclass correlations (ICCs) were calculated. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 20.0; SPSS, Inc.). A *P* value of <0.05 was considered significant.

Results

Baseline characteristics are given in Table 1. A total of 80 patients were included in the study, 11 patients died and 22 required non-elective hospital admissions during a median follow-up of 24 months (range 3–40 months). Of the remaining number of patients, 50 suffered from ischaemic heart disease, and, of them, 16 had a previous CABG and 13 a previous PCI. A proportion of patients ($n=23$) previously underwent cardiac resynchronisation therapy (CRT) before inclusion in the research study, 30 patients had been clinically approved to receive CRT and the remaining 27 did not qualify for CRT at the time of the study. Although no significant differences were found for the presence of ischaemic heart disease, there was a trend observed for hospitalisation ($P=0.25$) and survival ($P=0.15$) (Table 1).

No differences in age, sex, electrolytes, hypertension, left bundle branch block, diabetes, non-significant valvular heart disease, presence of CRT, previous CABG or PCI were observed between those with and without events. A difference was observed for the use of angiotensin II receptor blocker (ARB) and diuretics for patients who have been hospitalised. No other difference in drug history was observed (Table 1).

Of 480 available segments from TVI analysis, 92% were positively identified at rest vs 81% during stress echocardiography. All six myocardial segments were evaluable in 58 patients at rest and 34 patients during exercise. The septal and lateral systolic velocities were identified in all 80 patients at rest and in 78 patients during exercise. The apical long-axis view was most frequently not evaluable, in particular the anteroseptal segment. Nevertheless, in 79 patients at rest and in 72 patients during exercise, at least four segments were accurately identified. The mean TVI value of all six segments correlated well with the mean of the septal and the lateral walls for rest ($r=0.93$, $P<0.001$) and exercise ($r=0.94$, $P<0.001$).

Maximal exercise tolerance described using VO_2 peak was significantly higher in survivors than in non-survivors (1.2 ± 0.4 l/min vs 0.9 ± 0.3 l/min, $P=0.04$). However, no difference was found between patients who were hospitalised and those who were not (1.2 ± 0.5 l/min vs 1.1 ± 0.3 l/min). A regression analysis showed a weak

Table 1 Baseline clinical characteristics. Data are expressed as mean±S.D. or as number (%) of patients.

	All patients (n=80)	Survivors (n=69)	Non-survivors (n=11)	No hospitalisation (n=58)	Hospitalisation (n=22)
Age (years)	72±9	71±9	74±7	71±10	74±7
Male	51 (64%)	44	7	39	12
IHD	50 (63%)	41	9	34	16
Hypertension	23 (29%)	19	4	16	7
LBBB	42 (53%)	38	4	32	10
Diabetes mellitus	15 (19%)	14	1	10	5
Valvular heart disease	9 (11%)	7	2	6	3
CRT	23 (29%)	19	4	15	8
CABG	16 (20%)	15	1	11	5
PCI	13 (16%)	10	3	9	4
ACE inhibitor	50 (63)	42	8	32	18
β-blocker	57 (71%)	49	8	43	14
Digoxin	8 (10%)	7	1	6	2
Amiodarone	17 (21%)	13	4	11	6
ARB	24 (30%)	21	3	21*	3
Diuretic	59 (74%)	49	10	39*	20
Statin	54 (68%)	49	5	39	15
Serum creatinine (mmol/l)	105±35.9	103±34	121±45	101±32	118±42
Serum sodium (mmol/l)	139±3.0	139±3	140±3	140±3	139±3
Resting heart rate (beats/min)	68±15	67±15	71±16	68±16	67±11
Exercise heart rate (beats/min)	99±23	99±22	96±16	102±24	91±20
Resting cardiac output (l/min)	3.9±1.4	3.9±1.4	3.7±1.3	3.9±1.4	3.9±1.6
Exercise cardiac output (l/min)	6.7±2.2	6.9±2.3	5.4±1.6	6.9±2.3	6.3±2.0

*P<0.05; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; CRT, cardiac resynchronisation therapy; IHD, ischaemic heart disease; LBBB, left bundle branch block; PCI, percutaneous coronary intervention.

relationship between VO_2 peak and resting and exercise LVEF (r=0.35, P<0.05; r=0.5, P<0.05 respectively), while a moderate correlation was found for exercise S′ (r=0.66, P<0.001).

