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The use of a self-paced cardiopulmonary exercise test in the pre and post-operative care of patients with cardiovascular disease

The thesis is presented for the Degree of Doctor of Philosophy at the University of Kent

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Abstract

The aim of this thesis was to assess the ability of a self-paced (SPV) cardiopulmonary exercise test (CPET) in assessing patient fitness prior to elective surgery, and its ability to predict postoperative outcomes. The SPV is a 10 minute test which is comprised of 5 × 2 minute stages. Each stage is fixed to a level on the ratings of perceived exertion (RPE) scale, in an incremental format (RPE: 11, 13, 15, 17 and 20). This test eliminates the need of practitioners having to choose the most appropriate work rate increments to ensure a patient reaches volitional exhaustion within the recommended time period (8-12 min).

Study 1 aimed to assess the reliability of the maximal exercise test parameters obtained from the SPV. Twenty-five (12 females, 13 males) healthy participants completed three SPV tests on three separate occasions. Results demonstrated a coefficient of variation (CV) for $\dot{V}O_{2peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$) of 4.2% (95% CI: 3.4-5.6%) for trials 2-1, and 5.1% (95% CI: 4.2-6.8%) for trials 3-2. Repeated measures ANOVA analysis demonstrated no significant difference in $\dot{V}O_{2peak}$ across the repeated tests ($p > 0.05$). The limits of agreement (LOA) were ± 5.59 $ml \cdot kg^{-1} \cdot min^{-1}$ for trials 2-1, and ± 5.86 $ml \cdot kg^{-1} \cdot min^{-1}$ for trials 3-2. The mean intraclass correlation coefficient (ICC) was 0.95, which represents good reproducibility. It was concluded that the SPV is a reliable indicator of the main CPET derived variables in a healthy population, with comparable values to previous work on standard CPET protocols.

Study 2 investigated the physiological responses between the SPV and a standard CPET (sCPET) protocol between a young (18-30 years) and a middle aged to older adult (50-

75 years) population. This was in the attempt to gain an understanding of the response to the protocol and whether these responses differ with age. Expired gases, Q, SV, muscular deoxyhaemoglobin (deoxyHb) and electromyography (EMG) at the vastus lateralis were recorded throughout both tests. Results demonstrated a significantly higher $\dot{V}O_{2max}$ in the SPV (49.68 ± 10.26 ml·kg^{-1}·min^{-1}) vs. a sCPET (47.70 ± 9.98 ml·kg^{-1}·min^{-1}) in the young, but no differences in the middle aged to older adult group (> 0.05). Q and SV were significantly higher in the SPV vs. a sCPET in the young (< 0.05) but no differences in the middle aged to older adult group (> 0.05). No differences were seen in both age groups in the deoxyHb and EMG response (> 0.05). Findings from this study suggest that in the young group, the SPV produces higher $\dot{V}O_{2max}$ values as a result of an increase in oxygen delivery (enhanced Q). However, likely due to age-related differences, particularly in the cardiovascular response to exercise, the middle aged to older adult group achieved similar $\dot{V}O_{2max}$ values regardless of them reaching a higher physiological workload.

Study 3 aimed to assess the validity and reliability of the SPV in post myocardial infarction (post-MI) patients, this was the first study to assess the use of the SPV in a clinical population. Twenty-eight post-MI patients completed one sCPET and two SPVs in a randomised, counterbalanced crossover design. Each patient completed one sCPET and two SPVs. Results demonstrated the SPV to have a coefficient of variation for $\dot{V}O_{2peak}$ of 8.2%. The limits of agreement were $\pm$ 4.22 ml·kg^{-1}·min^{-1}, with intraclass correlation coefficient of 0.89. There was a significantly higher $\dot{V}O_{2peak}$ achieved in the SPV (23.07 ± 4.90 ml·kg^{-1}·min^{-1}) against the sCPET (21.29 ± 4.93 ml·kg^{-1}·min^{-1}). It was concluded that the SPV is a safe and valid test of exercise capacity in post-MI patients, with acceptable levels of reliability when compared to previous work on sCPET protocols.

Study 4 aimed to determine if the SPV can assess patient's preoperative risk similar to sCPET and if exercise variables obtained from the test can accurately predict post-operative outcome. Fifty patients with cardiovascular related co-morbidities completed one sCPET and one SPV, although only thirty of those patients when ahead with surgery. Post-surgery, patients were monitored for incidence of morbidity on postoperative days 3 and 5, length of hospital stay, and incidence of mortality in the 30 days after surgery. Patients achieved a significantly higher $\dot{V}O_{2peak}$, HR, $\dot{V}_E$, peak PO and TTE in the SPV compared to the sCPET ($P < 0.05$). Logistic regression analysis demonstrated that for the thirty patients who had surgery, none of the CPET variables were associated with postoperative morbidity at either day 3 or 5 ($P > 0.05$). Although when combining postoperative morbidity at days 3 and 5, logistic regression analysis showed that oxygen pulse at AT obtained from the SPV was significantly related to postoperative complications ($P < 0.05$). ROC curve analysis demonstrated oxygen pulse at AT to provide an AUC of 0.72 a.u. (95%CI 0.51 to 0.92), with an optimal cut-off point of 8.5 $ml/beat^{-1}$ which provided 72.7% sensitivity and 71.4% specificity. It was concluded that the SPV was able to assess preoperative fitness comparable to the sCPET. Although none of the CPET variable from either test were associated with postoperative morbidity, which is likely a result of the small sample size.

The conclusion for this thesis is that a self-paced CPET test is able to reliably assess cardiovascular patient's fitness comparable to traditional methods. This type of test may be seen as advantageous, this is because the SPV takes away the need of clinicians having to choose the most appropriate work rate increments, it allows patients to have full control

over the test, and it ensures that regardless of fitness all patients will be exercise for the recommended test time. The fixed test duration of 10 minutes may also help to improve the efficiency of running busy CPET clinics. There are clear benefits to using the SPV, although further research is required first to assess its ability of predicting postoperative outcome in a much larger sample, and to determine if it can be used to the same advantages sCPET protocols have previously demonstrated.

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Abbreviations

AAA	Abdominal aortic aneurysm
ANOVA	Analysis of variance
AT	Anaerobic threshold
ATP	Adenosine triphosphate
AUC	Area under the curve
a-vO_2 diff	Arteriovenous oxygen difference
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
Cao_2	Arterial oxygen content
CI	Confidence interval
Cvo_2	Mixed venous oxygen content
CMD	Central motor drive
CNS	Central nervous system
CPET	Cardiopulmonary exercise testing
CV	Coefficient of variation
deoxyHB	Deoxyhaemoglobin
DO_2	Global oxygen delivery
ECG	Electrocardiogram
EMG	Electromyography
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
h	Hours
HCO_3^-	Bicarbinate
HDU	High dependency unit

HR	Heart rate
ICC	Intraclass correlation coefficient
ICU	Intensive care unit
$L \cdot min^{-1}$	Litres per minute
LOA	Limits of agreement
LOS	Length of stay
MET	Metabolic equivalent
min	Minutes
MIVC	Maximal isometric voluntary contractions
Ml	Millilitres
$mL \cdot min^{-1}$	Millilitres per minute
$ml \cdot kg^{-1} \cdot min^{-1}$	Millilitres, per Kilogram of body weight, per minute
mmHg	Millilitres of mercury
mmol/L	Millimoles per litre
MVV	Maximal voluntary ventilation
n	Number
NIRS	Near-Infrared Spectroscopy
OER	Oxygen extraction ratio
OR	Odds ratio
OUES	Oxygen update efficiency slope
P	Significance level
PaO_2	Oxygen saturation
$P_{ET}O_2$	Partial end-tidal
$P_{ET}CO_2$	Partial end-tidal
PO	Power output
POMS	Postoperative morbidity survey

POSSUM	Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity
$\dot{Q}$	Cardiac output
RAMP	Standard incremental ramp test
RER	Respiratory exchange ratio
ROC	Receiver operator characteristic
RPE	Ratings of perceived exertion
rpm	Rates per minute
sCPET	Standard cardiopulmonary exercise test
SD	Standard deviation
secs	Seconds
SPV	Self-paced $\dot{V}O_{2peak}$ test
SV	Stroke volume
TTE	Time to exhaustion
VD	Dead space volume
$\dot{V}_E$	Minute ventilation
$\dot{V}_E/\dot{V}CO_2$	Minute ventilation for carbon dioxide production
$\dot{V}_E/\dot{V}O_2$	Minute ventilation for oxygen consumption
$\dot{V}CO_2$	Carbon dioxide production
VL	Vastus lateralis
$\dot{V}O_2$	Oxygen consumption
$\dot{V}O_2$/HR	Oxygen pulse
$\dot{V}O_{2max}$	Maximal oxygen consumption
$\dot{V}O_{2peak}$	Peak oxygen consumption
W	Watts
$W \cdot min^{-1}$	Watts increase per minute

Ethical Approval Reference Numbers

All of the individual research studies within this thesis were ethically approved by either the University of Kent's School of Sport and Exercise Sciences Research Ethics and f Governance Committee (Chapter 4 & 5), or the South East Coast, Brighton and Sussex, National Research and Ethics Committee (Chapters 6 & 7).

Table i. Ethical approval reference numbers for all research chapters.

	Ethical Reference Number
Chapter 4	Prop79_2012_13
Chapter 5	Prop123_2013_14
Chapter 6 & 7	12/LO/1737

Chapter 1. Introduction

1.1. Introduction

The health benefits of regular physical activity are indisputable, with exercise being strongly linked to general health, well-being, and reduced risk of disease (Cooper & Storer 2001). Exercise itself is considered as the truest test of an individual's health as it is the most common everyday stress that we undertake (Froelicher & Stahr 2005). Maximal exercise testing, in particular, has become a standard procedure in exercise physiology for assessing cardiovascular function (Andreacci, Lemura, Cohen, Urbansky, Chelland et al., 2002) and exercise capacity. In sport and fitness, exercise capacity is linked to performance outcomes and achievements, whereas exercise performance in a clinical setting is related to functional capacity and quality of life (Cooper & Storer 2001). The key values derived from the test can be used as a starting point for exercise prescription (Andreacci et al., 2002), with follow up tests being used to help determine the success of a specific training plan (Bassett & Howley 2000). Exercise testing in a clinical setting, also known at cardiopulmonary exercise testing (CPET), can provide valuable diagnostic and prognostic information for both cardiovascular and pulmonary patients (Balady, Arena, Sietsema, Myers, Coke et al., 2010). This is because CPET provides an assessment of the integrative responses to exercise involving the pulmonary, cardiovascular, respiratory, neuropsychological, and skeletal muscle systems (West, Jack & Grocott 2011). This non-invasive method represents a physiological overview of both submaximal and maximal exercise responses (Albouaini, Egred, Alahmar & Wright 2007) and can provide an objective assessment of the body's response to stress (Hopker, Jobson & Pandit 2011).

CPET is increasingly being used in a clinical setting for the evaluation of exercise tolerance and for the detection of functional capacity and impairment (Albouaini et al., 2007). Exercise tolerance is suggested to be the ability to complete a required physical task successfully. Everyone who exercises will have a particular level of exercise intolerance, but from a clinical perspective, the issue is whether a patient demonstrates an intolerance that is not representative of the norms (Palange, Ward, Carlsen, Casaburi, Gallagher et al., 2007). Exercise tolerance is dependent on the efficiency of pulmonary gas exchange, cardiovascular performance and skeletal muscle metabolism (Albouaini et al., 2007). Previous work has suggested that exercise tolerance correlates better with overall health status compared to resting measurements (Albouaini et al., 2007). In addition, exercise capacity has been shown to be one of the best predictors of mortality (Myers, Prakash, Froelicher, Partington & Atwood 2002), With these benefits, CPET is therefore considered a gold standard method for evaluating the response of the cardiopulmonary system when placed under stress, and is based on the principle that system failure usually occurs while the system (e.g. cardiovascular or pulmonary) is under stress (Palange et al., 2007).

There are a number of benefits to CPET, for example it can be used for the development of an exercise programme, determining functional capacity, evaluation of exertional dyspnea, risk stratification and heart failure prognosis, assess the effectiveness of medical and surgical therapies, and even determine the need for surgical repair in congenital heart disease (Milani, Lavie, Mehra & Ventura 2006). Among these many benefits of CPET, it is also proposed to provide an indication of a patient's ability to cope with the metabolic demands associated with major surgery (Hopker, Jobson & Pandit 2011; Smith, Stonell, Purkayastha & Paraskevas 2009). Major surgery is considered as any procedure which

places a high amount of stress on a patient's cardiopulmonary system (Reilly, McNeely, Doerner, Greenberg, Staiger et al., 1999), for example vascular and intra-abdominal surgery are deemed as high risk due to the extent, invasiveness and complexity of such procedures (Lee, Hamilton & Rhodes 2009). As such surgeries place a high amount of stress on the cardiopulmonary system, using a dynamic test which evaluates a patient's ability to deal with such stresses is seen as a useful predictor of postoperative morbidity and mortality. The benefit of CPET is that this objective assessment of the integrated body systems, during exercise, has the ability to determine cardiorespiratory reserve, diagnose diseases and identify underlying causes of exercise limitations (Burnside & Snowden 2014).

Whilst the use of CPET is increasing, it is acknowledged that this method is still relatively rare across the UK. Indeed, a recent survey investigated the use of preoperative CPET services in England (Huddart, Young, Smith, Holt & Prabhu 2013), and from this survey, 32% of all adult anaesthesia departments in England had a preoperative CPET service available, with 4% of these in the process of setting a service up. Whilst this number seems relatively low, in 2008 only 17% of the 115 NHS Acute Trusts contacted had CPET services available, with 7% of these in the process of being set up (Simpson, Sutton and Grocott, 2009). This is reassuring as it demonstrates a continuing increase in the use of preoperative CPET. The survey results also report that the main reason for the lack of services is predominantly related to the financial cost and lack of available resources. However, other reasons stated were a perceived lack of clinical need and insufficient evidence of the clinical benefit. There are however alternative, more simple and inexpensive methods available which are commonly used to assess the functional capacity of patient populations. For example, the submaximal six-minute walk test

(6MWT) and the incremental shuttle walk test (SWT), have both been shown to be moderate predictors of peak oxygen uptake and thus functional capacity (Fletcher, Ades, Kligfield, Arena et al., 2013; Miyamoto, Nagaya, Satoh, Kyotani et al., 2000; Morales, Montemayor & Martinez 2000; Wise & Brown 2005). However, unlike CPET, they do not provide a direct assessment of the cardiopulmonary response to exercise. These methods and others will be discussed in greater detail later on in this thesis.

When CPET is not used or is unavailable for preoperative assessment, assessing a patient's cardiopulmonary health prior to surgery is usually based on static, individual organ measures (e.g. echocardiography, spirometry etc.) (Forshaw, Strauss, Davies, Wilson, Lams et al., 2008). Surgical risk is then usually calculated based on the use of various scoring systems, for example, the American Society of Anesthesiologists (ASA) physical status classification (Wolters, Wolf, Stutzer & Schroder 1996), the Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM) system (Copeland 2002) and Lee's revised cardiac index (Lee, Marcantonio, Mangione, Thomas, Polanczyk et al., 1999) have all been used in preoperative assessment. Physical activity history is also integrated with these methods to help with the risk stratifications (Bhagwat & Paramesh 2010). A patient's walking distance, or their ability to climb stairs is often used as a subjective measure of exercise tolerance to help with the prediction of postoperative complications (Forshaw et al., 2008). However such methods are deemed as unreliable and fail to provide any specific detail of how the integrated systems work together under stress, making it difficult to gain a true representation of fitness from these type of tests. As previously mentioned, CPET is proposed to mimic the metabolic demands associated with major surgery (Hopker et al., 2011) giving a more objective risk assessment, which is not adequately reflected through

individual organ system measurements and by acquiring information on previous physical activity history (Bhagwat & Paramesh 2010). As a result patients may be wrongly allocated for their postoperative care when being assessed using these traditional methods. For example, an overestimation of a patient's health may cause them to be referred to ward care postoperatively, where they could deteriorate, develop organ failure, and have their hospital stay prolonged. Conversely, some patient's health may be underestimated in the pre-assessment, which could result in them being referred to the intensive care unit (ICU) postoperatively, which would place unnecessary demand on, what are already, limited resources (Bhagwat & Paramesh 2010).

Practitioners who already use CPET in preoperative assessment in England successfully use the information obtained from the test to help allocate appropriate level of post-operative care (ICU, ward etc), determine the level of intraoperative monitoring, modify surgical procedure (if possible) and in some cases even cancel or advise against the surgical procedure (Huddart, Young, Smith, Holt & Prabhu 2013). If this preoperative method is truly capable of providing a reliable indicator of post-operative morbidity and mortality, it could have a significant impact on the care of patients. By identifying those at a high risk the appropriate care and additional resources can be planned prior to surgery to reduce morbidity and mortality (Smith, Stonell, Purkayastha & Paraskevas 2009).

It is clear that CPET has the potential to be a useful tool in preoperative assessment and therefore it is of great importance for the protocol to be both valid and reliable. One of the key values obtained from CPET is peak oxygen uptake ($\dot{V}O_{2peak}$), which is defined as the highest amount of oxygen a person consumes during dynamic exercise (Bassett &

Howley 2000). As $\dot{V}O_{2peak}$ measures maximal aerobic capacity, it is considered a strong indicator of cardiovascular fitness (Smith et al., 2009). Current practice is to use a CPET protocol that encompasses an incremental exercise test, whereby the patient's required work rate gradually increases until volitional exhaustion is reached, and thus $\dot{V}O_{2peak}$ (Albouaini et al., 2007; Balady et al., 2010; Chaitman, Moinuddin & Sano 2007). It is suggested that in order to gain a true representation of fitness, the CPET protocol needs to ensure that the patient reaches volitional exhaustion between 8-12 minutes (min) (Buchfuhrer, Hansen, Robinson, Sue, Wasserman et al., 1983), therefore it is the responsibility of the person conducting the test to decide on the most appropriate starting work rate and stage increments that ensure exhaustion in this time period. This can sometimes be problematic as it is often difficult to judge how an individual is likely to tolerate the protocol until they actually commence the test: a test which lasts for too long, or is too short, reduces the validity of the results. It is suggested that a test which is short in duration (< 8 min) may underestimate $\dot{V}O_{2peak}$ due to increased glycolytic contribution to energy and enhanced fast-twitch muscle fibre recruitment (Astorino, Rietschel, Tam, Taylor, Johnson et al., 2004). Also a short test may only acquire limited information making it difficult to confidently assess fitness. Conversely, if a test lasts too long patients may stop due to such factors as boredom or increased local muscle fatigue (Astorino et al., 2004), rather than a result of their actual cardiopulmonary limit. There have also been a number of other limitations that have been brought to light regarding the general nature of the current CPET protocol (Noakes 2008), for example, the patient is unaware of the test duration and it is known that knowledge of exercise duration can facilitate performance (Mauger, Jones & Williams 2009), the test does not replicate any normal exercise behaviour, and finally the patient only has control over when they stop which

adds a psychological aspect to the test i.e. low motivation. These ideas will be discussed in greater detail later on.

Recent research has demonstrated the use of an alternative CPET protocol based on the use of perception of effort (Mauger & Sculthorpe 2012). This novel protocol, termed the self-paced $\dot{V}O_{2peak}$ (SPV) test, allows participants to self-regulate their work rate according to prescribed ratings of perceived exertion (RPE), whilst still maintaining an incremental test format. The SPV consists of 5 × 2 minute stages, so regardless of a person's fitness everyone exercises for the recommended time period of 10 min. This novel protocol has been previously used with both healthy (Mauger & Sculthorpe 2012) and trained (Mauger, Metcalfe, Taylor & Castle 2013) individuals, where it has been shown to produce higher $\dot{V}O_{2peak}$ values than the standard CPET (sCPET) protocol in both cycling and running. The SPV takes away the need for practitioners to decide on the most appropriate work rate increments to ensure a valid test, it also ensures all participants to exercise for the recommended duration of 10 min and provides participants with a clear end point to work towards. These factors provide a test that solves some of the issues associated with the current CPET protocols, therefore it would be advantageous to investigate if the SPV could be used on a clinical population in order to establish a more valid method for determining cardiorespiratory fitness prior to elective surgery. This thesis aims to identify if a self-paced CPET protocol can be used to identify preoperative risk and predict post-operative outcomes in patients with cardiovascular disease.

Chapter 2. Literature Review

2.1. Physiological demands of CPET

The ability to perform physical exercise is related to both the cardiovascular and pulmonary system to supply oxygen to the working muscles (Balady, Arena, Sietsema, Myers, Coke et al., 2010). There are a series of processes that occur to allow this supply in oxygen, these include; pulmonary ventilation, pulmonary diffusion, transportation of oxygen and carbon dioxide in the blood, and capillary gas exchange (Balady et al., 2010). In CPET, this physiological pathway of oxygen can be effectively assessed (Burnside & Snowden 2014). Any limitations in this process will limit the delivery of oxygen and therefore exercise capacity. As oxygen cannot be stored, a continuous and endless supply is required. It is the cardiovascular system's primary role to deliver this continuous supply of oxygen to tissue around the body to sustain aerobic metabolism. The oxygen supply available must match the metabolic demands, otherwise inflammation and organ dysfunction can occur (Lee, Hamilton & Rhodes 2009). This process must be energy efficient so that unnecessary cardiorespiratory work is avoided, but it must also be sensitive to the inconsistent demands of cellular metabolism (Leach & Treacher 1992).