Echocardiographic, exercise and functional parameters for survivors and non-survivors, as well as those who were and were not hospitalised, are presented in Table 2. There was a significant difference in systolic velocities at rest and exercise, LVEF at rest and exercise, E/E′ at rest and exercise, VO_2 peak, and end diastolic dimensions between survivors and non-survivors. Fewer differences were observed between those who were and

Table 2 Mean echocardiographic, exercise and functional parameters (mean±S.D.).

Mortality	Survivors	Non-survivors	No hospitalisation	Hospitalisation
S′ at rest (cm/s)	5.4±1.6	3.7±1.2[a]	5.3±1.7	4.5±1.5[b]
S′ at exercise (cm/s)	7.1±2.2	4.4±1.3[a]	7.2±2.4	5.5±1.6[b]
LVEF at rest	33±11	24±6[b]	33±10	27±11[a]
LVEF at exercise	40±14	28±8[a]	39±14	35±13
E′ at rest (cm/s)	6.4±2.6	5.4±2.1	6.4±2.6	5.9±2.3
E′ at exercise (cm/s)	10.1±4.6	7.1±2.3	10.2±4.7	8.5±3.8
E/E′ at rest	12.6±7.4	18.7±9.0[a]	12.6±7.9	15.0±7.2
E/E′ at exercise	12.1±7.2	18.2±7.1[a]	12.2±7.7	14.8±6.8
VO_2 peak (l/min)	1.2±0.4	0.94±0.3[a]	1.2±0.5	1.1±0.3
EDV	158±59	180±63	161±61	162±54
ESV	108±46	139±56	109±48	121±49
EDD	5.8±0.8	6.5±0.9[b]	5.8±0.8	6.3±0.9[b]
ESD	4.8±0.9	5.6±1.4	4.7±1.0	5.6±0.9[a]
LA diameter	3.9±0.8	4.4±0.6	3.9±0.8	4.2±0.6
NYHA	2.2±0.8	2.5±0.7	2.2±0.7	2.2±0.8

LVEF, left ventricular ejection fraction; S′, systolic velocity; E′, myocardial velocity early diastole; E/E′, transmitral-to-basal early diastolic velocity ratio; VO_2 peak, peak oxygen uptake; EDV, end-diastolic volume; ESV, end-systolic volume; EDD, end-diastolic dimensions; ESD, end-systolic dimensions; LA, left atrium; NYHA, New York Heart Association class.
[a]Survivors vs non-survivors or hospitalisation vs no hospitalisation P<0.01.
[b]Survivors vs non-survivors or hospitalisation vs no hospitalisation P<0.05.

Table 3 Univariate predictors of mortality and cardiac admission.

Mortality	HR (95% CI)	*P* value	Hospitalisation	HR (95% CI)	*P* value
S′ at rest (cm/s)	0.46 (0.29–0.75)	0.002	S′ at rest (cm/s)	0.67 (0.50–0.90)	0.008
S′ at exercise (cm/s)	0.47 (0.31–0.71)	<0.0001	S′ at exercise (cm/s)	0.65 (0.52–0.83)	<0.0001
LVEF at rest	0.91 (0.85–0.98)	0.01	LVEF at rest	0.94 (0.90–0.98)	0.008
LVEF at exercise	0.93 (0.88–0.98)	0.01	E/E′ at exercise	1.05 (1.00–1.09)	0.04
E/E′ at rest	1.07 (1.00–1.14)	0.03	EDD	1.82 (1.03–3.20)	0.04
E/E′ at exercise	1.07 (1.01–1.12)	0.01	ESD	2.23 (1.31–3.77)	0.003
VO_2 peak (l/min)	0.10 (0.01–0.76)	0.03	Creatinine	1.01 (1.00–1.02)	0.04
ESV	1.01 (1.00–1.02)	0.05	Diuretics	0.23 (0.05–1.00)	0.05

LVEF, left ventricular ejection fraction; S′, systolic velocity; E′, myocardial velocity early diastole; E/E′, transmitral-to-basal early diastolic velocity ratio; VO_2 peak, peak oxygen uptake; ESV, end-systolic volume.

were not hospitalised, although once again S′, LVEF at rest and end diastolic dimensions remained significant.