Oxygen consumption ($\dot{V}O_2$) is the total amount of oxygen consumed per minute. This can be measured directly by breath by breath analysis (Leach & Treacher 2002). $\dot{V}O_2$ can be described using the Fick equation, at rest it is shown as:

$$\dot{V}O_2 = (SV \times HR) \times (CaO_2 - CvO_2)$$

SV is stroke volume, HR is heart rate, CaO_2 is the arterial oxygen content and CvO_2 is mixed venous oxygen content. Oxygen uptake is usually normalised to body weight and

expressed in $ml \cdot kg^{-1} \cdot min^{-1}$. One metabolic equivalent (MET), which is resting oxygen uptake, is equal to 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$. At peak exercise the Fick equation is expressed as:

$$\dot{V}O_{2max} = (SVmax \times HRmax) \times (CaO_{2max} - CvO_{2max})$$

This demonstrates the ability of the body to maximally transport and use up oxygen, which defines an individual's aerobic capacity (Albouaini, Egred, Alahmar & Wright 2007). During increasing work rate, the body will increase oxygen delivery in attempt to maintain efficient energy production, this can been seen by an increase in minute ventilation ($\dot{V}_E$) and cardiac output ($\dot{Q}$) (Burnside & Snowden 2014). If during a maximal test the $\dot{V}O_2$ curve ($\dot{V}O_2$/work rate) represents a plateau, regardless of a continuous increase in work rate, then this can be referred to as $\dot{V}O_{2max}$ (Milani, Lavie, Mehra & Ventura 2006). Otherwise the term $\dot{V}O_{2peak}$ is commonly used as this defines the highest $\dot{V}O_2$ reached during a test and does not assume that a maximal physiological response has been reached, which is very uncommon in a clinical setting particularly in patients with cardiovascular and pulmonary disease (Albouaini et al., 2007; Balady et al., 2010). During exercise, the increase in oxygen uptake is mostly aided by an increase in $\dot{Q}$ (HR x SV). Additionally, to facilitate this greater oxygen delivery to the working muscles, blood is redistributed away from the tissues which are not in use. There is also an increase in blood flow to the lungs, which is supported by an increase in $\dot{Q}$ and by vasodilation of the pulmonary vessels. As the blood perfuses the muscles, there is also a widening of the arteriovenous oxygen difference (a-vO_2 diff) which also results in a greater oxygen extraction from the blood (Balady, Arena, Sietsema, Myers, Coke et al., 2010). All of these processes occur to aid oxygen uptake and delivery during exercise.

Global oxygen delivery (DO_2) is the total amount of oxygen delivered to the tissues per minute which is defined by both $\dot{Q}$ and CaO_2, and is considered to be independent of $\dot{V}O_2$ (Leach & Treacher 2002; Lee, Hamilton & Rhodes 2009). The oxygen extraction ratio (OER) is defined by $\dot{V}O_2$ as a fraction of DO_2 (Leach & Treacher 2002). During resting conditions, it is suggested that DO_2 exceeds $\dot{V}O_2$ (Lee et al., 2009), with the normal distribution of $\dot{Q}$ adequately meeting the oxygen demand and ensuring that aerobic metabolism is maintained (Leach & Treacher 2002). As $\dot{V}O_2$ increases or DO_2 decreases, OER will increase to maintain aerobic metabolism, this will continue to rise up to maximum OER where critical DO_2 is reached (Leach & Treacher 2002), at this point $\dot{V}O_2$ becomes supply dependent and anaerobic metabolism will occur (Lee et al., 2009). Further increases in $\dot{V}O_2$ or decreases in DO_2, beyond critical DO_2, will lead to tissue hypoxia (Leach & Treacher 2002), which can lead to cellular dysfunction and eventually organ dysfunction, failure and possibly death (Lee et al., 2009). Optimal level of DO_2 will depend on the metabolic demands but it is suggested that an inadequate DO_2 is confirmed by a very high OER, which is demonstrated by mixed venous oxygen saturations (SvO_2) of < 70% (Lee et al., 2009). It is suggested that the ability of tissues to increase OER is less efficient in the critically ill (Lee et al., 2009), indeed DO_2 has been shown to be an early and better predictor of multiple organ dysfunction after ruptured Abdominal Aortic Aneurysm (AAA) in comparison to previously identified risk factors. The inability to attain a normal DO_2 within 8 hours after AAA repair is strongly correlated with multiple organ dysfunction and mortality (Peerless, Alexander, Pinchak, Piotrowski & Malangoni 1998). Previous research has also demonstrated that complications and mortality post-surgery have been strongly linked to reduced DO_2 and $\dot{V}O_2$ (Kusano, Baba, Takao, Sane, Shimada et al., 1997; Russel, Ronco, Lockhat, Belzberg, Kiess et al., 1990). Therefore, with this knowledge, objectively assessing a patient's ability to cope with increased

metabolic demands via CPET is seen as a valid test for risk stratifying patient's prior surgery.

To sustain a given level of exercise, the cardiorespiratory response must be adequate to supply the oxygen needed to regenerate all the adenosine triphosphates (ATP) required for the working muscles (Wasserman, Hansen, Sue, Stringer & Whipp 2005a). As an individual progresses through an incremental exercise test their $\dot{V}_E$, $\dot{V}O_2$ and CO_2 production per minute ($\dot{V}CO_2$) all increase linearly in relation to work rate or time in order to supply all of the oxygen needed. However a point is reached when $\dot{V}CO_2$ increases disproportionately to $\dot{V}O2$. This sudden change is attributed to bicarbonate (HCO_3^-) buffering the lactate accumulation and consequently producing excess CO_2 (Smith, Stonell, Purkayastha & Paraskevas 2009). The increase in lactate production is caused by the onset of anaerobic glycolysis, in order to meet the ever increasing energy demands of the incremental exercise test (Wasserman, Whipp, Koyal & Beaver 1973). The increase in CO_2 output is sensed by chemoreceptors in the carotid bodies, which causes an increase in $\dot{V}_E$ (Milani, Lavie, Mehra & Ventura 2006). This metabolic transition is termed the anaerobic threshold (AT) (Smith, Stonell, Purkayastha & Paraskevas 2009), and is commonly defined as the work rate or oxygen consumption just below the point where metabolic acidosis and changes in gas exchange occur (Hopker, Jobson & Pandit 2011). This physiological point is also referred to as the ventilatory threshold (Gaskill, Ruby, Walker, Sanchez, Serfass et al., 2001), gas exchange threshold (Inbar, Oren, Scheinowitz, Rotstein, Dlin et al., 1994), and if determined via blood lactate analysis, the lactate threshold (Binder, Wonisch, Corra, Cohen-Solal, Vanhees et al., 2008). In the current thesis it will be referred to as AT and is measured via the use of gas exchange, unless stated otherwise.

As well as $\dot{V}O_{2peak}$ and AT, there are other important parameter which are obtained from CPET to assist in the evaluation of cardiopulmonary fitness, these include the relationship between $\dot{V}_E$ and $\dot{V}CO_2$ ($\dot{V}_E/\dot{V}CO_2$) (Arena, Myers, Aslam, Varughese & Peberdy 2004) and the relationship between $\dot{V}O_2$ and heart rate, known as oxygen pulse ($\dot{V}O_2/HR$) (Vassaux, Torre-Bouscoulet, Zeineldine, Cortopassi, Paz-Díaz et al., 2008). All of the key CPET derived variables will be discussed in greater detail in chapter 2.4 with regards to their predictive ability of postoperative outcome.

2.2. CPET vs. the demands of surgery

Major surgery is associated with a systemic inflammatory response (Tolchard, Angell, Pyke, Lewis, Dodds et al., 2014) and is suggested to place severe stress on a patient's cardiopulmonary reserve (Forshaw, Strauss, Davies, Wilson, Lams et al., 2008). The stress response to surgery is suggested to result in an increased secretion of stress hormones (Gutierrez, Hornigold & Pearce 2011) and activation of the sympathetic nervous system (Desborough 2000). In particular, the large endocrine response to surgery increases the secretion of catabolic hormones, which can result in the breakdown of muscle and fat causing patient weight loss and muscle wasting (Gutierrez et al., 2011). Increased activation of the sympathetic nervous system is known to have various cardiovascular effects including tachycardia and hypertension (Desborough 2000), and also influences renal, hepatic and pancreatic functions (Gutierrez et al., 2011). This significant systemic inflammatory response is directly associated with an increase in oxygen demand (Lees et al., 2009), usually requiring about 40% (or greater in some

instances) increase in oxygen delivery. This increase requires a concurrent increase in $\dot{Q}$ or oxygen extraction in order to meet this demand (Forshaw, Strauss, Davies, Wilson, Lams et al., 2008; Older & Hall 2004). For example, AAA repair surgery can result in an oxygen consumption of 4.5 to 5 $ml \cdot kg^{-1} \cdot min^{-1}$, which in older patients could be 50% or more over their resting values (Older, Smith, Courtney & Hone 1993). Cardiopulmonary exercise is said to closely mimic the postoperative situation and essentially assess how well a patient copes with oxygen demands at > 50% of their resting values. The inability to keep up with the increased oxygen demand results in an accumulative 'oxygen debt' and thus tissue hypoxia (Lees et al., 2009). Tissue hypoxia is known to contribute to inflammation and microcirculatory failure, which can result in organ dysfunction and/or failure and ultimately death (Lees et al., 2009). Therefore, those patients whose oxygen delivery is compromised during exercise will be therefore at an increased risk following surgery (Older, Hall & Hader 1999), particularly of myocardial infarction (MI) and death (Tolchard et al., 2014).

Determining risk for surgery is dependent on two main components, the type of surgical procedure and the functional capacity of the patient. Actual surgical risk relates to the extent, invasiveness, complexity and duration of the procedure (Lees et al., 2009). All of these factors have a direct influence to the oxygen demand required (Older & Hall 2004) and the stress response (Lees et al., 2009). For example laparoscopic surgery is deemed 'less invasive' and therefore causes less pain, leads to a faster recovery, and consequently shorter hospital stay, compared to those open surgical procedures (Reza, Blasco, Andradas, Cantero & Mayol 2006; Scott, Shohag, Kam, Jelinek & Khadem 2013). This may suggest that CPET is more important for patients undertaking those 'higher' risk procedures, indeed previous research has suggested that CPET is not a useful predictor

of risk in all surgery types (e.g. oesophagectomy) (Forshaw et al., 2008). The functional capacity of the patient also has a direct influence on surgical risk. It is suggested that patients with limited physiological reserve, and therefore unable to meet the increased oxygen demands, are more likely to suffer complications or death (Lees et al., 2009). Therefore determining a patient's functional capacity, via CPET, prior to surgery will contribute in the risk stratification and thus decision making process for patients. If surgery is agreed, then the right care can be assured during the perioperative period in the attempt to minimise any risks that there may be. When assessing a patients risk for surgery it is important to take both components into consideration, for example, a lower risk surgery may still treated as high risk if a patient has a reduced functional capacity.

2.3. The CPET Procedure

Despite CPET requiring a moderate to high level of exertion, it is well tolerated by the patient population, and is regarded as a safe procedure to conduct, even in older individuals with multiple co-morbidities (Older, Smith, Courtney & Hone 1993, West, Jack & Grocott 2011). CPET testing can be completed on either a cycle ergometer, treadmill or an arm ergometer (Bhagwat & Paramesh 2010). It is known that treadmill testing produces a 5 to 10% higher $\dot{V}O_{2peak}$ compared to cycle ergometry, primarily due to the recruitment of more muscle groups (Albouaini et al., 2007). Although, cycling is perceived as the preferred exercise modality for clinical testing due to greater upper body stability, making falls from equipment less likely (Smith, Stonell, Purkayastha & Paraskevas 2009), and electrocardiogram (ECG) and blood pressure (BP) measurements more reliable (Takken, Blank, Hulzebos, Brussel, Groen et al., 2009). Regardless of the

method of exercise used, a CPET test usually consists of incremental work stages where the patient is required to continue exercise until they can no longer do so. On a treadmill, work rate can be increased by speed and/or gradient, whereas on a cycle ergometer, work rate is incremented by increasing the resistance to cycling (Smith et al., 2009). The common cycling CPET protocol commences with a 2-5 minute rest period where the patient is required to remain stationary on the cycle ergometer to allow time for them to become accustomed to the equipment (Burnside & Snowden 2014). This stage also allows practitioners to gain some resting measurements and to ensure all the equipment is working correctly. Following the initial stage there is usually a 3 minute period of cycling against no resistance, often known as unloaded pedalling, to allow stabilization of any adverse baseline measures i.e. anxiety driven hyperventilation (Burnside & Snowden 2014). Following the unloading pedalling phase the main exercise test encompasses a continual ramped increase in cycling resistance whilst cadence is consistently maintained at a predetermined rate by the patient (Burnside & Snowden 2014). The work rate increment is chosen to allow patients to reach exhaustion at the recommended optimal duration of 10 min, these increments usually range between 5-25 $W \cdot min^{-1}$ (American Thoracic Society & American College of Chest Physicians 2003). Buchfuhrer et al., (1983) demonstrated that $\dot{V}O_{2peak}$ is significantly higher in tests lasting between 8-12 min compared to tests of longer and shorter duration, with 10 min being optimal.

Following volitional exhaustion resistance is removed from the cycle ergometer and the patient is required to complete a gentle cool down until their HR has returned within 10 $beats.min^{-1}$ (bpm) of their resting value. During the test a range of physiological variables are commonly measured including, breath-by-breath expired gas analysis (Grocott & Pearse 2010), BP, and ECG (Smith, Stonell, Purkayastha & Paraskevas 2009). Breath-

by-breath gas analysis enables the determination of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ (Milani, Lavie, Mehra & Ventura 2006). The continuous ECG readings assist in identification of ischaemic changes during the test, a signal for immediate test termination (Bhagwat & Paramesh 2010). Key physiological CPET derived variables often used by clinicians in risk stratification are $\dot{V}O_{2peak,}$ AT, $\dot{V}_E/\dot{V}CO_2$ at the AT and VO_2/HR (West, Jack & Grocott 2011).

2.4. CPET derived parameters and risk stratification

2.4.1. Peak Oxygen Consumption

The $\dot{V}O_{2peak}$ is the highest $\dot{V}O_2$ achieved during the CPET and generally occurs at or near maximal exercise capacity. As previously mentioned, $\dot{V}O_{2peak}$ is defined by the Fick equation: $\dot{V}O_{2peak}$ = (HR x SV) x (CaO_2 – (CvO_2), which represents the $\dot{Q}$ and a-vO_2 diff at peak exercise (Balady, Arena, Sietsema, Myers, Coke et al., 2010). If the $\dot{V}O_2$ curve represents a plateau, where the $\dot{V}O_2$ no longer increases regardless of an increase in work rate, this can be referred to as $\dot{V}O_{2max}$ (Milani, Lavie, Mehra & Ventura 2006). As $\dot{V}O_{2peak}$ measures maximal aerobic capacity, it is a useful indicator of cardiovascular fitness (Smith, Stonell, Purkayastha & Paraskevas 2009).

$\dot{V}O_{2peak}$ has previously been shown to be a consistent parameter when obtaining risk of patients going into major surgery. Walsh, Morice, Putnam, Nesbitt, McMurtrey et al., (1994) identified how those patients, considered for lung resection, who achieved a $\dot{V}O_{2peak}$ > 15 $ml \cdot kg^{-1} \cdot min^{-1}$ survived their operation with what they deemed as

'satisfactory' morbidity, whereas those patients with a $\dot{V}O_{2peak}$ of < 15 ml·kg^{-1}·min^{-1} had higher rates of morbidity and mortality. Further to this, Beckles, Spiro, Colice and Rudd (2003) concluded that a $\dot{V}O_{2peak}$ of > 20 ml·kg^{-1}·min^{-1} is perceived as no increased risk of complications or death after surgery, < 15 ml·kg^{-1}·min^{-1} is perceived as an increased risk of post-operative complications, and < 10 ml·kg^{-1}·min^{-1} is perceived as a very high risk for post-operative complications. Berchard & Wetsein (1987) also demonstrated that for a group of lung resection patients, those who had no complications post-surgery had a $\dot{V}O_{2peak}$ 17.01 ± 0.77 ml·kg^{-1}·min^{-1} (mean ± SD), whereas those who had complications post-surgery had a $\dot{V}O_{2peak}$ of 9.95 ± 1.52 ml·kg^{-1}·min^{-1}. These findings are supported by McCullough and colleagues (2006), who showed that from a group of patients undergoing bariatric surgery, those who achieved a $\dot{V}O_{2peak}$ of < 15.8 ml·kg^{-1}·min^{-1} had a 16.7% incidence rate of complications post-surgery. By contrast the authors only found 2.8% of those patients who achieved a $\dot{V}O_{2peak}$ > 15.8 ml·kg^{-1}·min^{-1} to experience post-surgical complications. Those factors that where classed as complications in this study where death, unstable angina, MI, venous thromboembolism, renal failure, stroke, length of hospital stay (LOS) and readmissions in the hospital (McCullough, Gallagher, deJong, Sandberg, Trivax et al., 2006). Mancini et al., (1991) also used CPET to determine whether measurements of peak $\dot{V}O_2$ can be used to identify patients in whom cardiac transplantation can be safely deferred, by comparing heart failure patients who were not accepted for cardiac transplantation with those who received a transplant. For all those not accepted for transplantation, a $\dot{V}O_{2peak}$ > 14 ml·kg^{-1}·min^{-1} produced higher survival rates compared to those after transplantation who had a $\dot{V}O_{2peak}$ < 10 ml·kg^{-1}·min^{-1}.

$\dot{V}O_{2peak}$ has not always been shown to significantly predict postoperative complications. Indeed, Nugent, Riley, Megarry, O'Reilly, MacMahon et al., (1998) failed to find a

significant relationship with postoperative complications in patients undergoing elective AAA repair. However, an underlying trend was observed in the data of Nugent and colleagues (1998), suggestive of higher complication rates in those patients with a $\dot{V}O_{2peak}$ of < 20 $ml \cdot kg^{-1} \cdot min^{-1}$. The authors propose that their results could have been influenced by the small sample size, and the reduced tendency of clinicians to operate clinically 'borderline' patients with AAA, compared with lung cancer patients. It has also been concluded by Forshaw et al., (2008) that $\dot{V}O_{2peak}$ does not strongly predict postoperative cardiopulmonary complications in patients undergoing oesophagectomy, which questions the need for CPET in such surgeries. Although, they did still find that $\dot{V}O_{2peak}$ was significantly lower in those patients who did develop cardiopulmonary complications postoperatively. It is also worth mentioning that for various reasons not all patients may be able to reach near maximal values (e.g. orthopaedic or muscular discomfort, low motivation etc.). In particular if incorrect work rates are selected then a patient may not achieve the recommended test time (8-12 min; Buchfuhrer et al., 1983) and thus fail to achieve near optimal $\dot{V}O_2$ values. This will ultimately lead to incorrect values which will reduce the validity of $\dot{V}O_{2peak}$ to accurately risk stratify patients prior to surgery. Therefore a test which may help patients achieve values closer to maximum would be advantageous.

2.4.2. Anaerobic Threshold

During CPET, there becomes a point where the oxygen supply cannot meet the increasing oxygen requirements at the exercising muscles, at this point anaerobic metabolism occurs (Albouaini et al., 2007). This metabolic transition results in $\dot{V}CO_2$ increasing disproportionately to $\dot{V}O_2$, which is a result of the buffering processes of lactic acid to lactate and consequently producing excess CO_2 (Smith, Stonell, Purkayastha & Paraskevas 2009), this physiological change in gas exchange is the AT (as previously

described). The AT is a more preferable parameter used by some physiologists in preoperative assessment compared to $\dot{V}O_{2peak}$, this is because it is an accurate objective assessment of cardiac function which does not require the patients to work to their maximum capacity, therefore not putting high physical stress on the patient (Older, Hall & Hader 1999). Additionally, surgery does not maximally stress the cardiopulmonary system, in fact the oxygen demand is said to be up to around 50% above their resting values (Older et al., 1993) so it raises questions as to whether peak exercise capacity is necessary. Although a number of studies have now provided evidence that both $\dot{V}O_{2peak}$ and AT are able predict postoperative outcome to the same effect as each other (Junejo, Mason, Sheen, Moore, Foster et al., 2012, West, Parry, Lythgoe, Barben, Kemp et al., 2014, West, Asher, Browning, Minto, Swart et al., 2016).