Significant univariate predictors are given in Table 3. None of the clinical characteristics in Table 1 were univariate predictors for death; for hospitalisation, only diuretics were a univariate predictor (Table 3). Aetiology of HF was not a univariate predictor for either mortality or hospitalisation. After all the variables that predicted mortality and hospitalisation (Table 3) on univariate Cox's regression analysis were entered into a forward multivariate Cox's regression model, only exercise S′ emerged as a significant predictor of mortality (HR: 0.36; 95% CI: 0.19–0.67; $P=0.001$) and hospitalisation (HR: 0.62; 95% CI: 0.45–0.85; $P=0.003$). This model retained its predictive power when exercise S′ was substituted by the average septum and lateral S′ for mortality (HR: 0.42; 95% CI: 0.24–0.73; $P=0.002$) and hospitalisation (HR: 0.54; 95% CI: 0.37–0.81; $P=0.003$).

A ROC analysis was performed for mortality and systolic velocity has the largest area under the curve of 0.86 (95% CI: 0.75–0.96). A cut-off of 5.3 cm/s for exercise S′ showed a sensitivity and specificity of 82 and 80%, respectively, for mortality. Similarly, for hospitalisation, a ROC analysis for exercise S′ has an area under the curve of 0.71 (95% CI: 0.58–0.83), which resulted in a cut-off of 5.7 cm/s representing a sensitivity of 59% and a specificity of 74%. Kaplan–Meier curves were generated using these cut-offs (see Fig. 1).

Interobserver variability measured by ICC was stronger for exercise S′ (ICC: 0.96; 95% CI: 0.88–0.99) compared with exercise LVEF (ICC: 0.57; 95% CI: −0.82 to 0.92), exercise E′ (ICC: 0.83; 95% CI: 0.38–0.95) and exercise E/E′ (ICC: 0.84; 95% CI: 0.40–0.96). Similarly, for the intraobserver variability, the ICC was stronger for TVI-derived parameters, exercise S′ (ICC: 0.97; 95% CI: 0.86–0.99) and exercise E′ (ICC: 0.99; 95% CI: 0.94–0.99) compared with exercise LVEF (ICC: 0.88; 95% CI: 0.50–0.96) and exercise E/E′ (ICC: 0.85; 95% CI: −0.24 to 0.98).

Discussion

This study suggests that, in patients with systolic HF, S′ at peak exertion calculated from the averaged spectral TVI systolic velocity of six myocardial segments, or using a

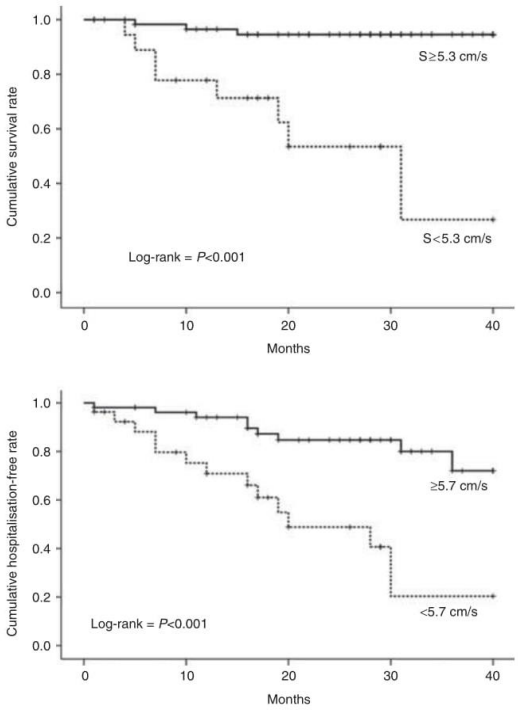

Figure 1
Kaplan–Meier curves for mortality (top) and hospitalisation (bottom).

simplified measure of two myocardial segments, is a powerful predictor of future events and stronger than LVEF, diastolic velocities at rest or exercise, and VO_2 peak. It retains its prognostic value after adjustment for clinical data, peak exercise capacity, functional parameters and other echocardiographic data. Cut-off points of 5.3 cm/s for death and 5.7 cm/s for hospitalisation provided optimum sensitivity and specificity, which were 82 and 80% for mortality and 59 and 74% for hospitalisation. Surprisingly, exercise S′ proved to be a stronger predictor than VO_2 peak despite being moderately co-correlated, and VO_2 peak having been highly predictive of mortality in other studies (24, 25). This study confirms the limitation of resting echocardiography in predicting either prognosis or exercise capacity in patients with systolic HF (9, 10, 24, 26, 27). Inter- and intraobserver variabilities were excellent for S′ at exercise unlike LVEF at exercise, which was less reliable; this is in agreement with previous studies (28, 29).

The most widely used parameter to characterise HF is resting LVEF, but this measurement can be challenging. The reasons why LVEF relates poorly to both functional capacity (5, 6, 7, 30) and prognosis are complex (8, 9, 10, 11, 24). The reproducibility of measurement remains sub-optimal, due partly to image quality and anatomical factors (31). LVEF is a reflection of whole systolic myocardial displacement and may be more dependent on loading conditions than on other measures such as velocity (6, 31, 32). Furthermore, LVEF poorly describes longitudinal myocardial function, which is often affected early in a variety of heart diseases. Previous studies have documented only a weak relationship between LVEF either at rest or under stress conditions and exercise capacity, which is in agreement with our findings (6). LVEF during dobutamine stress, where loading conditions can be very different, has been shown to predict adverse outcome during echocardiography and nuclear scintigraphy (33, 34, 35). The inability to increase LVEF during stress echocardiography has been shown to be a strong predictor for mortality (15).

Both systolic and diastolic TVI measures, at rest and during exercise, have previously been demonstrated to predict exercise capacity (20, 36, 37). A moderate relationship between VO_2 peak and S′ was demonstrated and both resting and stress recorded TVIs were univariate predictors of mortality. The concept of diastolic reserve has gained considerable interest, particularly in patients with HF and preserved ejection fraction, where changes in E and E′ velocities predict exercise performance (37, 38). Resting tissue velocity data, particularly those describing diastole such as E′ and A′, have been shown to have a prognostic value (9, 10, 27). A large study by Grewal *et al.* (38) found an independent association between left ventricular diastolic dysfunction and exercise capacity. Systolic function was not reported as all patients had a preserved LV. Similar incremental prognostic results have been observed in both systolic HF (9) and HF with preserved LVEF (38, 39) for E′ and E/E′. One complication when analysing all these data is the relatively close relationship between S′ and E′, making it difficult to determine which is the dominant influence. Hence, while the primary end point of these studies may relate to diastolic reserve, there is also a significant positive association with systolic function that may not be fully appreciated. One of the main determinants of early diastolic motion (caused by mitral annular descent) is the release of energy stored during systole, and therefore, S′ and other systolic measures also inevitably describe in part the behaviour of the myocardium during early diastole (40, 41).

Strain imaging is an alternative for describing myocardial deformation (42). An important disadvantage for TVI-derived strain is the low spatial resolution, which results in low reproducibly and, therefore, it is not routinely used in clinical practice (42). Two-dimensional strain speckle tracking has the clear advantage of being angle independent, but requires higher frame rates that may not be sufficient to properly track the increased heart rates at stress. This may result in under sampling, especially during exercise. Recent studies have suggested a potential benefit of speckle track-derived strain and strain rate in detected reversible ischaemia during dobutamine stress echocardiography, but routine use especially during exercise stress echocardiography is limited due to the limited range of heart rates that can be sampled (12, 43).