Older et al., (1993) studied 187 preoperative patients who were over the age of 60 years. Each patient completed a CPET prior to their major intra-abdominal surgery. It was concluded that patients with an AT of < 11 $ml \cdot kg^{-1} \cdot min^{-1}$ and where myocardial ischemia was present, their risk of postoperative complications almost doubled. To mitigate the risk they suggested that all those patients scheduled for major intra-abdominal surgery with an AT of < 11 $ml \cdot kg^{-1} \cdot min^{-1}$ should be admitted to ICU after surgery. These findings have been further supported by Older et al., (1999) and Wilson, Davies, Yates, Redman and Stone (2010) as both studies identified that an AT < 11 $ml \cdot kg^{-1} \cdot min^{-1}$ is a strong predictor of mortality after major abdominal surgery. The use of the AT has additionally been used in the prediction of both short-term (6 months) and long-term (2 years) survival of patients with chronic heart failure, showing high prognostic strength (Gitt, Wasserman, Kilkowski, Kleemann, Kilkowski et al., 2002). It is suggested that the average oxygen consumption following major surgery is 4.5 to 5 $ml \cdot kg^{-1} \cdot min^{-1}$, but it is not uncommon to

see levels rise by 6 to 7 $ml \cdot kg^{-1} \cdot min^{-1}$, therefore patients incapable of achieving an AT of > 8.5 $ml \cdot kg^{-1} \cdot min^{-1}$ would result in them being unable to meet the increased oxygen demands and $\dot{Q}$ associated with major surgery (Older, Smith, Courtney & Hone 1993). It is clear that AT is a strong predictor of post-operative complications, however, some studies suggest that AT is not a consistently strong predictor across all surgical procedures such as oesophagectomy (Junejo, Mason, Sheen, Moore, Foster et al., 2012). A further issue is that the reproducibility of AT on a test-retest basis is lower than parameters such as $\dot{V}O_{2peak}$. Specifically, previous studies have demonstrated AT to have a coefficient of variation (CV) 9.3% (Scott, Haykowsky, Eggebeen, Morgan, Brubaker et al., 2012) to 10% (Kothmann, Danjoux, Owen, Parry, Turley et al., 2009) compared to the CV for $\dot{V}O_{2peak}$ being 4.9% (Scott, Haykowsky, Eggebeen, Morgan, Brubaker et al., 2012) to 6% (Elborn, Stanford & Nicholls 1990). With this in mind using a maximal CPET, rather than submaximal, allows measurements of both variables which can be used in combination to predict risk, indeed previous research has demonstrated that assessing CPET derived variables in combination is beneficial when predicting postoperative outcomes (West et al., 2014).

2.4.3. Ventilatory Equivalents for Carbon Dioxide

The ventilatory equivalents for carbon dioxide production ($\dot{V}_E/ \dot{V}CO_2$) at the AT has also been used as a predictor of post-operative outcomes. In healthy individuals, $\dot{V}_E$ increases linearly with increasing work rate. As an individual inhales air into their lungs, only some of the tidal volume actually reaches the alveoli. The remaining air that is not included within the gas exchange is known as the dead space volume (VD) (Balady, Arena, Sietsema, Myers, Coke et al., 2010). During exercise, dilation of the respiratory passages

causes the VD to increase, but due to an increase in tidal volume, adequate gas exchange can be maintained. This can be referred to as normal ventilation-perfusion matching (Balady et al., 2010). During exercise, the $\dot{V}_E/\dot{V}CO_2$ ratio decreases as work rate increases. When AT is reached there is an increase in the $\dot{V}_E$ for $\dot{V}O_2$ ($\dot{V}_E/\dot{V}O_2$) ratio and a levelling of $\dot{V}_E/\dot{V}CO_2$, this point is used as a confirmatory point when determining AT (Burnside & Snowden 2014). Larger values for $\dot{V}_E/\dot{V}CO_2$ (> 34) are suggestive of a large dead space and a ventilation-perfusion mismatch, and are particularly linked with conditions such as cardiac failure or respiratory disease (Burnside & Snowden 2014). For example, in pulmonary disease, there is a higher dead space as there are fewer healthy tissues in the lungs where gas exchange can take place, which ultimately limits exercise capacity (Balady et al., 2010). Carlisle and Swart (2007) demonstrated that patients who had a $\dot{V}_E/\dot{V}CO_2 < 43$ were found to have improved 30 day and mid-term survival post-operatively, following elective AAA repair, compared to those with a higher $\dot{V}_E/\dot{V}CO_2$. A few years later it was then concluded by Wilson et al., (Wilson, Davies, Yates, Redman & Stone 2010) that a $\dot{V}_E/\dot{V}CO_2 > 34$ is associated with an increased risk of hospital mortality following major intra-abdominal non-vascular surgery. A few studies have also used $\dot{V}_E/\dot{V}CO_2$ to help determine cardiac mortality and hospitalization in patients who were diagnosed with heart failure. It has been shown that in those patients with a $\dot{V}_E/\dot{V}CO_2$ of ≥ 34 higher rates of mortality and hospitalization were seen compared to those with a $\dot{V}_E/\dot{V}CO_2 < 34$ (Arena, Myers, Aslam, Varughese & Peberdy 2004; Nanas, Nanas, Sakellariou, Dimopoulos, Drakos et al., 2006).

2.4.4. Oxygen Uptake Efficiency Slope

The oxygen uptake efficiency slope (OUES) was first recognised by Baba and colleagues (1996) who revealed that it could provide an objective estimation of cardiorespiratory function, related to pulmonary dead space and metabolic acidosis. The OUES is derived from the logarithmic relationship between $\dot{V}O_2$ and $\dot{V}_E$ during incremental exercise, and theoretically represents how effectively the oxygen is extracted by the lungs and then taken into the body (Akkerman, van Brussel, Hulzebos, Vanhees, Helders et al., 2010; Baba, Nagashima, Goto, Nagano, Yokota et al., 1996; Van Laethem, Bartunek, Goethals, Nellens, Andries et al., 2005). A correlation between $\dot{V}O_{2peak}$ and OUES has also been shown in previous research, with OUES being shown to not be greatly affected by whether or not the CPET was maximal or not (Baba et al., 1996). This was evidenced by there being no differences in OUES from the first 90% of the exercise data compared to 100% of the data. This suggests that OUES can be determined from submaximal exercise, although OUES was slightly lower from the data accumulated from the first 75% of the test (Baba et al., 1996). Kasikcioglu Toker, Tanju, Arzuman, Kayserilioglu et al., (2009) evaluated the ability of the OUES to predict postoperative cardiorespiratory morbidity in patients following lung resection. The authors discovered that patients who had postoperative complications possessed an OUES that was significantly lower (11.1 ± 1.2) than those who had no postoperative complications (13.3 ± 2.1). Furthermore, Davies Wensel, Georgiadou, Cicoira, Coats et al., (2006) also demonstrated strong prognostic value of the OUES in patients with chronic heart failure. Specifically, the OUES was significantly lower in patients with left ventricular (LV) dysfunction, compared to those patients with normal LV function (Van Laethem et al., 2005). Arena, Myers, Hsu, Peberdy, Pinkstaff et al., (2007) also provide support for the use of OUES as a predictor of mortality in patients with heart failure. Study results demonstrated that patients with a lower OUES had a significantly higher incidence of major cardiac events within a 3 year

period following surgery. Interestingly, even though the OUES was a strong predictor of morbidity, the $\dot{V}_{E/}\dot{V}CO2$ slope was shown to have better prognostic value (Arena et al., 2007).

2.4.5. Oxygen Pulse

The oxygen pulse is a measure of the amount of oxygen consumed per heart beat ($\dot{V}O_2$/HR), and provides an indication of SV and a-vO_2 diff (Vassaux, Torre-Bouscoulet, Zeineldine, Cortopassi, Paz-Díaz et al., 2008). Oxygen pulse is suggested be more dependent of cardiac function as it incorporates HR response which is not reflected in other measures such as $\dot{V}O_{2peak}$ (Lavie, Milani & Mehra 2004). During incremental exercise oxygen pulse increases due to linear rises in $\dot{V}O_2$ and HR, and eventually plateaus during maximal exercise. Patients with conditions such as chronic obstructive pulmonary disease (COPD) and chronic heart failure demonstrate a flattened oxygen pulse response (Burnside & Snowden 2014). This flattened response is a result of a reduced stroke volume and/or an inability to adequately increase oxygen extraction (American Thoracic Society & American College of Chest Physicians 2003). The oxygen pulse response to exercise has therefore been shown to be a strong indicator of exercise induced myocardial ischaemia (Belardinelli, Lacalaprice, Carle, Minnucci, Cianci et al., 2003). Very few studies have identified the prognostic value of oxygen pulse regardless of its strong diagnosis of cardiac function. One previously published study found that peak oxygen pulse has the capability to risk stratify patients, but suggests that peak oxygen pulse should be recorded for those patients who are unable to reach a peak respiratory exchange ratio (RER) of > 1.0 (Ingle, Witte, Cleland & Clark 2008). However,

other research has shown oxygen pulse to have no significant prognostic value (Cohen-Solal, Barnier, Pessione, Seknadji, Logeart et al., 1997).

2.4.6. Pulmonary Function Testing

Resting pulmonary function testing (spirometry) is a standard procedure done prior to a CPET, this is because it provides an assessment of a patient's lung mechanics and whether or not they are likely to be limited during exercise (Balady et al., 2010). This test is typically performed to determine two key values, forced vital capacity (FVC), which is the total volume of air exhaled during a maximally forced expiration, and the other is the forced expiratory volume in 1 second (FEV_1), which is the volume delivered in the first second of the FVC (Miller, Hankinson, Brusasco, Burgos, Casaburi et al., 2005). Testing for resting lung function can help determine if a patient has a respiratory disorder and particularly if it is obstructive and/or restrictive dysfunction (Pellegrino, Viegi, Brusasco, Crapo, Burgos et al., 2005). Lung function values expressed as a percentage of the predicted values have been shown to predict postoperative outcome in patients undergoing lung cancer surgery (Win, Jackson, Sharples, Groves, Wells et al., 2005). From the resting spirometry, maximum voluntary ventilation (MVV) can be indirectly calculated ($MVV = FEV_1 \times 40$) (Balady et al., 2010). The MVV represents respiratory muscle strength (Datta & Lahiri 2003) and can be used during CPET to help determine a patient's exercise breathing reserve, this can be identified by assessing how closely $\dot{V}_E$ is in relation to MVV by the end of exercise (maximum $\dot{V}_E$/MVV) (Balady et al., 2010). If $\dot{V}_E$ exceeds $\geq$ 85% of MVV and the patient is evidently not trained, then confirmation of an obstructive or even a restrictive lung disease can be assumed (Palange, Ward, Carlsen, Casaburi, Gallagher et al., 2007).

2.4.7. Oxygen Saturation

Oxygen saturation (PaO_2) is a parameter that is often continuously monitored throughout a CPET. Observation of desaturation during the test has been linked with an increased risk of postoperative complications (Beckles, Spiro, Colice & Rudd 2003; Markos, Mullan, Hillman, Musk, Antico et al., 1989). Ribas Diaz, Barbera, Mateu, Canalis et al., (1998) discovered that those patients who did not survive after lung resection surgery, had a greater decrease in PaO_2 during exercise when compared to those who survived the procedure. Ninan et al., (1997) also concluded that exercise oximetry was highly predictive of risk for lung resection surgery. Those patients with a resting PaO_2 of less than 90%, or those who demonstrated desaturation greater or equal to 4% during exercise, had a heightened risks of morbidity and prolonged ICU (Ninan, Sommers, Landreneau, Weyant, Tobias et al., 1997). However, as with oxygen pulse, there is limited literature concerning the predictive nature of PaO_2 from CPET.

2.4.8. Electrocardiogram

The use of an ECG is standard practice in clinical CPET, primarily to ensure patient safety. Due to exercise causing an increase in HR and a reduction in diastolic time, the time for coronary perfusion is reduced, therefore coronary artery disease is more likely to be identified during exercise, when HR is elevated (Wasserman, Hansen, Sue, Stringer & Whipp 2005b). Conditions like stress induced myocardial ischemia can also be confirmed on the basis of ST segment changes (depression/elevation), angina, ventricular arrhythmias, and a drop in systolic blood pressure whilst a continued increase in exercise

intensity (Belardinelli, Lacalaprice, Carle, Minnucci, Cianci et al., 2003). Myocardial ischemia is attributed to an inadequate oxygen supply to the myocardium and the inability to support the increased cardiac work (Wasserman et al., 2005b). Previous literature has used the presence of myocardial ischemia during CPET, combined with AT, to help triage patients post-operative location in the attempt to minimise risk of complications (Older, Smith, Courtney & Hone 1993). Therefore it is essential to monitor ECG during exercise in order to determine any cardiac limitation and also to ensure the patient is safe.

2.4.9. Blood Pressure

Blood Pressure is dependent on $\dot{Q}$ and peripheral resistance (Chaitman et al., 2007) and monitoring blood pressure response during exercise is seen as important for assessing cardiovascular function (Robinson, Sue, Huszczuk, Weiler-Ravell & Hansen 1988). During incremental exercise, systolic blood pressure will increase progressively whilst diastolic blood pressure remains fairly constant, although a slight decline may occur in the diastolic blood pressure if the heart function continues to keep up with the increases in $\dot{Q}$. An abnormal blood pressure responses can include an excessive rise, or a fall. An excessive rise in blood pressure is commonly seen in patient with resting hypertension, but an abnormal rise with exercise, when resting blood pressure is normal, may be suggestive of abnormal blood pressure control (American Thoracic Society & American College of Chest Physicians 2003). A reduction in blood pressure during exercise is a sign of an inability of $\dot{Q}$ to compensate for the exercise-induced systemic vasodilation (Albouaini, Egred, Alahmar & Wright 2007) which could be suggestive of a cardiac limitation or abnormality in blood pressure control. The exercise test should be immediately stopped if blood pressure falls whilst exercise intensity increases, this

response could indicate heart failure, ischemia, aortic stenosis, pulmonary vascular disease, or venous obstruction (American Thoracic Society & American College of Chest Physicians 2003). During CPET it is noted that the test should be stopped if there is a fall in systolic blood pressure > 20 millilitres of mercury (mmHg) or if blood pressure is > 250 mmHg for systolic and > 120 mmHg for diastolic (Albouaini, Egred, Alahmar & Wright 2007).

2.4.10. Recovery Heart Rate

The rise in HR during CPET is said to be a result of vagal withdrawal and sympathetic activation, therefore it is suggested that the fall in HR seen after exercise is a result of vagal reactivation (Cole, Blackstone, Pashkow, Snader & Lauer 1999; Imai, Sato, Hori, Kusuoka, Ozaki et al., 1994). This rapid recovery in HR is deemed important so that excessive cardiac work is avoided after exercise (Imai et al., 1994). Patients with cardiovascular disease have been shown to have a decreased vagal activity (Imai et al., 1994). With this information recovery HR after graded exercise has previously been shown to be a strong predictor of mortality (Cole et al., 1999), although it is not highly documented as a fundamental measure in CPET. Further research is required to determine if recovery HR is predictive of post-operative mortality and morbidity like other CPET variables ($\dot{V}O_{2peak}$, AT, $\dot{V}_E/\dot{V}CO_2$ at AT) have been shown to do (West et al., 2014).

To summarise, it is clear from the above section that there is an extensive amount of evidence supporting the association of key CPET derived variables on postoperative outcome, in a range of major elective surgeries. It seems that majority of the research is

primarily focused around the predictability of $\dot{V}O_{2peak}$ and AT, although there is increasing research supporting other CPET derived variables ($\dot{V}_E/\dot{V}CO_2$ at AT).

2.5. The use of CPET for patient optimisation strategies

Using CPET as part of the preoperative assessment has the scope to determine those patients with a low cardiorespiratory reserve who can then be provided with right interventions in the attempt to improve their risk and reduce their hospital LOS. One preoperative optimisation strategy which has recently been considered to improve a patient's postoperative outcome is preoperative exercise training (Jones, Peddle, Eves, Haykowsky, Courneya et al., 2007), although there is very limited research to support this notion. Changes in various lifestyle factors such as alcohol consumption (Tonnesen & Kehlet 1999), smoking (Bluman, Mosca, Newman & Simon 1998) and dietary factors (Bozzetti, Gianotti, Braga, Di Carlo & Mariani 2007) have all been linked with increasing post-operative complications. As a consequence preoperative lifestyle modifications have been suggested to reduce patient risk and improve surgical outcome (Kehlet & Wilmore 2002). Research studies have also shown that the use of blood transfusions in anaemic adults leads to significantly higher exercise capacity including an increase in AT, $\dot{V}O_{2peak}$, peak power output (PO), OUES and a lower $\dot{V}_E/\dot{V}CO_2$ at AT (Wright, Pearce, Snowdon, Anderson & Wallis 2014), which should therefore improve their risk going into elective surgery. Perioperative beta-blocker treatment has also been associated with a reduced risk of in-hospital mortality (Lindenauer, Pekow, Wang, Mamidi, Gutierrez et al., 2005) and 30-day mortality (Wijeysundera, Beattie, Wijeysundera, Yun, Austin et al., 2014) in high risk patients undergoing major non-cardiac surgery. Again there is still limited research

to support these ideas, but if CPET can be used to initially identify those patients at an increased risk for elective surgery, then strategies can be implemented with the right patients in the attempt to optimise them preoperatively, and thus reducing the risk of postoperative morbidity and mortality.

Obtaining a valid and reliable representation of a patient's cardiopulmonary fitness and their associated level of preoperative risk has been shown to provide better allocation of post-operative destination and care (Khan, Amoroso & Gulati 2013). Older and colleagues (1999) were the first group to use the information from CPET (AT and evidence of myocardial ischemia) to aid their decision making on post-operative triage (ICU, high dependency unit (HDU), or ward). Moreover, Prentis Trenell, Vasdev, French, Dines et al., (2013) also used AT to triage their patients to a level of post-operative care, demonstrating that AT strongly correlated with postoperative outcome and LOS. Allocating patients to the most appropriate level of care post-surgery has potential to reduce the number of patients deteriorating postoperatively in the ward (Hoyland, Vasdev, Adshead & Thorpe 2014). These patients commonly end up needing to be admitted to ICU, which could have been prevented if the right level of care was provided immediately after surgery (Bhagwat & Paramesh 2010). Appropriate triage and post-operative care also has the potential to reduce costs by ensuring patients admitted to ICU postoperatively are only those who truly need this level of care (Bhagwat & Paramesh 2010; Hoyland et al., 2014).

2.6. CPET Protocols

Since the work of A.V. Hill, various CPET protocols have been designed for determining and predicting $\dot{V}O_{2peak}$ (Takken, Blank, Hulzebos, Brussel, Groen et al., 2009). It was initially common to use discontinuous protocols (Taylor, Buskirk & Henschel 1955), where exercise stages were performed on consecutive days until a subject had reached their $\dot{V}O_2$ plateau. For obvious reasons, these protocols were very impractical in clinical settings due to the time constraints. Thus more realistic exercise protocols were designed with much shorter times between stages, and now it is common for practitioners to use continuous exercise protocols where stages can vary from a couple of seconds (secs) up to 5 min (Takken et al., 2009).

The Bruce protocol, which was developed in the 1960s, is known to be one of the most popular protocols used when measuring $\dot{V}O_{2peak}$, particularly in the clinical setting. The test involves a change of speed and elevation every three min. In the modified version of the Bruce protocol, the speed stays constant for the first three stages and after this, work rate increase every three min (Takken et al., 2009). However, the large increments in work rate (3 min) is suggested to reduce the accuracy of $\dot{V}O_{2peak}$, mainly due to this type of test creating a nonlinear relation between oxygen uptake and work rate (Fletcher, Balady, Amsterdam, Chaitman, Eckel et al., 2001). This nonlinear increase in oxygen uptake may also make the identification of the AT difficult to interpret (Myers & Bellin 2000). The large increments within the Bruce protocol have also been suggested to cause patients to terminate the test earlier than expected due to musculoskeletal discomfort and/or the inability to tolerate the large increments, potentially causing an underestimation of a patients “true” maximal exercise capacity (Fletcher et al., 2001). Despite the extensive popularity of the Bruce protocol, it has been recognised that there

is a need for more gradual and individualised approaches to testing (Myers & Bellin 2000).

Another common CPET protocol is the ramped Bruce exercise test, which involves work rate to be systematically increased as a function of time until the participant is unable to continue (Poole, Wilkerson & Jones 2008). An advantage of the ramp protocol is that the test can be individualised to the particular patient, this is because the increases in work rate are continuous and constant, and the rate of increase can be adapted to the patient's own capabilities (Myers & Bellin 2000). The test has also been shown to have an improved ability to predict $\dot{V}O_{2peak}$ compared against those protocols that have larger increments in both patient and healthy populations (Myers, Buchanan, Walsh, Kraemer, McAuley et al., 1991), this is a primary result of the constant linear increase in work rate over $\dot{V}O_2$ (Myers, Buchanan, Smith, Neutel, Bowes et al., 1992). The ramped designed exercise test involves a continuous and gradual increase in work rate, which avoids sudden changes in neuromuscular motor unit recruitment or metabolic changes, which is associated with other incremental protocols which involve larger step increments (3-5 min), such as the traditional Bruce protocol (Myers et al., 1991; Takken et al., 2009). Research has demonstrated that ramped like protocols provide an improved haemodynamic and gas exchange response in comparison to protocols with longer exercise stages, therefore it is suggested that identification of the anaerobic threshold is easier to determine in more ramp like protocols, primarily a result of the constant linear increase in $\dot{V}O_2$ (Myers et al., 1991; Takken, 2009). The ramp protocol appears to be a popular method for clinical testing, with many studies using the ramp protocol when testing exercise capacity in patients prior to surgery (Brutsche, Spiliopoulos, Bolliger, Licker, Frey et al., 2000; Brunelli, Belardinelli, Refai, Salati, Socci et al., 2009; Gitt,

Wasserman, Kilkowski, Kleemann, Kilkowski et al., 2002; Older, Hall & Hader 1999, Older, Smith, Courtney & Hone 1993; Walsh, Morice, Putnam, Nesbitt, McMurtrey et al., 1994; Wilson, Davies, Yates, Redman & Stone 2010).

CPET requires maximal effort and provides a direct measure of $\dot{V}O_{2peak}$, although this direct method of assessing functional capacity can be perceived as fairly complex and expensive (Morales et al., 2000). More simple and inexpensive indirect methods have been developed and are commonly used for the assessment of functional capacity. A specific example of an indirect method for assessing function capacity is the 6MWT, this is a submaximal exercise test which measures the distance walked in 6 min and has been shown to modestly correlate with $\dot{V}O_{2peak}$ (Fletcher et al., 2013; Miyamoto et al., 2000). The 6MWT has also been shown to be a predictor of mortality in chronic heart failure patients (Ingle, Cleland & Clark 2014; Ian, Rigby, Carroll, Buttery et al., 2007). An alternative method is the SWT, which involves patients walking back and forth between two cones placed 10 meters apart with walking pace increased by 0.17 m/sec every minute, for a maximum of 12 stages. The patient is required to continue until they can no longer keep with the pace (Wise & Brown 2005). The SWT has been shown to strongly and independently predict $\dot{V}O_{2peak}$ in patients with chronic heart failure (Morales et al., 2000) and COPD (Singh, Morgan, Hardman, Rowe & Bardley 1994). Out of these two methods, the SWT has been shown to predict outcome better than the 6MWT in patients with moderate to severe chronic heart failure (Morales et al., 2000). Even though there are clear benefits associated with these types of methods (simple, safe, inexpensive etc.), these do not provide a direct assessment of exercise capacity and are therefore less reliable than CPET. In addition, other important CPET derived variables such as AT, $\dot{V}_E/\dot{V}CO_2$ and oxygen pulse are also unable to be obtained from these indirect methods.

2.7. Problems Associated with Current CPET Protocols

Most current CPET protocols involves a maximal incremental exercise test to exhaustion, whereby the intensity (usually treadmill speed/incline or cycling PO) increases by a set amount, at set given periods of time during the test (e.g every minute), until volitional exhaustion is reached (Albouaini et al., 2007). Even though this type of CPET is widely used in the fields of clinical exercise testing, and more widely in exercise physiology, a number of concerns have been raised in regard to the general nature of the protocol (Noakes 2008). Firstly, there is no clear test endpoint, and therefore the participant is unaware of the expected exercise duration (Noakes 2008). Knowledge of the exercise duration is known to optimise exercise performance as the subject can accurately regulate their work rate (Mauger, Jones & Williams 2009). Secondly, the fixed progressive intensity of the protocol does not replicate normal exercise behaviour, which questions the validity of the test (Mauger & Sculthorpe 2012). Thirdly, the only part of the test the patient has control over is when they stop exercising, which adds a more subjective component to the test. Many patients may terminate the test earlier than expected as a result of various psychological factors (e.g. low motivation, low self-efficacy etc.) (Noakes 2008), potentially resulting in a submaximal effort. Fourthly, the recommended duration of an MIE is 8-12 min in order to achieve peak $\dot{V}O_2$ values (Buchfuhrer et al., 1983). The experimenter must therefore estimate the most appropriate starting intensity, and work rate increments, in order to achieve volitional exhaustion within the 8-12 min time period. Appropriately setting the work rate therefore requires a good level of experience of CPET, and prior knowledge of the patient. Incorrect estimation of starting

intensity and work rate increment can result in a test which lasts too long, or is too short, thus limiting the validity of the test.

It has been demonstrated that enforced paced exercise causes a significantly greater physiological and thermoregulatory challenge to homeostasis when compared to self-paced exercise, despite there being no difference in performance (Lander, Butterly & Edwards 2009). Lander et al., (2009) found reductions in blood lactate, core temperature and integrated electromyography in the self-paced compared to the enforced paced exercise. They concluded that these different responses, between the self-paced and fixed paced exercise, are most likely a result of the self-pace exercise enabling individual's to self-manage their effort in response to subconscious physiological feedback in order to protect homeostasis. It is suggested that physiological variables (i.e. blood lactate, core temperature, arterial saturation, ventilatory rates and HR) are used as peripheral afferent signallers to the brain to regulate exercise intensity (Tucker 2009), therefore having the ability to make slight adjustments in PO is suggested to be an important regulatory process in order to prevent a catastrophic system failure occurring (Lambert, St Clair Gibson & Noakes 2005; Lander, Butterly & Edwards 2009). During sCPET protocols, the test is driven by progressive increases in work rate requirements which is dictated by the treadmill or cycle ergometer. No alterations in intensity can be made by the individual, therefore the increasing afferent signallers can only be attenuated by volitional exhaustion (Mauger & Sculthorpe 2012), with this the participant only has two options, continue to match the increasing exercise requirements, or to stop. Unless the individual has high levels of motivation, which may be lacking particularly in patient populations, they are likely to choose to stop which may lead to early termination of the test and an underestimation of their $\dot{V}O_{2peak}$.

It is proposed that exercise intensity is regulated through the conscious perception of effort to protect the athlete and to ensure that optimal performance is achieved (Tucker 2009). This exercise performance model is termed the anticipatory feedback model, as it utilises physiological and psychological inputs prior to exercise to establish initial pace (Noakes 2011), and regulate pacing strategy during (Tucker 2009). The model allows exercise intensity to be pre-set before exercise actually begins which is based on previous experience (Mauger, Jones & Williams 2010). Pre-setting exercise intensity is beneficial to ensure that initial high work rates are avoided to prevent premature fatigue (Tucker 2009). Other factors that are likely to influence the pre-set pace usually consist of the subject's physiological state at the start of exercise, the expected exercise duration, and the individuals level of motivation (Noakes 2011). The model also allows the regulation of pacing strategy during exercise, which as previously mentioned, is achieved via continuous subconscious physiological feedback from afferent signals that in turn allow exercise behaviour to be continuously regulated and protect the body from a catastrophic physiological failure (Noakes 2011). Although, pre-setting exercise intensity and self-regulation during exercise is not possible in the sCPET protocols due to the predetermined work rates and fixed intensities, which could lead to a premature termination of the test in order to protect homeostasis from the continuous increase in the afferent signallers.

As previously mentioned, knowledge of exercise duration has been proven to facilitate exercising performance in trained populations (Baden, McLean, Tucker, Noakes & St Clair Gibson 2005; Eston, Stansfield, Westoby & Parfitt 2012; Mauger, Jones & Williams 2009), although this has not shown to be the case in a group of healthy, untrained

individuals (Williams, Bailey & Mauger 2012). Williams et al., (2012) demonstrated that untrained populations were able to complete a 4 km time trial (TT) in similar times, regardless of whether distance knowledge, distance feedback or prior experience is provided. These findings challenge the notion that anticipatory feedback is crucial for a successful pacing strategy to be adopted. Williams et al., (2012) also concluded that this result demonstrated that participants relied more on afferent feedback when pacing the 4 km TT, rather than the distance information they received. This suggests that untrained individuals do not rely on these pieces of information in order to successfully complete an exercise test, this is likely a result of the unfamiliarity of such tasks, which questions whether the same would apply in a more clinical populations. It must also be acknowledged that factors such as prior experience would not be applicable in clinical populations as many patients tend to be inactive who live sedentary lifestyles, and therefore would lack in previous exercise experience.

The ability to tolerate exercise induced pain or discomfort is recognised as a critical influence of a successful performance (Anshel & Russell, 1994). During exercise the development of peripheral fatigue is monitored by the central nervous system (CNS) via sensory feedback from the locomotor muscles (Amann et al., 2009). This feedback adjusts central motor drive (CMD) to limit the level of peripheral fatigue development, and consequently avoid intolerable levels of effort/pain, and excessive muscle dysfunction (Amann et al., 2009). If these neuromuscular signals are consciously interpreted as pain or discomfort, then those individuals with a higher pain tolerance may be more capable to push their selves further compared to those with a lower pain tolerance (Mauger et al., 2010). Based on this, patient populations who are unaccustomed to the feelings associated with maximal exercise may interpret higher levels of discomfort or pain mainly due to

the unfamiliarity of the task (Mitros, Gabriel, Ainsworth, Lee, Herrmann et al., 2011). As the sCPET protocol involves gradual increases of an enforced pace, individuals are unable to adjust their effort to attenuate any muscle pain or discomfort that they might be experiencing. Thus, as pain tolerance is suggested to be an important determinant of successful performance (Anshel & Russell, 1994), termination of the exercise test could be a result of the individual's pain intolerance rather than their actual cardiorespiratory limit. Consequently, if self-regulating pace can reduce these premature responses and control an individual's discomfort during the test, it could be plausible that a higher and more representative $\dot{V}O_{2peak}$ is attainable in a self-paced based protocol.

2.8. Self-paced $\dot{V}O_{2peak}$ protocol (SPV)

Mauger and Sculthorpe (2012) recently developed a novel maximal incremental exercise test design to assess $\dot{V}O_{2peak.}$ The novel protocol allows subjects to self-pace their work rate according to a given end point, whilst maintaining the usual incremental format used in sCPET. In their study, Mauger and Sculthorpe (2012), recruited sixteen untrained subjects who were required to complete two tests, one being the proposed self-paced $\dot{V}O_{2peak}$ (SPV) protocol and the other being the traditional $\dot{V}O_{2peak}$ test. The SPV design consisted of 5 × 2 minute stages equalling a total test time of 10 min, whereby each stage was fixed to a level on the RPE scale (11, 13, 15, 17 & 20). Participants were able to continuously self-manage their work rate according to the specific RPE for each stage. The traditional $\dot{V}O_{2peak}$ test compromised of the standard incremental design, where subjects started at a PO of 60 watts (W), which was increased by 30 W every two min, until the subject reached volitional exhaustion, or the cadence dropped below 60 rate per minute (rpm). Results from Mauger and Sculthorpe (2012) demonstrated a significant

difference in $\dot{V}O_{2peak}$, with participants achieving an 8% higher $\dot{V}O_{2peak}$ in the SPV when compared to the traditional test. A significant difference was also observed in PO between the tests, with participants achieving a higher peak PO in the SPV (273 ± 58 W) than in the traditional test (238 ± 55 W). Similar observations have been demonstrated in more recent studies in both cycling (Astorino, McMillan, Edmunds & Sanchez 2015) and treadmill running (Faulkner, Mauger, Woolley & Lambrick 2015; Hogg, Hopker & Mauger 2014; Mauger, Metcalfe, Taylor & Castle 2013), although not all studies have found the SPV to produce a significantly higher $\dot{V}O_{2peak}$ values (Chidnok, DiMenna, Bailey, Burnley, Wilkerson et al., 2013; Straub, Midgley, Zarvorsky & Hillman 2014). Table 2.1 presents studies which have used the SPV protocol. All studies to date have shown at least similar $\dot{V}O_{2peak}$ values achieved in the SPV when compared against a traditional protocol.

Table 2.1 Summary of studies that have used RPE-clamped maximal exercise test protocols for the determination of $\dot{V}O_{2peak}$. The studies are organised in descending order of publication date. $\dot{V}O_{2peak}$ data is displayed at mean ± SD.

Study	Subjects	Mode	Protocol	$\dot{V}O_{2peak}$
Hanson et al., 2016	Thirteen recreationally active males and females	Cycle ergometer & Treadmill	Cycling SPV. RPE clamped, 5 × 2-min	48 ± 8 mL·kg^{-1}·min^{-1}*
			Treadmill SPV. RPE clamped, 5 × 2-min	56 ± 5 mL·kg^{-1}·min^{-1}
			Standard Bruce protocol	56 ± 7 mL·kg^{-1}·min^{-1}
Astorino et al., 2015	Thirty recreationally active males and females	Cycle ergometer	SPV. RPE clamped, 5 × 2-min stages	50 ± 10 mL·kg^{-1}·min^{-1}*
			RAMP 1. Start 50-80 W, increased 25-40 W min^{-1}	47 ± 10 mL·kg^{-1}·min^{-1}
			RAMP 2. Start 50-80 W, increased 25-40 W min^{-1}	46 ± 10 mL·kg^{-1}·min^{-1}
Faulkner et al., 2015	Thirteen recreationally active males	Treadmill	SPV. RPE clamped, 5 × 2-min stages	64 ± 3 mL·kg^{-1}·min^{-1}*
			GXT. Speed increased 1 km·h^{-1} every 2 min	61 ± 5 mL·kg^{-1}·min^{-1}
Hogg et al., 2014	Fourteen trained male distance runners	Treadmill	SPV incline-based. RPE clamped, 5 × 2-min stages	71 ± 4 mL·kg^{-1}·min^{-1}*
			SPV speed-based. RPE clamped, 5 × 2-min stages	68 ± 4 mL·kg^{-1}·min^{-1}
			GXT. Speed increased 1 km·h^{-1} every 2 min	69 ± 6 mL·kg^{-1}·min^{-1}
Straub et al., (2014)	Twelve male and four female trained cyclists	Cycle ergometer	SPV. RPE clamped, 5 × 2-min stages	3.87 ± 0.72 L·min^{-1}
			Ramp. Start at 80 W, increased by 30 W min^{-1} for men and 20 W min^{-1} for women. Repeated twice	3.86 ± 0.73 L·min^{-1}
Mauger et al., (2013)	Fourteen trained male runners	Treadmill	SPV. RPE clamped, 5 × 2-min stages	64 ± 8 mL·kg^{-1}·min^{-1}*
			GXT. Speed increased by 1 km·h^{-1} every 2 min	61 ± 7 mL·kg^{-1}·min^{-1}
Chidnock et al., (2013)	Seven recreationally active males	Cycle ergometer	SPV. RPE clamped, 5 × 2-min stages	4.33 ± 0.60 L·min^{-1}
			RAMP 1. 3 min unloaded, 30 W min^{-1}	4.31 ± 0.62 L·min^{-1}
			RAMP 2. 3 min unloaded, 30 W min^{-1}	4.36 ± 0.59 L·min^{-1}
Mauger and Sculthorpe (2012)	Sixteen untrained, healthy males and females	Cycle ergometer	SPV. RPE clamped, 5 × 2-min stages	40 ± 10 mL·kg^{-1}·min^{-1}*
			GXT. Started at 60 W, 30W increase every 2 min.	37 ± 8 mL·kg^{-1}·min^{-1}

* significantly different ($P < 0.05$).

It has been acknowledged, by Mauger and Sculthorpe (2012), that in their first study on the SPV protocol the mean test duration (13 ± 3 min) for the traditional test was longer than the self-paced test, and that recommended for achieving optimal $\dot{V}O_{2peak}$ values (8-12 min) (Buchfuhrer et al., 1983). Test durations have been demonstrated to be of great importance in achieving $\dot{V}O_{2peak}$, suggesting that too long or too short tests may result in the subject reaching their limit of exercise tolerance or experiencing peripheral fatigue before maximum $\dot{V}O_2$ values are reached (Midgley, Bentley, Luttikholt, McNaughton & Millet 2008). Therefore, it is possible that the higher $\dot{V}O_2$ values achieved in the self-paced test in the study by Mauger and Sculthorpe (2012) was due to the standard incremental test lasting too long, and as a result participants being unable to achieve 'optimum' values in the test. Although, there was no significant difference between test duration in the later study (Mauger et al., 2013) where significantly higher values where achieved in the SPV. The differences in test time highlights one of the suggested drawbacks associated with sCPET protocols. Unless repeated tests are able to be completed, which is unlikely in a clinical setting, then an "optimal" test cannot be guaranteed. If an alternative test is available that can increase the likelihood of individuals reaching their peak effort within the recommended time period, it warrants further investigation.

The recommended test duration of 8-12 min originated from an early study by Buchfuhrer et al., (1983). In this study five healthy males each performed five treadmill and three cycle ergometer incremental exercise tests, each test had different test durations, with the mean times ranging from 5.8 - 26.4 min. It is not denied that the work from Buchfuhrer

et al. (1983) had a great influence on today's knowledge and practice of maximal exercise testing, although when under scrutiny a number of flaws can be identified, which limit the dependability of the conclusions drawn out from their study. The first being the very small sample size, which therefore causes the results to be underpowered. Secondly, $\dot{V}O_{2peak}$ was only significantly lower in the shortest test times (7 min for treadmill; 5.8 min for cycling) which raises questions as to why the authors suggest the upper boundary of 12 min. Although, Buchfuhrer et al., (1983) did conclude that tests lasting more than 12 min do not provide any additional information which is the main reason they used this as the upper cut off limit for test duration. Finally, all participants were healthy males, so there is no evidence to prove that the same results would be representative in various other populations. Aside from these limitations a few recent studies have supported the findings from Buchfuhrer's (1983) early study. For example, one study required 12 male cyclists/triathletes to each complete a slow, medium and fast ramp cycling protocol (Weston, Gray, Schneider & Gass 2002). The three mean test durations were 7.2, 11.1 and 27.9 min. The results demonstrated that there were no differences in $\dot{V}O_{2peak}$ between 7.2 and 11.1 min, but the mean $\dot{V}O_{2peak}$ value achieved in a test lasting 27.9 min was significantly lower (Weston et al., 2002). Whereas, some studies have disputed the findings from Buchfuhrer's (1983) early work, finding no differences in $\dot{V}O_{2peak}$ between various test durations ranging from 9.1 to 25.9 min (Bentley & McNaughton 2003; Bishop, Jenkins & Mackinnon 1998).

It is clear that there is limited and mixed evidence to support the optimal test duration for CPET. Nevertheless, regardless of the limitations mentioned above, it seems that the original work by Buchfuhrer (1983) has become the accepted reference for test duration. In this regard, it seems irrational to rely on one single study, conducted on a small sample

size, to guide current practice. In a recent review article, Midgley et al., (2008) concluded that to obtain a 'true' $\dot{V}O_{2max}$ in healthy individuals, a cycling protocol should last between 7 and 26 min, and treadmill tests should last between 5-26 min, but the authors acknowledge that further research is required. Indeed, it is likely that optimal test time will vary dependant on populations; for example, shorter incremental test times may be more suitable for trained individuals due to their accelerated $\dot{V}O_2$ kinetics compared to untrained individuals (Caputo, Mello & Denadai 2003). Conversely, shorter protocols may not be suitable for patient populations with impaired cardiorespiratory function (Midgley et al., 2008). Indeed, Agostoni, Bianchi, Moraschi, Palermo et al. (2005) report that when HF patients completed a CPET in 5 min, they achieved a significantly lower $\dot{V}O_{2peak}$ compared to when the test was completed in 10 and 15 min. They suggested that hard work rates early on in exercise forces the patient to stop exercising because of limited O_2 transport, and consequently, early muscle fatigue. It appears that even though there is still limited evidence, optimal CPET time may vary from person to person, although it does seem that there is at least a minimum test time requirement of 5 minutes.

There are conflicting findings from previous studies investigating differences in $\dot{V}O_{2peak}$ between SPV and sCPET protocols (Astorino et al., 2015; Faulkner et al., 2015; Hogg et al., 2014; Mauger & Sculthorpe 2012; Mauger et al., 2013; Chidnok et al., 2013; Hansen et al., 2016; Hogg et al. 2014; Straub et al., 2014). A possible reason for these conflicting findings are due to methodological differences in the SPV protocol used. For example, research by Chidnok and colleagues (2013) does not support the original findings of Mauger and Sculthorpe (2012) that a self-paced exercise test results in a higher $\dot{V}O_{2peak}$ than a sCPET protocol. However, key differences between the protocols and instructions provided to participants about the final maximal stage of the test are likely to explain the

discrepancy in the findings. Specifically, Chidnok et al., (2013) asked participants to interpret RPE 20 as the highest work rate that they could sustain for the duration of the final stage, whereas Mauger and Sculthorpe (2012) asked individuals to rate their maximal effort on a moment to moment basis. The subtle differences in test protocol instructions are borne out by PO profiles from the two studies. In Chidnok's study participants maintained a fairly even PO during the final stage of the test, dropping by less than 20W in the entire 2 min stage (Chidnok et al., 2013). By contrast, Mauger and Sculthorpe (2012) demonstrated a drop in PO of more than 70 W in the final stage, indicating that their participants used an all-out pacing strategy, rather than an a more evenly paced effort as evident in Chidnok's study. Therefore, it is possible that the lack of difference between SPV and sCPET protocols in Chidnok's study is likely due to the participants not exerting themselves to an RPE 20 on a moment to moment basis. Similar reasoning could also be used to explain a lack of differences between SPV and traditional protocols in the studies of Straub et al. (2014) and Hansen et al. (2016), although this cannot be confirmed as they did not provide the PO profile for the final stage in their manuscripts, or state how they described the final stage to their participants.