TVI is available on most echocardiography platforms and peak systolic and diastolic velocities are reproducible and easy to obtain both at rest and on exercise (44). The ability to achieve systolic velocities with a high degree for inter- and intra-reproducibility was confirmed in this study, unlike LVEF. The biggest challenge in achieving averaged TVI measurements is that all walls cannot always be assessed in all patients due to image quality. In this study, more than half of the echocardiographic TVI measures were not satisfactory obtained from all six myocardial walls, and hence the protocols simplified, where only average reading for the septal and lateral walls were tested. This simplified protocol gave results that were not significantly different from the average of all six walls. This may be because, although an underlying segment

may be akinetic, unlike deformation imaging, it still shows an apical long-axis velocity because it is tethered to other contracting segments. Thus, the annular velocity at any one point is an aggregate of myocardial contractility in that and adjacent segments.

Study limitations and areas for further research

A significant weakness of this study is that E′ was measured only in the lateral wall and not averaged over multiple segments and, thus, may have misrepresented patients with regional wall motion abnormalities. Møller *et al.* (45) reported that E/E′ was a strong independent predictor of death and readmission in a cohort of patients with previous myocardial infarction. Strain analysis either by TVI or by speckle tracking was not used in this study and this might have provided further insights into global and regional deformation. The only CPET variable analysed was VO_2 peak. Although VO_2 peak correlated with exercise S′, it failed to reach statistical significance as a predictor of hospitalisation. There might be a closer relationship with a submaximal parameter such as oxygen uptake efficiency slope or the ventilatory threshold. All patients were considered if clinically stable from an ischaemic point of view at enrolment, and hence formal wall motion scoring was not undertaken, hence it is possible that this might have produced similar results due to inducible ischaemia. Study population was small and selective as patients were elderly and over half of the patients suffered from stable ischaemic heart disease. Death and hospitalisations were analysed separately as in retrospective analysis, and it can be more challenging to interpret hospitalisation data with absolute certainty and hence a single combined end point was not deemed appropriate.

Conclusion

While contractile reserve is recognised as a predictor of adverse cardiac events, this is the first study to demonstrate that the measurement of peak systolic myocardial velocities derived from TVI during exercise predicts death and hospital admissions to a greater extent than either diastolic reserve or LVEF. A simplified two-wall protocol, which makes evaluation even more straightforward, gave equivalent results. Resting echocardiographic and clinical parameters were less supportive in predicting future events in this study including VO_2 peak. While prospective studies should test the hypotheses and particularly the cut-off points identified in this study, the results suggest that measuring S′ during exercise echocardiography might have an important role in understanding the likelihood of adverse clinical outcomes in patients with HF.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Pitfalls in the interpretation of cardiopulmonary exercise testing data

Dear Sirs

Cardiopulmonary exercise testing (CPET) is non-invasive, safe,[1] and reproducible.[2] CPETs provide objective information on exercise capacity. Peak oxygen uptake (VO_2peak) – the primary parameter when investigating a decrease in exercise tolerance – is affected by many cardiac and non-cardiac diseases and is a validated independent predictor for hospitalisation and death.[3–5] The oxygen uptake efficiency slope (OUES) is another valuable measurement to assess exercise tolerance and is valid even when patients are not able to exercise till their maximum.

In daily practice, CPET data can be difficult to interpret. Several different formulae are available to predict normal exercise tolerance. These formulae provide a variety of results as they use different input functions and mathematical assumptions. The 2003 American Thoracic Society/American College of Chest Physicians (ATS/ACCP) statement[6] acknowledges the absence of optimal CPET reference values and recommends that each exercise laboratory select an appropriate set of reference values, but failed to state how to make this selection. Different statements have recommended the use of different formulae. The validity of reference ranges has been noted to be uncertain in older patients, tall patients, in over- or underweight patients, and in women.[7] All formulae use similar demographic factors and make adjustment in the same direction. When applied to a typical cardiac patient, however, the formulas give markedly different results.

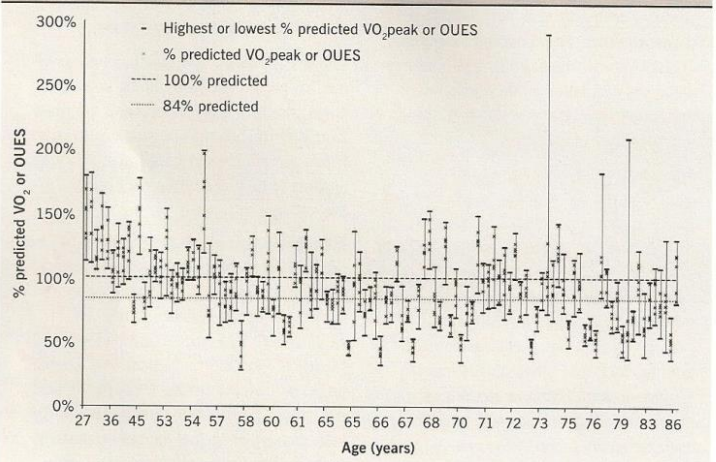
Applying formulae to clinical patients

Seven different formulae for VO_2peak (Wasserman,[7] Neder,[8] Hansen,[6] Jones,[9] Koch[10]) and for OUES (Hollenberg,[11] Buys[12]) were applied to 111 patients with systolic heart failure (n=33), patients with paroxysmal atrial fibrillation (n=69) and healthy individuals (n=9), who were participating in previous studies undertaken at our institution. When the formulae were applied to our patient population, a large variety in predicted values was observed. One patient in this study, for example, achieved a VO_2peak of 290% predicted in the Jones formula, but only 72% predicted by the Koch formula. All formulae, however, except the Wasserman's, returned either a maximal or minimal value for at least one patient, highlighting that the extent of discrepancies applies to all formulas.

The ATS/ACCP statement suggests a threshold of >84% for normal predicted VO_2peak.[6] In 44 out of 111 (40%) patients, one formula suggested predicted peak exercise capacity was over 100%, whilst another suggested it was below the 84% threshold predicted. This could have dramatic effect when interpreting CPET results as patients could be wrongly labelled as having a normal or abnormal VO_2peak. Figure 1 shows output of all seven formulae displayed for each individual. These are ordered in age order to emphasise that there is variation observed across age.

The ATS/ACCP statement[6] noted several methodological limitations in studies reporting reference ranges. These included small sample size, retrospective study design, lack of randomisation and inclusion of smokers. Furthermore, the commonly-used Wasserman formula is a modified form of

Figure 1. Predicted peak oxygen consumption (VO_2peak) or oxygen uptake efficiency slope (OUES) values for all seven formulae displayed per individual, ordered in age order



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the Hansen formula, but the rationale and evidence basis for the modification has not yet been published or peer-reviewed. Moreover, studies[13] are still emerging computing new predicting equations to better fit certain populations, demonstrating the need for an improved validated predicting equation. The authors of the Koch formula have noted systematic differences between their estimates and others', particularly in older patients.[14] The Buys formula for OUES was based on volunteers aged 20 to 60, and so may not be applicable to the patients within this analysis. A large discrepancy was observed between the Buys and the Hollenberg formula for OUES.

Implications for daily clinical practice

Across various populations, from normal controls to those with advanced heart failure, different references ranges for peak exercise capacity can give markedly differing results. These discrepancies between formulae may have significant and important implications for the interpretation of CPET reports in the clinical setting and in comparing studies published in the literature. Until more research is done to clarify the formulae that best predicts clinical outcome in these populations, physicians should consider percentage predicted VO_2 and OUES parameters in their clinical decision-making with caution. In particular, percentage predicted from other equipment or between institutions needs to be treated with extreme caution. Proper reference ranges with consistent methodology should be developed which will permit the accurate, reliable reproducible use of CPET in daily cardiac assessment.

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Conflict of interest

None declared.

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