Mauger et al., (2013) propose that the all-out effort produced at the start of the final RPE 20 stage, with a subsequent drop off in PO, could be the reason for the higher $\dot{V}O_{2peak}$ attainment in the SPV compared to a traditional ramp or step protocol. Specifically, Mauger et al. (2013) state that the large increase in PO at the start of the stage significantly increases the oxygen demand of the working muscles, with the subsequent reduction in PO creating the optimal physiological conditions to meet this demand. This theory can be supported by recent findings demonstrating that during a high intensity work bout where

VO2peak is obtained, a subsequent reduction in work rate can still capable of maintaining $\dot{V}O_2$ at the $\dot{V}O_{2peak}$ (Billat, Petot, Karp, Sarre, Morton et al., 2013).

Interestingly, Straub et al., (2014) identified a significantly higher $\dot{V}O_{2peak}$ in their participant's preferred test protocol, being either the SPV or traditional test, with there being a 4% higher $\dot{V}O_{2peak}$ being achieved in comparison to their non-preferred test. Although, the authors acknowledge that this difference may be due the participants stating their preferred test as the one that they perceived they did better in, or the test they felt less mentally or physically fatigued on the day of the test. They also recognised that the 4% higher $\dot{V}O_{2peak}$ may not actually be physiologically meaningful, as this 4% increase in $\dot{V}O_{2peak}$ (140 $mL \cdot min^{-1}$) was less than the smallest measureable difference of 180 $mL \cdot min^{-1}$ and only slightly higher than the measurement error of 130 $mL \cdot min^{-1}$ for the self-paced protocol. Nonetheless, Straub et al., (2014) concluded that having an alternative option and the choice between protocols may act as advantageous to both the individual being tested and the person conducting the test. These findings were also replicated in the study by Hanson, Scheadler, Lee, Neuenfeldt, Michael et al., (2016) who found that 65% of their participants achieved their highest $\dot{V}O_2$ in their preferred test. Choosing the most appropriate test on an individual basis may help optimize the results (as shown in the study by Straub et al., 2014 and Hanson et al., 2016), it may improve adherence if repeated/follow up tests are needed, and it may also improve the general feelings towards maximal exercise testing (Straub et al., 2014). Although, it must be acknowledged that having a choice between protocols could be problematic for research based testing as this will cause within group differences, failing to make the experimental procedures 'controlled'.

Research has also demonstrated the use of submaximal RPE clamped protocols in the attempt to predict $\dot{V}O_{2peak}$ in cycling (Eston, Lambrick, Sheppard & Parfitt 2008; Eston, Faulker, Mason & Parfitt 2006; Eston, Lamb, Parfitt & King 2005; Faulkner & Eston 2007), running (Eston, Evans, Faulkner, Lambrick, Al-Rahamneh et al., 2012; Evans, Parfitt & Eston 2013; Morris, Lamb, Hayton, Cotterrell & Buckley 2010; Smith, Eston, Norton & Parfitt 2015), and even arm ergometery (Al-Rahamneh & Eston 2011c). The above studies used a protocol similar to Mauger and Sculthorpe (2012), although in these studies stages started at a lower RPE (9) and ended at either 15 or 17 on the scale, with each stage lasting between 2-4 min. Coquart, Tabben, Farooq, Tourny and Eston (2016) completed a meta-analysis on the 10 studies cited above which had looked at the predictive ability of determining $\dot{V}O_{2peak}$ from a submaximal RPE clamped protocol. It was concluded that $\dot{V}O_{2peak}$ can adequately be predicted in various populations (i.e. young, old, active, and sedentary) when using the linear relationship of RPE (9-15) and $\dot{V}O_2$ (Coquart et al., 2016). In addition to the above studies, the ability of submaximal RPE values to predict $\dot{V}O_{2peak}$ in paraplegic and poliomyelitis participants has also been tested (Al-Rahamneh & Eston 2011a; Al-Rahamneh & Eston 2011b; Al-Rahamneh, Faulkner, Byrne & Eston 2011). Results from these studies suggested that for those higher RPE values (15 and 17), there is acceptable predictability of $\dot{V}O_{2peak}$ (Al-Rahamneh & Eston 2011a; Al-Rahamneh & Eston 2011b). Although one study concluded that there is considerable variability in the consistency when predicting $\dot{V}O_{2peak}$ (Al-Rahamneh, Faulkner, Byrne & Eston 2011). Submaximal exercise testing has been suggested to be advantageous particularly as the risk of an adverse event is reduced, also these tests do not require high amounts of motivation (Coquart et al., 2016). It is reassuring to see that this type of exercise testing can also be used in the form of a submaximal protocol,

although there are obvious disadvantages to measuring $\dot{V}O_{2peak}$ indirectly, with direct assessment being considered the most accurate way to determine exercise capacity (Beekley, Brechue, Dehoyos, Garzarella, Werber-Zion et al., 2004). Additionally the submaximal RPE clamped protocol has not been tested on any other clinical population, and it is evident that the physiological responses to exercise can differ depending on disease state (Palange et al., 2007), so it is unclear as to whether you could accurately predict $\dot{V}O_{2peak}$ in other patient populations.

The physiological responses to the SPV and why a higher $\dot{V}O_{2peak}$ is achievable is still unclear. One study investigated the $\dot{Q}$ response to the SPV in comparison to a sCPET protocol, in the attempt to identify the underlining mechanisms (Astorino et al., 2015). Astorino et al., (2015) concluded that the higher $\dot{V}O_{2peak}$ values achieved in the SPV was a result of a greater oxygen delivery available, which is evident from the higher maximal $\dot{Q}$ and HR achieved in the SPV vs. a sCPET. Additionally, a change in oxygen extraction at the working muscles has also been suggested to be the main cause of the increased $\dot{V}O_{2peak}$ seen in the SPV (Mauger et al., 2013). This hypothesis was based on their participants achieving a lower peak HR in the SPV and there being no differences in $\dot{V}_E$ (Mauger et al., 2013). These findings would suggest that oxygen intake and delivery is not in fact enhanced by the SPV, which goes against those findings by Astorino et al., (2015). Although, no study has looked in to the physiological response to the SPV at a muscular level to confirm this, therefore further research is needed to fully understand the physiological mechanisms behind the SPV so we can gain more of an understanding as to why a higher $\dot{V}O_{2peak}$ is achievable in such a test.

In the studies mentioned in this review the primary focus was the validity of determining $\dot{V}O_{2peak}$. There is limited evidence to show that this protocol has the capability to reliably determine other important variables such as AT, which as previously mentioned, has become a vital measure in clinical CPET. The SPV has also only been tested on younger, healthy populations so it is unclear as to whether it can be effectively used in an older and clinical population. Finally, it is unclear if the SPV can be effectively used as a diagnostic and prognostic tool to aid important clinical decisions, like the sCPET protocol has been shown to do (Balady et al., 2010; Palange et al., 2007). Therefore, further research is necessary in order to determine if the SPV can be used to the same effect and extent as a sCPET.

Overall the SPV protocol has, on a number of occasions, been demonstrated to provide higher (Mauger & Sculthorpe 2012, Mauger et al., 2013), or at least similar $\dot{V}O_{2peak}$ values (Chidnok et al., 2013; Straub et al., 2014), when compared to a sCPET protocol, and should be considered as a viable alternative. The nature in which the SPV is conducted could be deemed as advantageous, especially in a clinical setting. Specifically, the SPV may be a more 'patient-friendly' test, primarily as a result of the self-administered work rates with individuals having control over their own exercise intensity. The fixed test duration may also enable patients to provide a true maximal effort during the final stage of the SPV. In this regard, knowing the test will soon come to an end may make any muscular discomfort they are experiencing more tolerable. In addition, the defined test length (10 min) ensures that regardless of ability and fitness, and assuming the test is not symptom limited, all patients will be exercising for the 'loosely' recommended time of 10 min (Buchfuhrer et al., 1983). This prevents the risk of obtaining unreliable data from a test that does not last long enough to elicit optimal peak values (> 5 min; suggested by

Midgley et al., 2008). If an unreliable test data is obtained from a given protocol it represents a waste of valuable clinician time, effort and resources. Moreover, this would be problematic in some surgical pathways with strict time frames (e.g. cancer pathway), as there will not be enough time to repeat the test. In a more practical sense, the defined test length may also help to improve the general running and efficiency of a CPET clinic, because the length of time needed for each patient will be more consistent due to the defined test duration. However, it is clear that further research is necessary to determine if the SPV be used in clinical populations, and whether important physiological values can be reliably determined in order to assess patient fitness and assist with clinical decision making.

2.9. Summary

Overall, the use of CPET in pre-operative assessment is a valuable method for identifying risk in patients going in to elective surgery. Research has demonstrated how the use of CPET is a reliable indicator of risk, which aids in the decision making process of surgery, and planning of appropriate post-operative care (ICU, HDU and ward based care). However, limitations are evident in the traditional incremental CPET protocol, and consequently questions have been asked about its' ability to determine a 'true' reflection of exercise capacity. With this in mind, the self-paced protocol has been developed, and shown to produce higher (Mauger & Sculthorpe 2012; Mauger, Metcalfe, Taylor & Castle 2013), or similar (Chidnok et al., 2013; Straub et al., 2014), $\dot{V}O_{2peak}$ values when compared to a sCPET protocol. The self-paced protocol may indeed provide patients with the feeling of control over their effort, and eliminates the need for practitioners to choose

suitable starting intensities. In this regard, the test will enable patients to provide a true maximal effort, as well as ensure that they exercise for the recommended duration of 10 min. With all of these factors in mind, it is plausible to suggest that the SPV may be a more valid and reliable way for determining exercise capacity in clinical patients, and therefore in preoperative assessment. Any test which can improve the efficacy of CPET should be of interest, as there is now a large body of evidence showing that CPET is valuable in the perioperative care of patients. If the most accurate representation of a patients risk can be provide before surgery, then the right decisions and care can be assured in the attempt to minimise the risk of postoperative morbidity and mortality, and also ensure that the expensive and limited intensive care facilities are used for those patients who truly need it. To date the SPV has only been used with healthy populations, so it is unclear whether it will elicit the same responses in clinical patients but due to the potential benefits of this type of test in clinical CPET, further investigation in warranted.

2.10. Thesis Aims and hypotheses

The overall aim of this thesis was to assess the ability of a novel self-paced CPET to assess cardiopulmonary exercise fitness prior to major elective surgery and its ability to predict postoperative outcomes. Although before this was assessed, a greater understanding of the SPV was required in the attempt to support and build on the current body of literature. Therefore, the following chapters presents a series of studies which contribute to the overall aim of the thesis. The aims and hypotheses of each experimental chapter are as follows:

1. As current literature lacked information on the reliability, the first experimental chapter aimed to assess the general reliability of the SPV in a healthy population (chapter 4).

- Aim: To assess the test re-test reliability of key CPET variables obtained from three repeated SPVs.
- $H1_{0:}$ The SPV will not produce reliable values of the key exercise parameters when compared against previous research using sCPET protocols.
- $H1_{1}$: The SPV will produce reliable values of the key exercise parameters when compared against previous research using sCPET protocols.

2. Due to the lack of research, a greater understanding of the physiological responses associated with the SPV was needed. Additionally, because the test had only previously been used in younger populations it was unclear as to whether or not the SPV could be used to the same effect in an older aged population and whether the physiological responses to the test would differ with age. This is particularly important as the older aged group is more reflective of the type of patients needing to undertake preoperative CPET, and so this provides a safer initial assessment of the use of the SPV before testing in a clinical population.

- Aims: To assess the SPV in a middle aged to older adult healthy population, and to assess the physiological responses between both young and the older to middle aged participants. The older aged group was used to reflect the general age seen in preoperative CPET (chapter 5).
- $H2_{0:}$ The SPV will not be shown to be a valid determinate of exercise capacity in an older healthy population.

- $H2_1$: The SPV will be shown to be a valid determinate of exercise capacity in an older healthy population.
- $H3_0$: The SPV will not demonstrate a higher $\dot{V}O_{2peak}$ in both the young and middle to older aged group when compared against a sCPET.
- $H3_1$: The SPV will demonstrate a higher $\dot{V}O_{2peak}$ in both the young and middle to older aged group when compared against a sCPET.
- $H4_0$: The SPV will not demonstrate an enhanced oxygen delivery and oxygen muscle extraction in both group when compared against a sCPET.
- $H4_1$: The SPV will demonstrate an enhanced oxygen delivery and oxygen muscle extraction in both groups when compared against a sCPET.

3. The SPV had only been tested on healthy and trained groups of individuals, therefore there was a lack in evidence as to whether or not the SPV could effectively be used in a clinical population.

- Aim: To determine both the validity and reliability of the key exercise parameters obtained via the SPV in a 'stable' clinical population (post-MI patients) when compared against a sCPET.
- $H5_0$: The SPV will not be shown to be a valid and reliable determinant of exercise capacity in post-MI patients.
- $H5_1$: The SPV will be shown to be a valid and reliable determinant of exercise capacity in post-MI patients.

4. As previously discussed in the literature review, preoperative CPET is of great importance for assessing surgical risk. Therefore ensuring the test provides the

opportunity for all patients to demonstrate a true reflection of their fitness is essential, and with the SPV overcoming some of the drawbacks associated with sCPET methods, this should be at the very least considered as a means of testing.

- Aim: To determine if the SPV can accurately assess patient's preoperative fitness, and whether important CPET variables obtained from the test can predict postoperative outcomes (LOS, 30-day morbidity and mortality), like previous research has shown the sCPET protocol to do.
- $H6_0$: The SPV protocol will not provide an accurate representation of a patient's cardiovascular fitness, and therefore not be a reliable predictor of post-operative outcome.
- $H6_1$: The SPV protocol will provide an accurate representation of a patient's cardiovascular fitness, and therefore be a reliable predictor of post-operative outcome.

Chapter 3. General methods

3.1. Ethics Approval and Recruitment

All hospital based studies (Chapters 6 & 7 / studies 3 & 4) were approved by the South East Coast, Brighton and Sussex, National Research and Ethics Committee (see Appendix A for ethical approval document). All other studies (Chapters 4 & 5 / studies 1 & 2) were approved by the University of Kent Ethics Committee prior to the recruitment of any participants (see Appendix B & C for ethical approval documents). After being provided with all the necessary information about the experimental procedures, requirements and potential risks, participants provided their written consent. Prior to testing, all participants were required to complete a health questionnaire to ensure they were safe to exercise. For all clinical testing, patients deemed suitable and safe to test were referred by either consultants or nurses following an initial health screening. The absolute and relative contraindications used for the clinical based studies were those defined by Chaitman et al. (2007). All participants were free from cold, coughs etc., during the preceding 2 weeks. Participants were also encouraged not to exercise the day prior to each visits, and they were also asked to refrain from consuming food, caffeine or smoking 2 hours before testing.

3.2. Experimental Procedure

3.2.1. Equipment and calibration methods

Every participant had their stature and weight measured. Throughout the duration of all exercise tests expired gases were measured with the use of an online breath-by-breath

analysis system (Cortex Metalyzer, Cortex, NL). Before each test the gas analyser was fully calibrated in accordance to the manufactures guidelines, using a calibration gas and 3-litre syringe. A two-point gas calibration was completed using a measurement of ambient air and a measurement of standard compressed gas of 17% O_2 and 5% CO_2. The 3-litre syringe (Hans Rudolph Inc. Kansas, USA) was used to calibrate the flow sensor and turbine, which was moved in time with a set flow rate. Heart rate was measured using a Polar Heart Rate Chest Strap T31 (New York, USA). When testing the clinical populations (study 3 & 4), on the first visit, each patient completed a resting lung function test in order to determine their FEV_1 and FVC (MircoLab, CareFusion, Germany). Resting lung function was conducted in accordance to the recommendations (Miller et al., 2005), they were completed in a seated position and repeated at least 3 times. A 12 lead ECG trace (Meta Control 3000), blood pressure and oxygen saturation were all also measured throughout the duration of all tests, this was to ensure the safety of the patient population.

3.2.2. Self-paced $\dot{V}O_{2peak}$ Protocol (all studies)

The test design was replicated from the initial study by Mauger and Sculthorpe (2012) on the self-paced $\dot{V}O_{2peak}$ protocol (SPV). The test was completed on a cycle ergometer Wattbike, UK), the handlebars and saddle height were adjusted for participant comfort. The test consists of 5 × 2 minute stages, to total a test time of 10 min. For each stage the participants were able to continuously vary their PO, but with Borg's RPE 6-20 scale (Borg, 1982) anchored to a fixed level for each stage. Prior to starting the test, all participants were provided with an A4 page description of the RPE scale, this description provided guidance and examples of using RPE scale to regulate work rate (see Appendix

D). Following this, participants were also given a verbal explanation where relative examples were used in the attempt to facilitate their understanding (i.e. “RPE 11 should feel like an intensity that you could maintain for a long period of time with a small amount of effort involved”); this also gave them the opportunity to ask questions if they were still unsure. PO adjustments were facilitated by the participants manually adjusting the cycle ergometer air brake in order to produce a level of resistance that allows them to match the target RPE required for each stage. Stage 1 (0-2 min) of the SPV was fixed at an RPE of 11, stage 2 (2-4 min) fixed to an RPE of 13, stage 3 (4-6 min) fixed at an RPE of 15, stage 4 (6-8 min) fixed to an RPE of 17 and stage 5 (8-10 min) fixed to an RPE of 20. Throughout each stage participants were continually reminded of the required RPE that they needed to be working at for that particular stage, the RPE scale was always in view. Participants were reminded to vary their PO to match the RPE for each given moment, rather than to pace themselves according to the projected end-point of the test. Using this design allows participants to vary their work rate according to the RPE required at each stage, but the progressive RPE clamps allowed the test to retain an incremental format. Changes in PO were facilitated by the patients manually adjusting the cycle ergometer air brake in order to produce a level of resistance that allowed them to match the target RPE for each stage of the SPV. Verbal encouragement was also used in the later stages of the test to ensure maximal effort.

3.2.3. Standard CPET Protocol (study 2, 3 & 4)

The incremental ramp protocol was used for the sCPET protocol, the test was completed on an electronically braked cycle ergometer (Lode Corival), the handlebars and saddle height were adjusted for participant comfort. The ramped design involves a continuous

and gradual increase in work rate (Myers, Buchanan, Walsh, Kraemer, McAuley et al., 1991) and is a popular test used in preoperative assessment (Brutsche, Spiliopoulos, Bolliger, Licker, Frey et al., 2000, Brunelli, Belardinelli, Refai, Salati, Socci et al., 2009, Gitt, Wasserman, Kilkowski, Kleemann, Kilkowski et al., 2002, Older, Hall & Hader 1999, Older, Smith, Courtney & Hone 1993, Walsh, Morice, Putnam, Nesbitt, McMurtrey et al., 1994, Wilson, Davies, Yates, Redman & Stone 2010). The sCPET protocol commenced with a 3-5 min baseline cycling, the intensity was dependent on the participant's fitness, for example, clinical patients started with unloaded pedalling, whereas healthy populations either started at 20 W or 50 W. The baseline cycling was followed by an incremental ramp of either 5, 10, 15 or 20 $W \cdot min^{-1}$. Participants were instructed to cycle at the minimum of 60 rpm and were asked to maintain this cadence until they felt like they reached volitional exhaustion. The test was terminated when the participant could no longer keep above 60 rpm for more than 5 s. Participants were asked to rate their RPE every 1-2 min. Verbal encouragement was given in the latter stages of the test to ensure maximal effort.

3.2.4. Physiological measures (all studies)

For each participant $\dot{V}O_{2peak}$ (L·min-1 and $ml \cdot kg^{-1} \cdot min^{-1}$) was determined by the highest 30 s average value during the entire test. The term $\dot{V}O_{2peak}$ was used as a $\dot{V}O_2$ plateau was not determined (Milani, Lavie, Mehra & Ventura 2006). Anaerobic threshold (AT), determined by ventilatory measures, was determined using the V-slope method with confirmation of the ventilatory equivalents ($\dot{V}_E/\dot{V}O_2$ and $\dot{V}_E/\dot{V}CO_2$) and the partial end-tidal ($P_{ET}O_2$ and $P_{ET}CO_2$) methods (Hopker, Jobson & Pandit 2011). The decided AT was secondary checked either by a clinician or another researcher. Minute ventilation ($\dot{V}_E$),

RER and maximal cycling PO (W) were all calculated as the highest 30 second average value during the entire test.

3.3. General Statistical Analysis

3.3.1. Statistical differences analysis

All data was analysed using IBM SPSS Statistics version 21. Descriptive data is presented as mean ± standard deviation (SD) throughout unless stated otherwise. Statistical significance was set at 95% ($P < 0.05$). Normality of each variable as checked through the Shapiro-Wilk test. Differences in CPET derived variables were assessed either using a paired sample T-Test (chapters 5, 6 & 7 / studies 2, 3 & 4) or, a one-way repeated measures analysis of variance (ANOVA) if comparisons were made with more than two trials (Chapter 4 / study 1).

3.3.2. Reliability analysis

Limits of agreement (Bland & Altman 1986), coefficient of variation (CV) and intraclass correlation coefficients (ICC) (Hopkins 2001) were calculated to assess the reliability of the SPV in Chapters 4 and 6 (studies 1 & 3). It has been suggested that a CV of < 5% (Hopkins 2000), and an ICC close to 1 both indicate good test-retest reliability (Atkinson & Nevill 1998), with classifications for ICC ranging from 'questionable' (0.7 to 0.8) to 'high' (> 0.9) (Vincent 1994 referenced by Atkinson & Nevill 1998).

Chapter 4. The reliability of a self-paced $\dot{V}O_{2peak}$ test in a healthy population

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Aspects of the following chapter have been included within the following manuscript: Jenkins LA., Mauger A., Fisher, J. and Hopker JG. (2017). Reliability and validity of a self-paced cardiopulmonary exercise test in post-MI patients. International Journal of Sports Medicine, 38(4):300-306.

4.1. Abstract

The SPV has been shown to produce higher $\dot{V}O_{2peak}$ values when compared to sCPET protocols. This study aimed to assess the reliability of the maximal exercise test parameters obtained from the SPV. Twenty-five (12 females, 13 males) healthy participants (age = 26 ± 6 yrs, weight = 68 ± 10 kg, stature = 172 ± 9 cm, BMI = 23.0) completed three SPV tests on three separate occasions, with at least 24 hours rest between each test. Results demonstrated a CV for $\dot{V}O_{2peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$) of 4.2% (95% confidence interval (CI): 3.4-5.6%) for trials 2-1, and 5.1% (95% CI: 4.2-6.8%) for trials 3-2. Repeated measures ANOVA analysis demonstrated no significant difference in $\dot{V}O_{2peak}$ across the repeated tests ($P > 0.05$). The LOA were ± 5.59 $ml \cdot kg^{-1} \cdot min^{-1}$ for trials 2-1, and ± 5.86 $ml \cdot kg^{-1} \cdot min^{-1}$ for trials 3-2. The mean ICC was 0.95, which represents good reproducibility. The current study results demonstrate that the SPV is a reliable method for determining peak oxygen consumption in healthy populations.

4.2. Introduction

The SPV has been shown to produce either the same (Chidnok et al., 2013; Straub et al., 2014) or higher (Mauger & Sculthorpe 2012; Mauger et al., 2013) $\dot{V}O_{2peak}$ values in comparison to traditional MIE protocols, although for it to be accepted as a viable test for assessing exercise capacity it must have good test-retest reliability. To date the reliability of the SPV has not been tested, one study did report some reliability findings that demonstrated the SPV to have a day-to-day variability of 3% (Straub et al., 2014), although this was not the main aim of the study and the variability was only assessed between the familiarisation trial and the main trial. Therefore, the purpose of the current study was to determine the test-retest reliability of maximal exercise test parameters obtained from the SPV.

4.3. Methods

4.3.1. Participants

Twenty-five (12 females, 13 males) healthy participants (age = 26 ± 6 yrs, weight = 68 ± 10 kg, stature = 172 ± 9 cm, BMI = 23.0) volunteered to participate in this study. Written informed consent was given from each participant once they had received all the required information.

4.3.2. Experimental Procedure

Each participant visited the exercise testing laboratory on three separate occasions to complete an SPV. Tests were separated by at least 24 hours to allow full recovery and

were completed at the same time of the day (± 2 hours). Participants were required to complete a 10-min warm-up at a self-selected intensity, where participants were also familiarised with the process of freely adjusting their PO on the cycle ergometer (Wattbike Pro, UK).

4.3.3. SPV protocol

For each visit participants were asked to complete an SPV, which was described in the general methods chapter (Chapter 3).

4.3.4. Physiological Measures

Expired gases ($\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$), HR and PO were continuously recorded for the duration of all three tests. The anaerobic threshold (AT) was determined using the methods stated in Chapter 3, all AT were secondary checked by an additional researcher.

4.3.5. Statistical analysis

Differences in $\dot{V}O_{2peak}$, maximal 30 second PO, AT, HR and $\dot{V}_E$ were all assessed using one-way repeated measures ANOVA. LOA (Bland & Altman 1986), CV and ICC (Hopkins 2001) were calculated to assess the reliability of SPV across the three repeated tests.

4.4. Results

The mean and SD of the physiological variables recorded over the three repeated SPVs are displayed in table 4.1. When separating the data into gender groups there were no -

significant differences in $\dot{V}O_{2peak}$, AT, HR, $\dot{V}_E$ and PO between the three repeated SPV tests in both males and females (P > 0.05).

4.4.1. $\dot{V}O_{2peak}$ (ml·kg^{-1}·min^{-1})

There was a mean group typical error, expressed as a CV, of 4.2% (95% CI: 3.4-5.6%) for trials 2-1 and 5.1% (95% CI: 4.2-6.8%) for trials 3-2. The total mean CV for all three tests was 4.7% (95% CI: 3.8-6.2%). A high level of agreement was found between trials 2-1 (ICC = 0.95) and trials 3-2 (ICC = 0.94). The LOA were ± 5.59 ml·kg^{-1}·min^{-1} for trials 2-1 and ± 5.86 ml·kg^{-1}·min^{-1} for trials 3-2 (Figure 4.1). A repeated measures ANOVA demonstrated that $\dot{V}O_{2peak}$ was not significantly different across each trial (F (2, 48) = 0.849, p= 0.43). When separating the data based on gender, the results demonstrated that for the male group the mean CV was 4.5% (95% CI: 3.4-6.8%) and the ICC was 0.95. For the female group the CV was 5.0% (95% CI: 3.7-7.9%) and the ICC was 0.85.

Table 4.1: Peak values for physiological variables recorded during repeated SPV tests in the healthy population.

	SPV1	**SPV2**	**SPV3**
$\dot{V}O_{2peak}$ (L·min^{-1})	3.30 ± 0.86	3.23 ± 0.90	3.25 ± 0.92
$\dot{V}O_{2peak}$ (ml·kg^{-1}·min^{-1})	48.56 ± 8.93	47.87 ± 9.28	47.85 ± 9.40
AT (ml·kg^{-1}·min^{-1})	27.00 ± 6.83	26.67 ± 7.26	26.95 ± 7.34
HR (bpm)	184 ± 10	183 ± 11	182 ± 11
$\dot{V}_E$ (L·min^{-1})	137.8 ± 38.9	133.3 ± 41.0	128.4 ± 39.1*
Peak PO (W)	312 ± 93	299 ± 109	304 ± 101

*significantly different to SPV1 (< 0.05), data are mean ± SD.

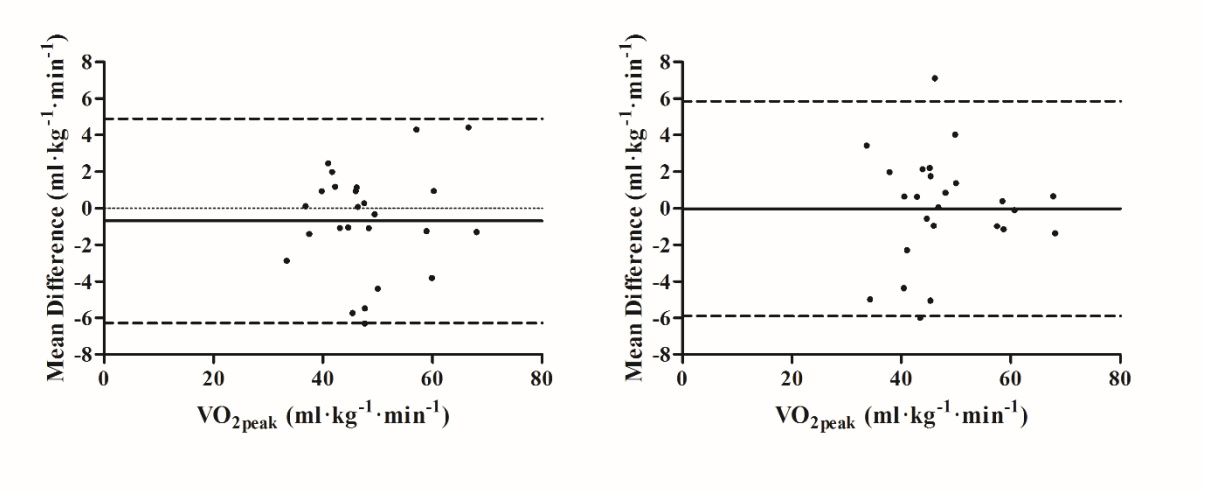

Figure 4.1: Bland-Altman plots of $\dot{V}O_{2peak}$ (ml·kg^{-1}·min^{-1}) differences between trials 1 and 2 (left) and 2 and 3 (right). The solid horizontal line represents mean difference, whilst the dashed lines represent the 95% limits of agreement.

4.4.2. Anaerobic Threshold (AT)

The $\dot{V}O_2$ (ml·kg^{-1}·min^{-1}) at the anaerobic threshold was assessed. Data demonstrated there was a mean CV of 5.2% (95% CL: 4.2-6.9%) for trials 2-1 and a mean CV of 5.8% (95% CL: 4.7-7.7%) for trials 3-2. The ICC was 0.96 for trials 2-1 and trials 3-2 which represents a high level of agreement. The limits of agreement were ± 3.99 ml·kg^{-1}·min^{-1} for the measure of trials 2-1 and ± 4.57 ml·kg^{-1}·min^{-1} for the measure of trials 3-2 (figure 4.2). A repeated measures ANOVA demonstrated that AT in ml·kg^{-1}·min^{-1} was not significantly different between each trial (F (2, 48) = 0.328, p= 0.72). When separating the data based on gender, the results demonstrated that for the male group the mean CV was 7.4% (95% CI: 5.6-11.4%) and the ICC was 0.95. For the female group the CV was 4.0% (95% CI: 2.9-6.2%) and the ICC was 0.97.

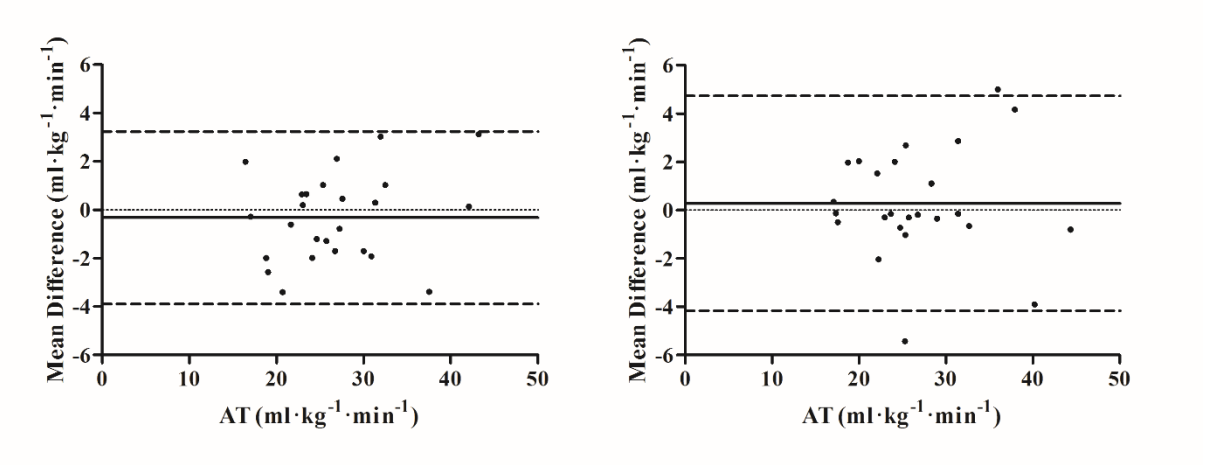

Figure 4.2: Bland-Altman plots of the AT (ml·kg^{-1}·min^{-1}) differences between trials 1 and 2 (left) and 2 and 3 (right). The solid horizontal line represents mean difference, whilst the dashed lines represent the 95% limits of agreement.

4.4.3. HR, V_E and RER

For HR there was a CV of 1.7% (95% CL: 1.4-2.3%) and an ICC of 0.93. For $\dot{V}_E$, the CV was 7.2% (95% CL: 5.8-9.6%) with an ICC of 0.95, and for RER the CV was 3.1% (95% CL: 2.5-4.1%) with an ICC of 0.82. When separating the data based on gender, the results demonstrated that for HR in the male group the mean CV was 1.6% (95% CI: 1.2-2.4%) and the ICC was 0.97. For the female group the CV was 1.9% (95% CI: 1.4-2.8%) and the ICC was 0.81. For $\dot{V}_E$ in the male group the CV was 6.3% (95% CI: 4.8-9.7%) with an ICC of 0.94, and for the female group the CV was 8.4% (95% CI: 6.2-13.3%) with an ICC of 0.85.

4.4.4. Power Output

There was a mean group typical error expressed as a CV of 8.9% (95% CL: 7.1-11.9%) for trials 2-1 and 6.8% (95% CL: 5.5-9.2%) for trials 3-2. The ICC was 0.94 for trials 2-1 and 0.97 for trials 3-2, representing a high level of agreement. The limits of agreement were + 81 W for the measure of trials 2-1 and ± 51 W for the measure of trials 3-2 (Figure 4.3). When separating the data based on gender, the results demonstrated that for the male group the mean CV was 8.8% (95% CI: 6.6-13.8%) and the ICC was 0.88. For the female group the CV was 6.4% (95% CI: 4.7-10%) and the ICC was 0.94. Figure 4.4 represents the average PO throughout the duration of the test for the three trials. Although peak PO was significanlty different across the three repeated trials, the overall patterns of response were very similar.

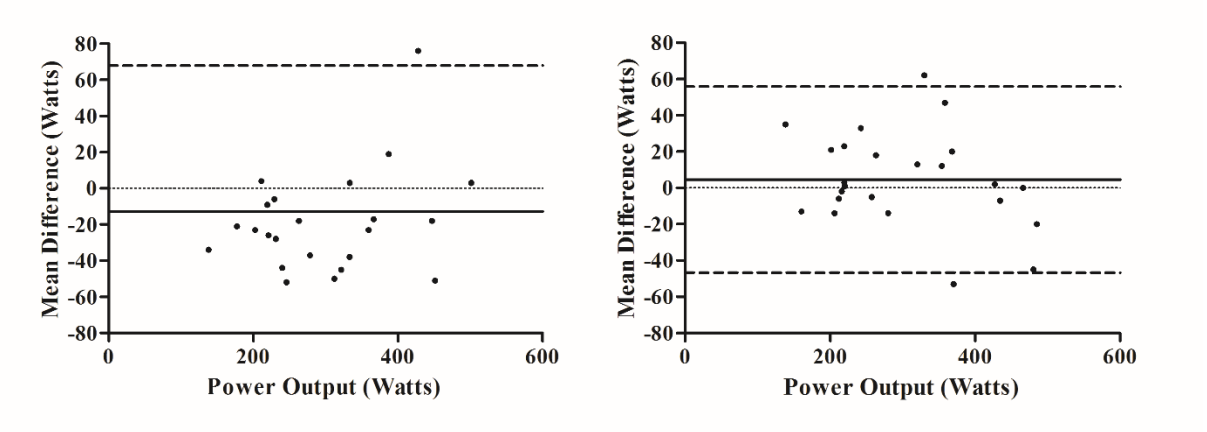

Figure 4.3: Bland-Altman plots of the PO (W) differences between trials 1 and 2 (left) and 2 and 3 (right). The solid horizontal line represents mean difference, whilst the dashed lines represent the 95% limits of agreement.-

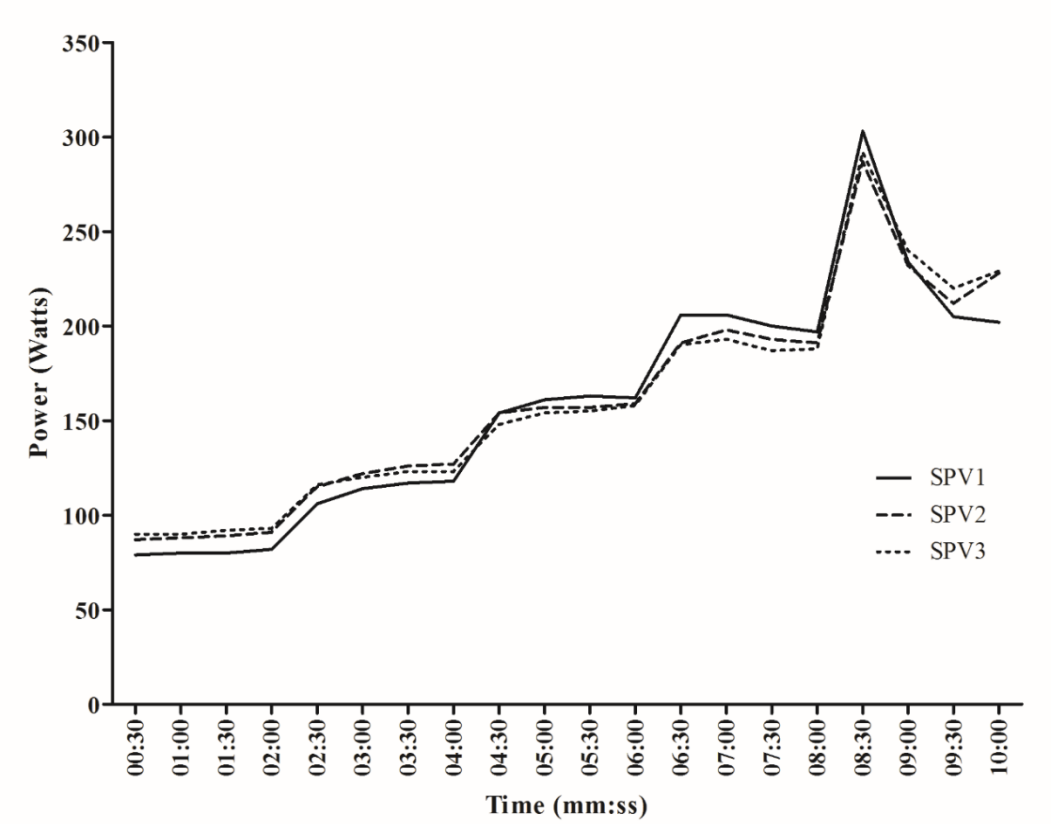

Figure 4.4: Mean PO for every 30 secs for the duration of the test for all three repeated tests.

4.5. Discussion

The results of the current study demonstrate that the $\dot{V}O_{2peak}$ values obtained via the use of the SPV protocol are reliable. The mean CV of 4.7% for $\dot{V}O_{2peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$) is lower than the accepted upper limit of 5% suggested by Hopkins (Hopkins 2000). The limits of agreement analysis suggest that there is 95% probability that test-retest differences, would at worst lie between ± 5.73 $ml \cdot kg^{-1} \cdot min^{-1}$. Furthermore, repeated measures ANOVA found no significant differences in $\dot{V}O_{2peak}$ across the repeated trials ($P > 0.05$).

An interesting finding was that the CV in $\dot{V}O_{2peak}$ increased from trials 2-1 to trials 3-2, this would suggest that there was no 'learning effect' related to the SPV protocol. Based on these findings the SPV is considered to be a reliable test for $\dot{V}O_{2peak}$. However, it is interesting that the highest $\dot{V}O_{2peak}$, HR, $\dot{V}_E$ and PO were obtained in the first SPV compared to the following two. This may be a result of potential behavioural changes that may negatively influence the results, individuals may change pacing strategy to avoid the high levels of discomfort they experienced in first test. Figure 4.4 supports this suggestion as PO appears to be higher throughout the final two stages, with a larger reduction in PO during the final stage of SPV1 (102 W), compared to SPV2 (60 W) and SPV3 (61 W). This would suggest that for optimal results, just one SPV test is needed and that a familiarisation session may negatively affect the result. Interestingly, previous studies reporting significantly higher $\dot{V}O_{2peak}$ values in SPV protocols (Astorino et al., 2015; Faulkner et al., 2015; Mauger et al., 2013; Mauger & Sculthorpe 2012) do not report that a familiarisation was used. In contrast some of the studies that failed to find differences in $\dot{V}O_{2peak}$ between SPV and traditional protocols (Chidnok et al., 2013; Straub et al., 2013) did incorporate a familiarisation session into their study design.

Previous literature has demonstrated the reproducibility of maximal exercise parameters when using standard MIE protocols. Mauger et al. (2013) most recently presented data on a subset of participants that they used to determine the test-retest reliability of a MIE protocol. They discovered a low CV of 3.7% for $\dot{V}O_{2peak}$. Froelicher et al. (1974) found that for three maximal treadmill exercise protocols, the Bruce, Balke and Taylor protocol, the CV for $\dot{V}O_{2peak}$ ranged from 4.1-5.8%. A succession of MIE tests have also been

completed on patients with cardiac failure in order to determine long-term reproducibility of gas exchange measurements during maximal exercise, with the average CV for $\dot{V}O_{2peak}$ being 5.7% (Janicki, Gupta, Ferris & McElroy 1990). Some studies have also considered the reproducibility of a cycling MIE test in patients with various respiratory conditions, where the coefficient of variation ranged from 3.5-6.9% (Cox, Hendrink, Binkhorst, Folgering & van Herwaarden 1989; Marciniuk, Watts & Gallagher 1993; McKone, Barry, FitzGerald & Gallagher 1999). It was concluded that all of these tests had good test-retest reliability. Whether the SPV would demonstrate similar level of test-retest reliability in clinical patients is yet to be investigated.

In addition, one study had already investigated the reliability of the physiological variables obtained from the SPV (Straub et al., 2014), although this was not the main aim of their study. Straub and colleagues (2014) wanted to determine the efficacy of the SPV in comparison to a standard ramp test in trained cyclists, but as each participant completed both test twice, the first of each test being a familiarisation trial, they also reported some reliability findings. They concluded the SPV to have similar day-to-day variability (CV = 3%) as the ramp test (CV = 4%), and suggested that no familiarisation session is needed to obtain valid test results. These findings are similar to that of the current study.

The intraclass correlation coefficient (ICC) is an increasingly popular method used for reliability studies, and it is suggested that an ICC close to 1 indicates excellent reliability (Atkinson & Nevill 1998). In the current study, the ICC for $\dot{V}O_{2peak}$ in trials 2-1 was 0.95 and 0.94 for trials 3-2, suggesting very good reproducibility. Previous research has

demonstrated similar ICC of 0.93 for $\dot{V}O_{2peak}$ when determining test-retest reliability on cycling maximal incremental exercise tests (Eng, Dawson & Chu 2004).

Even though there was high variance in peak PO across the repeated trials in the current study, individual participant PO profiles demonstrated a relatively similar pacing profile across the three tests (see figure 4.4). Indeed, previous research has demonstrated that pacing strategies in self-paced cycling time trials are broadly similar (Albertus, Tucker, Gibson, Lambert, Hampson et al., 2005; Thomas, Stone, Thompson, Gibson & Ansley 2012), although with a higher degree of variability at the start and the end of trials (Thomas et al., 2012). The findings of this study demonstrate that irrespective of the self-paced nature of the SPV, participants generally showed consistency in the way that they performed the test. Differences between trials seemed to lie at the end of the test where potentially, as previously mentioned, behavioural changes may have influenced the variation. Interestingly, the CV for peak PO decreased from trials 2-1 (8.9%) to trials 3-2 (6.8%), with peak PO being highest in SPV1. However, it is interesting to see that this high variability in PO seems to have very little effect on the variability of $\dot{V}O_{2peak}$ between the repeated tests; 4.2% (95% CI: 3.4-5.6%) for trials 2-1 and 5.1% (95% CI: 4.2-6.8%) for trials 3-2.

An unexpected finding was the significant differences in $\dot{V}_E$ ($P < 0.05$) between repeated tests, with pairwise comparison demonstrating that the main difference was between SPV1 and SPV3, with $\dot{V}_E$ being significantly lower in SPV3. This variability in $\dot{V}_E$ may explain some of the discrepancy of the findings in $\dot{V}_E$ between the previous studies using the SPV (Chidnok et al., 2013; Mauger & Sculthorpe 2012; Mauger et al., 2013; Straub

et al., 2014). Mauger et al., (2013) recently stated that because HR was significantly lower in the SPV and there were no changes in $\dot{V}_E$, this indicates that oxygen intake and delivery were not enhanced during the SPV and that the higher peak $\dot{V}O_2$ was likely to be due to a change in oxygen extraction at the working muscles. The observation in the current study that $\dot{V}_E$ differed across repeated tests, yet $\dot{V}O_{2peak}$ remained unchanged, suggests that the mechanisms underpinning $\dot{V}O_{2peak}$ in this protocol are multifactorial, and may occur at any point down the oxygen cascade. Further research is essential in order to fully understand the mechanisms behind the SPV protocol and why participants are able to achieve a higher $\dot{V}O_{2peak}$ in some studies (Mauger & Sculthorpe 2012; Mauger et al., 2013).

4.6. Conclusion

The results of the current study demonstrate that the SPV is a reliable method for determining exercise capacity in healthy populations; therefore, the null hypothesis ($H1_0$) stated in chapter 2.10 can be rejected. Combined with earlier studies, this work suggests that the SPV is a valid and reliable measure of $\dot{V}O_{2peak}$ in healthy populations, and should be considered as an accepted means of testing for maximal oxygen uptake. Finally, these findings demonstrate that well-instructed participants, who are familiarised with the RPE scale and ergometer work rate changes, do not require an SPV familiarisation bout for accurate measures to be achieved.

What is already known about this topic

- There are problems associated with sCPET methods, the SPV was produced to overcome some of these. Previous research has demonstrated the SPV to be a valid test of exercise capacity, with some studies showing it to produce higher $\dot{V}O_{2peak}$ values. No studies had looked the reliability of the SPV.

What this study adds

- This study shows that the SPV is a reliable test for determining $\dot{V}O_{2peak}$ in a healthy population. Other important CPET variables such as AT via gas exchange can be determined from the SPV, with good test re-test reliability.

Chapter 5. Differences in the physiological responses between a self-paced and a standard incremental ramp $\dot{V}O_{2peak}$ test

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Aspects of the following chapter have been included within the following manuscript, Jenkins, L.A., Mauger, A.R. & Hopker, J.G. (2016). Age differences in physiological responses to self-paced and incremental VO2max testing. European Journal of Applied Physiology. 117(1): 159–170.

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5.1. Abstract

A self-paced maximal exercise protocol has demonstrated higher $\dot{V}O_{2peak}$ values when compared against traditional tests. The aim of the study was to assess the physiological response to the SPV protocol in comparison to a sCPET in young adults and middle aged to older adults. Forty-four participants (22 = 18-30 yrs; 22 = 50-75 yrs) completed both tests in a randomised, counter-balanced, crossover design. The SPV included 5 × 2 minute stages where participants were able to self-regulate their PO by using incremental 'clamps' in RPE. The sCPET consisted of either a 15 or 20 W min^{-1} ramp, depending on training status. Expired gases, Q, SV, muscular deoxyhaemoglobin (deoxyHb) and electromyography (EMG) at the vastus lateralis (VL) were recorded throughout. Results demonstrated a significantly higher $\dot{V}O_{2peak}$ in the SPV (49.68 ± 10.26 $ml \cdot kg^{-1} \cdot min^{-1}$) vs. the sCPET (47.70 ± 9.98 $ml \cdot kg^{-1} \cdot min^{-1}$) in the young, but no differences in the middle to older aged group ($P > 0.05$). Q and SV were significantly higher in the SPV vs. the sCPET in the young ($P < 0.05$) but no differences in the middle to older aged group ($P > 0.05$). No differences were seen in both age groups in the deoxyHb and EMG response ($P > 0.05$). Findings suggest that in the young group, the SPV produces higher $\dot{V}O_{2peak}$ values as a result of an increase in oxygen delivery (enhanced Q). However, likely due to age-related differences, particularly in the cardiovascular response to exercise, the middle to older aged participants achieved similar $\dot{V}O_{2peak}$ values regardless of them reaching a higher physiological workload.

5.2. Introduction

The SPV has been shown to allow young participants to achieve a higher $\dot{V}O_{2peak}$ when compared against a standard incremental exercise test in both cycling and running exercise (Mauger & Sculthorpe 2012; Mauger et al., 2013). Although, not all studies have found differences in $\dot{V}O_{2peak}$ when comparing the SPV vs. standard exercise protocols (Chidnok et al., 2013; Faulkner et al., 2015; Straub et al., 2014), but for those studies who have found differences (Astorino et al., 2015; Mauger & Sculthorpe 2012; Mauger et al., 2013) a mechanistic explanation is yet to be identified.

Maximal oxygen consumption is suggested to be limited by factors such as: pulmonary diffusion capacity, maximal cardiac output, oxygen carrying capacity of the blood, or skeletal muscle characteristics (Bassett & Howley 2000). Mauger et al. (2013) suggested that a higher $\dot{V}O_{2peak}$ may be achieved during an SPV protocol due to changes in oxygen extraction at the working muscles, rather than any increase in oxygen delivery. The authors based this hypothesis on the observation that participants achieved a lower HR in the SPV without differences in peak $\dot{V}_E$; they suggested that if the higher $\dot{V}O_{2peak}$ were a result of an increase in the oxygen delivery it would be expected that both HR and VE would be increased by the SPV (Mauger & Sculthorpe 2012; Mauger et al., 2013). Although it is also possible that increases in SV, which was not measured in either study (Mauger & Sculthorpe 2012; Mauger et al., 2013), may have compensated for the lower HR achieved which would mean an increase in oxygen delivery and thus $\dot{V}O_{2peak}$ (Bassett & Howley 2000). Nevertheless an increased oxygen extraction in the SPV may still arise from the participant being able to adjust work rate, potentially creating optimal conditions

that allow enhanced rates of muscle oxygen extraction and allows higher work rates to be achieved. Indeed, previous research demonstrates that muscle blood flow, and thus oxygen extraction, is reduced when both muscle force and duration of contractions increase (Bjorklund, Stoggl & Holmberg 2010, Hoelting, Scheuermann & Bartow 2001). Research has also suggested that decreased blood transit time is associated with reduced rates of oxygen extraction (Bassett & Howley 2000; Kalliokoski, Oikonen, Takala, Sipila, Knuuti et al., 2001). In traditional tests, this continuous increase in force and consistent duration of each contraction cannot be adjusted, this may therefore result in a constriction in the amount of blood flow available at the muscle and reduced time for extraction to take place. Both force and duration of muscle contractions are free to vary by the participant in the SPV, which may contribute in optimising the muscle blood flow at the working muscles. Additionally, it has been suggested that the self-regulation of work rate during the SPV may improve the efficiency of muscle recruitment, i.e. affording greater reliance on more oxygen efficient muscle fibres (Type I) particularly in the earlier stages (Mauger & Sculthorpe 2012; Mauger et al., 2013). This self-regulation may help to conserve more Type II fibres for the final stage (RPE 20) which ultimately allows high work rates to be achieved. Although this is very speculative with no evidence to support this concept.

A more recent study has demonstrated that the SPV may elicit a greater Q and peak HR when compared against a standard incremental ramp protocol (Astorino, McMillan, Edmunds & Sanchez 2015). This was the first study to assess $\dot{Q}$ and suggests that the higher $\dot{V}O_{2peak}$ may be explained by an increase in oxygen delivery (Mortensen, Dawson, Yoshiga, Dalsgaard, Damsgaard et al., 2005), rather than an increase in the oxygen extraction as previously suggested. Astorino and colleagues (2015) suggested the increase

in Q during the SPV protocol is likely the result of participants adequately pacing their effort to minimise fatigue in the early stages of the test. This leads to a greater work rate being achieved in the final stage of the SPV, potentially because they have preserved the use of type II fibres in the earlier stages, resulting in a greater HR, Q and $\dot{V}O_{2peak}$.

In a clinical setting, those patients who require preoperative CPET are generally middle aged to older adults. It is well accepted that there is a decline in $\dot{V}O_{2peak}$ with aging, this is suggested to be predominantly the result of reductions in maximal Q and muscle blood flow (Betik & Hepple 2008). Cardiac function (Lakatta & Levy 2003), lung performance (Chaunchaiyakul, Groeller, Clarke & Taylor 2004; Janssens, Pache & Nicod 1999) and muscle oxidative capacity (Betik & Hepple 2008; Russ & Kent-Braun 2004) have all been shown to reduce with age, which contribute to the deterioration in $\dot{V}O_{2peak}$. This deterioration in $\dot{V}O_{2peak}$ will be more pronounced in those patient groups where cardiac and respiratory function is further reduced. Therefore, the limiting factors to $\dot{V}O_{2peak}$ may differ between young and older populations. Consequently, selecting a protocol which adequately stresses the limiting physiological system may be an important decision when testing different age groups. Indeed, a previous study has demonstrated that the SPV produces higher Q and $\dot{V}O_{2peak}$ values vs. traditional methods (Astorino et al., 2015). It could therefore be speculated that a self-paced exercise test provides a better assessment of the cardiorespiratory system, which may be particularly beneficial in those patient groups where cardiac function is already limited. Furthermore, examining the cardiopulmonary and muscular response to an SPV (compared with a standard test), may help explain why a higher $\dot{V}O_{2peak}$ is often seen from this test. Therefore, the aim of the current study was to assess the physiological responses to the SPV in comparison to a sCPET in healthy younger adults (18-30) and middle aged to older adults (50-75), and to

objectively test whether responses differ between the two groups. The ages chosen for the middle to older adult group were selected to reflect the age of typical patient groups requiring preoperative CPET assessments (West, Jack & Grocott 2011).

5.3. Methods

5.3.1. Participants

Forty-four male and female healthy participants, comprising of twenty two 18-30 year olds (age = 25 ± 4 years; stature = 174 ± 11 cm; weight = 69 ± 9 kg, BMI = 22.8) and twenty two 50-75 year olds (age = 59 ± 6 years; stature = 171 ± 8 cm; weight = 73 ± 13 kg, BMI = 25.0), volunteered to take part in the current study. All participants were apparently healthy, free of disease, free of any risk factors associated with cardiovascular disease and were all physically active (> 90 min of moderate activity per week). This information was obtained via a health questionnaire. For the middle aged to older adult participants a resting blood pressure measurement was taken on their first visit to ensure they were not hypertensive. All participants who volunteered gave their written informed consent.

5.3.2. Experimental procedure

Each participant visited the laboratory on two separate occasions, where they were asked to complete either an SPV, or a traditional ramp $\dot{V}O_{2peak}$ test in a randomised order and counter-balanced, crossover design. Tests were separated by at least 24 hours to allow full recovery and were completed at the same time of the day (± 2 hours). Participants were asked to refrain from drinking alcohol (24 h abstinence), eating (2 h abstinence),

and not to perform any exercise in the 24 h prior to each test. Prior to each test participants were required to complete a 5 minute warm-up at approximately 50W. In the SPV condition during the warm-up, participants were familiarised with the process of freely adjusting their PO, this could be achieved by participants making adjustments in both the resistance and/or cadence on the cycle ergometer.

SPV protocol

The SPV was completed on an air-braked cycle ergometer (Wattbike Ltd, Nottingham, UK), which allowed participants to continually vary their PO throughout the test. The SPV was conducted in accordance with the procedures previously outlined in the general methods chapter (Chapter 3). Participants were able to view their cadence and PO throughout the test, they also received feedback on elapsed time particularly when approaching the end of a stage.

RAMP protocol

The sCPET was completed on an electro-magnetically braked cycle ergometer (Corival, Lode, Groningen, Netherlands), so that for each stage PO could be fixed according to the test requirements. The test followed a standard incremental ramp design. The cycle ergometer was set in hyperbolic mode to ensure that any changes in cadence did not influence PO. Participants were instructed to keep their cadence above 60 rev.min^{-1}. The ramp commenced with a 3 minute period of baseline cycling where a various range of work rate starting points were selected for each participant (20, 50 and 100 W), according to self-reported fitness levels. This 3 min period was then followed by ramp increments of either 15 or 20 W min^{-1}. The starting point and the rate of increase in work rate was selected on an individual basis in the attempt to optimise the protocol for each participant.

The test was stopped when the participant could no longer continue or if they were unable to maintain a cadence of more than 60 rev.min^{-1}, despite verbal encouragement.

5.3.3. Physiological measures

Expired gases

Expired gases, HR and PO were measured throughout both tests. $\dot{V}O_{2peak}$ and AT were determined using the those methods stated in Chapter 3.

Near-Infrared Spectroscopy

Muscle deoxyhaemoglobin (deoxyHb) was measured using a Near-Infrared Spectroscopy (NIRS) device (Portamon, Artinis Medical Systems, Elst, Netherlands). The device uses small skin surface lasers to measure light absorbance, operating at wavelengths between 760 and 850 nm with an average optode distance of 35 mm and a sampling rate of 10 Hz. The device was placed longitudinally on the VL of the left leg, and was situated 10 cm above the patella (Wang, Xu, Tian, Sun, Sun et al., 2012). Before placement of the NIRS device, the NIRS system was calibrated and the skin was carefully shaved. The device was secured to the site using adhesive tape, which covered the whole device to reduce light loss. Afterwards, the deoxyHb data were exported into 1 s values and then averaged into 30 s at 10 time points over both tests. A baseline deoxyHb from the NIRS was averaged from the final 30 s of the first stage, and the peak was determined from the average of the final 15 s of each test. The deoxyHb for each time point was then normalized to the total amplitude of response (peak – baseline) (Boone, Koppo, Bartow & Bouckaert 2010). This was then plotted as a function of percentage of time to exhaustion (%TTE).

Electromyography (EMG)

Surface EMG was recorded using a wireless BioPac MP150 (Biopac Sytems Inc, CA, USA), two surface electrodes were placed on the VL of the right leg and a reference electrode was placed on the patella of the same leg. The skin was prepared by carefully shaving and cleaning the area with skin preparation alcohol wipes. EMG was recorded at a sampling frequency of 1000 Hz. Prior to each maximal test, participants performed three maximal isometric voluntary contractions (MIVC) of the VL muscle in order to determine the EMG signal at maximal contraction. The MIVCs were completed on a Cybex Isokinetic Dynamometer (HUMAC Norm, CSMi, Stoughton, MA, USA). Before the MIVCs a series of submaximal contractions were completed as a preparatory warm-up. Each MIVC lasted 5 s, with 1 min rest between each. Participants were also required to complete one MIVC directly after both maximal tests to determine the level of muscle fatigue, this occurred 1 min after the test or as close to 1 min as possible; depending on how quickly the participant was safely able to move off the bike and onto the dynamometer. The time was kept consistent between tests for each individual. Maximum EMG was calculated by averaging the highest 1 s EMG value from each MIVC trial. The 30 s average EMG signals from each stage of the SPV and sCPET was then normalized to the maximum EMG from the MIVC. Data were plotted as a function of %TTE from each maximal test. It was decided to include the whole 30 s of the EMG signal within the average, thus the inactive periods were included. The authors are aware that including the inactive periods between each contraction may been seen as a limitation, as variations in cadence would influence the average of EMG (e.g. higher cadence would results in a higher EMG average), although for the nature of the study it was felt that excluding the inactive periods would not be necessary as we purely wanted to get an idea of the overall muscle activity which occurred at each stage.

Cardiac Output and Stroke Volume

A non-invasive thoracic impedance device (PhysioFlow, Manatec Biomedical, France) was used to measure stoke volume (SV) and Q throughout the duration of both exercise tests. Electrodes were positioned in the following areas; above the supraclavicular fossa (participants' left side), xiphoid process and two additional electrodes were placed to determine a single ECG signal at V1 and V6 positions. Prior to electrode placement, all skin sites were carefully cleaned, and shaved where necessary. In accordance with the manufacturer recommendations, the equipment was auto-calibrated prior to each test by establishing impedance waveforms over 30 heart beats. Peak Q and SV were determined by the highest 30 s average value over the entire duration of the test. A 30 s average of SV and Q was plotted, for every 2 min, as a function of percentage of time to exhaustion (%TTE) from each exercise test.

Blood Lactate

A finger-tip capillary blood sample was taken directly at the end of each test to determine end-exercise blood lactate concentrations (Biosen C-Line, EKF Diagnostic, London, UK).

5.3.4. Statistical analysis

The mean maximum values for $\dot{V}O_{2peak}$, AT, PO, HR, $\dot{V}_E$, blood lactate, Q and SV were all compared between the protocols using a paired sample t-test. The percentage difference between the pre and post MIVC (highest 1 s EMG and torque) from the SPV and sCPET was also compared using a paired sample t-test. Differences ($P < 0.05$) between Q, SV, deoxyHb and EMG for the last 30 s of each stage, in both the SPV and

sCPET test were assessed using a repeated measured ANOVA (2 x 10 for NIRS and EMG; 2 x 6 for Q and SV). Violation of the assumptions were assessed using the Mauchly's test of sphericity, if p was > 0.05 then sphericity was assumed but if p was < 0.05 then Greenhouse-Geisser corrections were used. If an interaction was present then pairwise comparisons with a Bonferroni correction was used to identify where the interaction occurred. The two defined group, 18-30 years (young) and 50-75 years (middle aged to older adults), were analysed separately.

5.4. Results

Table 5.1 presents data from the physiological parameters measured during the two tests for both age groups. In the young population there was a significantly higher $\dot{V}O_{2peak}$ ($L \cdot min^{-1}$ and $ml \cdot kg^{-1} \cdot min^{-1}$), peak $\dot{V}_E$, peak RER, peak Q, peak SV and peak PO achieved in the SPV when compared to the sCPET protocol ($P < 0.05$). There were no differences in AT, peak HR, end-exercise lactate and TTE. ($P > 0.05$). In the middle to older aged population there was only significant differences in peak RER, peak PO and TTE ($P < 0.05$). Figure 5.1 shows the $\dot{V}O_2$ response over time, in the SPV and sCPET, of a representative participant from each group. These participant's were selected as those who were representative of the mean $\dot{V}O_{2peak}$ values and the average differences between the two tests.

Table 5.1: Measured physiological variables recorded during SPV and sCPET tests for both young and old populations.

	Young (18-30 yrs)			Middle Aged and Older Adults (50-75 yrs)		
	sCPET	**SPV**	**P-Value**	**sCPET**	**SPV**	**P-Value**
$\dot{V}O_{2peak}$ ($L \cdot min^{-1}$)	3.34 ± 0.88	3.45 ± 0.87*	0.02	2.74 ± 0.76	2.78 ± 0.74	0.79
$\dot{V}O_{2peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	47.70 ± 9.98	49.68 ± 10.26*	< 0.01	38.99 ± 9.54	39.12 ± 8.61	0.84
AT ($ml \cdot kg^{-1} \cdot min^{-1}$)	25.36 ± 6.71	24.55 ± 5.18	0.32	21.69 ± 6.17	22.34 ± 6.36	0.23
HR (bpm)	181 ± 10	183 ± 9	0.19	164 ± 12	164 ± 12	0.93
$\dot{V}_E$ ($L \cdot min^{-1}$)	130.7 ± 32.9	147.7 ± 37.4*	< 0.01	122.8 ± 31.4	129.4 ± 29.6	0.08
RER	1.24 ± 0.05	1.31 ± 0.08*	< 0.01	1.22 ± 0.09	1.32 ± 0.12*	< 0.01
Peak Q ($L \cdot min^{-1}$)	23.1 ± 5.5	26.7 ± 4.1*	< 0.01	24.5 ± 5.1	26.0 ± 5.0	0.24
Peak SV (ml)	132.1 ± 34.8	154.5 ± 28.7*	< 0.01	158.5 ± 29.7	167.6 ± 28.4	0.24
End-exercise Lactate (mmol/L)	8.06 ± 1.74	9.52 ± 2.85	0.06	6.15 ± 1.88	7.21 ± 2.89	0.05
Peak PO (W)	265 ± 69	336 ± 122*	< 0.01	226 ± 63	245 ± 74*	< 0.01
TTE (secs)	637 ± 153	600 ± 0	0.26	695 ± 149	600 ± 0*	< 0.01

*Significantly different from the sCPET ($P < 0.05$). Data are presented as mean ± SD

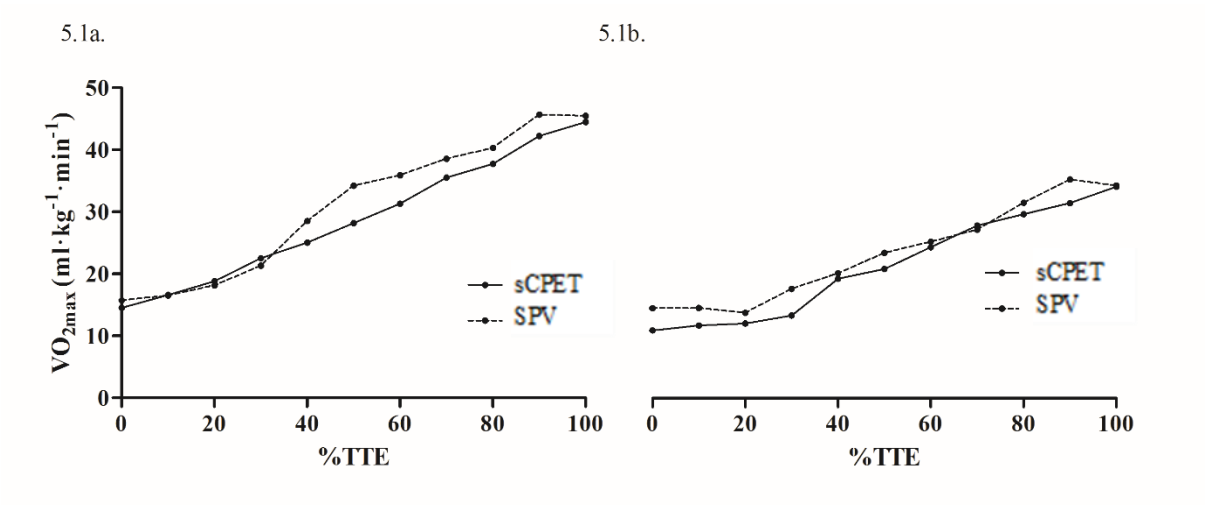

Figure 5.1: $\dot{V}O_2$ response over %TTE in the sCPET and SPV in a representative: a) young and b) middle to older aged participant.

5.4.1. NIRS

Prior to analysis, data from three participants in the young and six in the older group were excluded due to a poor quality NIRS signal. There was no interaction effect, as there were no differences between the protocol and increase in deoxyHB ($P > 0.05$). Figure 5.2 demonstrates the relative change in deoxyHb over the duration of both the sCPET and SPV, in both the age groups. There was a main effect of time, as deoxyHB increased significantly over %TTE in both age groups ($P < 0.01$), post hoc testing was used to determine differences between each successive time point. Results demonstrated that for the young group in the sCPET there were no differences between 70-80%, 80-90% and 90-100% of TTE ($P > 005$), in the SPV there were differences between 30-40%, 40-50% and 60-70% of TTE ($P < 005$). For the middle to older aged group in the sCPET there were differences between 20-30%, 30-40% and 40-50% of TTE ($P < 0.05$), in the SPV there were differences between 30-40%, 40-50%, 50-60% and 60-70% of TTE ($P < 0.05$).

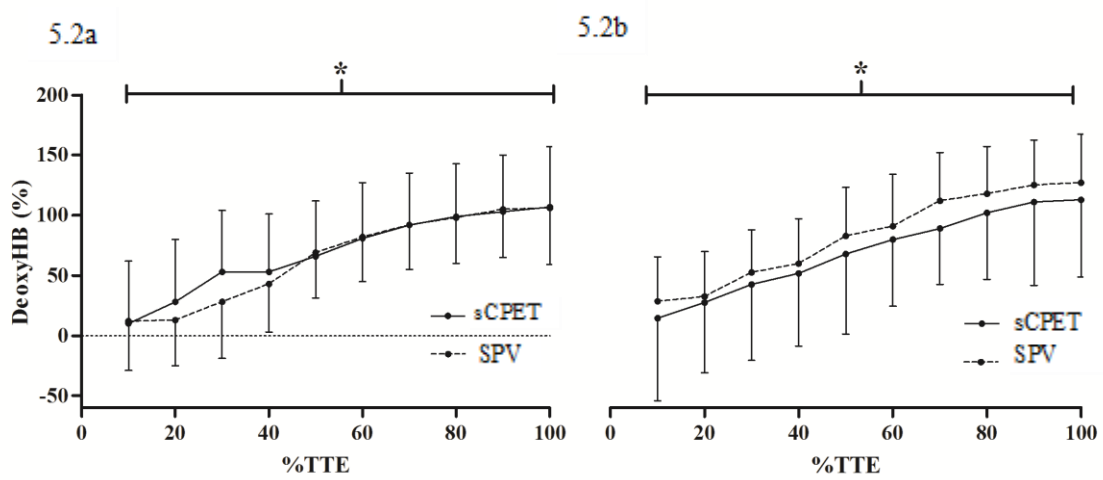

Figure 5.2: Relative change in deoxyHB versus %TTE in the sCPET and SPV for: a) young and b) middle to older aged population. * Main effect ($P < 0.05$). Data are mean $\pm$ SD.

5.4.2. EMG

There was no interaction effect in the young group as there were no differences in the increase of relative EMG between the protocols. However in the middle to older aged population there was an interaction effect, with post hoc testing demonstrating a significantly higher EMG at 70% of TTE in the SPV compared to the sCPET ($P < 0.05$). There was a main effect of time as the relative EMG increased significantly in relation to %TTE in both age groups ($P < 0.01$; Figure 5.3), although, for the young group, post hoc analysis showed there to only be a significant difference between 80-90% of TTE for the sCPET, and only between 20-30% TTE for the SPV. For the middle to older aged group, post hoc analysis only showed a significant difference between 90-100% of TTE from the sCPET, and no significant differences between the successive stages in the SPV. There were no differences for the percentage difference of the pre and post MIVC in EMG and torque between the SPV and sCPET ($P > 0.05$).

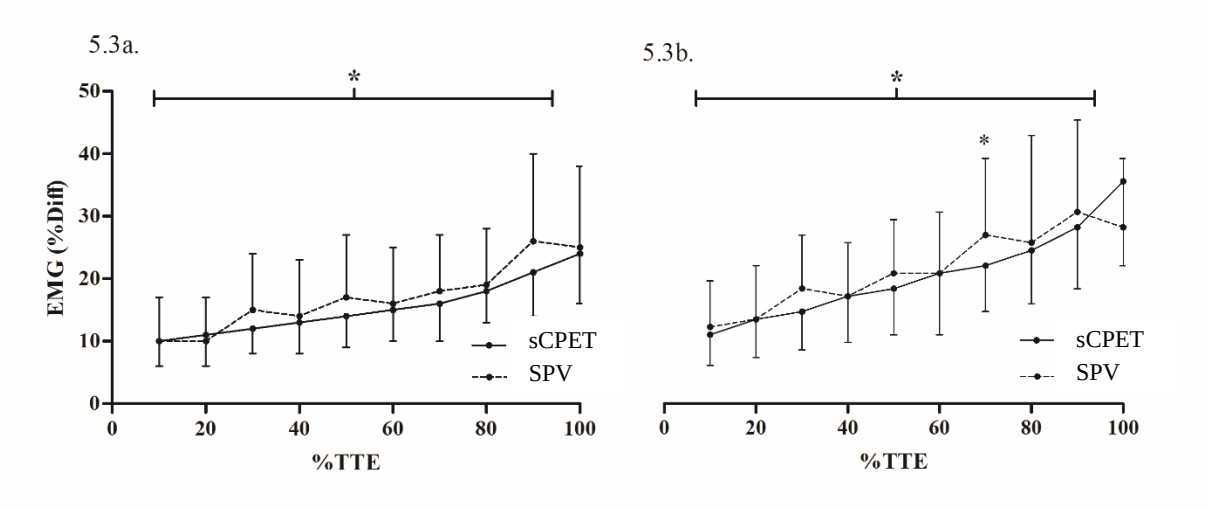

Figure 5.3: Normalized EMG relative to %TTE over the sCPET and SPV for: a) young and b) middle to older aged populations. * Main effect ($P < 0.05$). Data are mean $\pm$ SD.

5.4.3. Cardiac Output and Stroke Volume

Prior to analysis, data from four participants in the middle to older aged group (total n = 18) were excluded due to a poor quality signal. In figure 5.4, the mean and SD for Q and SV is presented over time. For the young population there was an interaction effect of the protocol in both Q and SV over time, with post hoc testing demonstrating differences between the two tests at 6 min, 8 min and the final 30 s for Q, and 6 min and the final 30 s of the test for SV ($P < 0.05$). There was a main effect of time, as both Q and SV increased significantly over time, although post hoc testing demonstrated that over both tests differences specifically occurred between baseline to 8 min for CO, and only between baseline and 2 min for SV ($P < 0.05$). For the middle to older aged population there was no interaction effect as there were no differences between the protocol and the increase in Q and SV ($P > 0.05$). There was an overall main effect of time ($P < 0.05$), although post hoc testing showed that for the sCPET there were differences from baseline to 8 min for CO and from baseline to 4 min for SV. For the SPV there were differences from baseline to 6 min for CO and for SV differences occurred between baseline to 2 min, and 4 min to 6 min ($P < 0.05$).

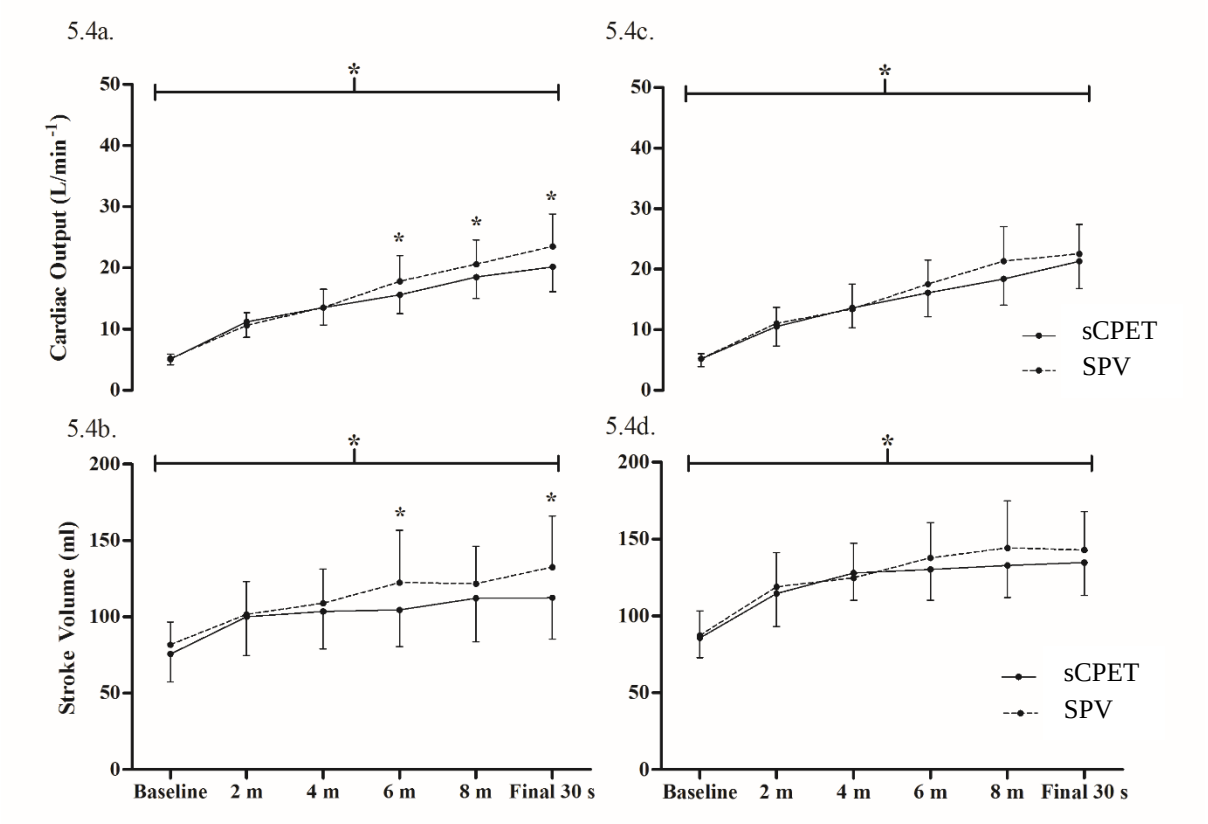

Figure 5.4: Average of Q and SV relative to test time over the sCPET and SPV: a) Q and b) SV for young population, c) Q and d) SV for middle to older aged population. * Main effect ($P < 0.05$). Data are mean $\pm$ SD.

5.4.3. Power output profile

Figure 5.5 displays the mean PO values for each stage of the SPV for both the young and middle to older aged group. Further analysis demonstrated that within stage PO variability in the young group was consistent through the first three stages of the SPV (CV = 3.68%, 2.95%, 2.95%), but increased in stage 4 (CV = 5.79%), with variability being highest in the final stage (CV = 7.72%). In the older age group, the variability of PO was consisted through the first four stages (CV = 3.59%, 3.31%, 2.43%, 3.84%), and increased for the final stage (CV= 6.64%).

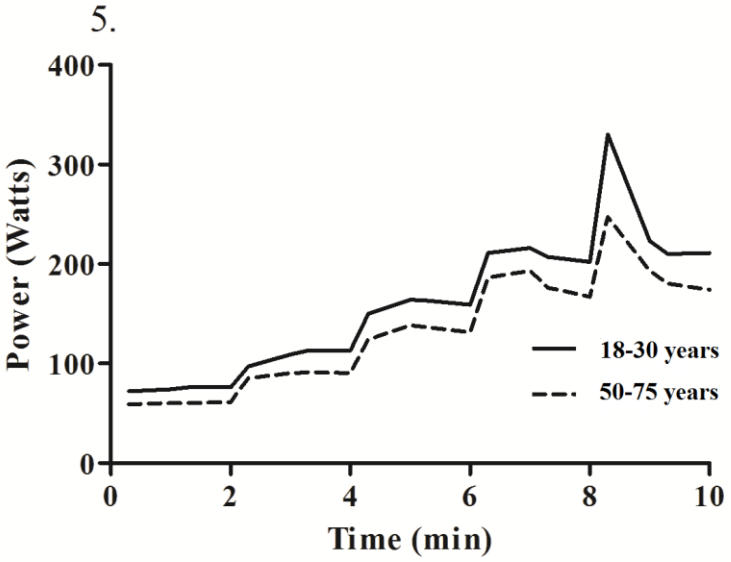

Figure 5.5: Power output profile from the SPV in the young and middle to older aged group.

5.4.4. Gender differences

Some sub-analysis was completed which investigated sex differences, in the young group there was twelve male and ten females. For the male participants there was a 2.22 ml·kg^{-1}·min^{-1} higher $\dot{V}O_{2peak}$ achieved in the SPV vs. the sCPET (P = 0.02), and a 1.69 ml·kg^{-1}·min^{-1} higher $\dot{V}O_{2peak}$ achieved in the SPV vs. the sCPET in the female participants (P = 0.06). In the older age group there were seventeen males and five females. When separating between males and females there were no differences in $\dot{V}O_{2peak}$ between the SPV and the sCPET (P > 0.05).

5.5. Discussion

In support of previous literature (Astorino et al., 2015; Mauger & Sculthorpe 2012; Mauger et al., 2013), the results of the current study demonstrate that younger participants were able to achieve a significantly higher $\dot{V}O_{2peak}$ in the SPV when compared to the sCPET. However, this was not evident in the middle aged to older adult population where there were no differences in $\dot{V}O_{2peak}$ between the two protocols. The results also demonstrate that the SPV produced a higher peak Q and peak SV in the young group, which was statistically different between the SPV and sCPET at the latter stages of the test. No differences for these parameters between tests were seen in the older aged group. The SPV also allowed a higher physiological work rate in both age groups, evidenced by the significantly higher RER and peak PO. These findings suggest that even though both populations achieved a higher work rate in the SPV, this only led to a higher $\dot{V}O_{2peak}$ in the young group. In turn this suggests that the limiting factor to $\dot{V}O_{2peak}$ and the mechanisms behind the SPV may differ between young and older aged populations. Although this may also suggest that PO is not responsible for the differences seen in $\dot{V}O_{2peak}$, in fact previous research has demonstrated that once $\dot{V}O_{2peak}$ has been achieved further increases or even decreases in exercise intensity do not effect these values (Billat, Petot, Karp, Sarre, Morton et al., 2013; Milani, Lavie, Mehra & Ventura 2006). Additionally, the current study also demonstrated a lack of protocol specific patterns of deoxyHB and muscle recruitment of the VL, suggesting that oxygen extraction was not enhanced by the SPV. Mauger et al. (2013) did not measure SV therefore it is possible that the lower HR values seen in their study may have be compensated by a higher SV, which would explain a higher $\dot{V}O_{2peak}$ being achieved, even if HR was lower. This is the first study to assess both the cardiovascular and muscular response to the SPV in comparison to a sRAMP, and also the first to assess the protocol in a middle aged to older adult popultation.

In support of the current study, Astorino et al. (2015) found a significantly higher $\dot{Q}$ and $\dot{V}O_{2peak}$ in the SPV when compared against a standard test. The authors suggested that the higher $\dot{Q}$ during the SPV is responsible for the higher $\dot{V}O_{2peak}$ observed due to an increased oxygen delivery to the working muscles. It is well accepted that there is a strong linear relationship between $\dot{Q}$ and $\dot{V}O_2$, with $\dot{Q}$ being a principal limiting factor for $\dot{V}O_{2peak}$ during whole-body exercise (Bassett & Howley 2000). Therefore, it would be expected that a higher $\dot{Q}$ would result in a greater $\dot{V}O_{2peak}$ being achieved. Results from the current study demonstrate a significantly higher $\dot{Q}$ achieved in the SPV vs. the sCPET in the young, but not in the old aged population. Interestingly, with $\dot{V}O_{2peak}$ only being significantly higher in SPV in the young group, this suggests that $\dot{Q}$ is the primary limiter. The same maximal HR achieved from both protocols suggests that the enhanced $\dot{Q}$ seen in the young group is predominantly the result of the higher SV achieved in the SPV vs. sCPET, although this cannot be confirmed as peak SV and peak HR may not have necessarily occurred at the same time point. Indeed, previous literature has suggested that differences in $\dot{V}O_{2peak}$ between individuals are primarily a result of the differences in maximal SV, as less inter-individual variation is seen in maximal HR (Bassett & Howley 2000). In traditional $\dot{V}O_{2peak}$ tests it is known that SV begins to plateau/fall prior to $\dot{V}O_{2peak}$ being reached, whilst HR continues to increase to maximal level, thus causing a plateau in Q (Mortensen, Dawson, Yoshiga, Dalsgaard, Damsgaard et al., 2005). This demonstrates an impairment of the circulatory system to continue supplying a linear increase in oxygen delivery at higher exercise intensities (Mortensen et al., 2005). The main cause for the plateau/fall in SV is suggested to be predominately attributed to a decrease in diastolic filling time as a result of the increasing HR (Higginbotham, Morris, Williams, McHale, Coleman et al., 1986; Vella & Robergs 2005). From the data presented

in Figure 5.4 it is evident that SV in the young group increases to a greater extent in SPV than the sCPET. A plateau in SV is also evident between the final two time points in the sCPET, which does not seem to occur in the SPV (although there were no significant differences between these two time points). As a result, the increase in Q during the final stage of the SPV test is greater than in the sCPET protocol. In the middle to older aged group a SV plateau is evident in both tests, although in the SPV this appears to be delayed until the fourth time point (6 min), compared to a plateau occurring at approximately 4 min in the sCPET (no significant increase between each successive time point after 4 min; $P > 0.05$). It may be that the self-paced nature of the SPV, particularly in the younger populations, contributes in preventing this early plateauing in SV. This may be a result of participants making self-adjustments in work rate and potentially creating optimal physiological conditions to maintain adequate oxygen delivery. Although at this stage the underlining reasons why this may occur are still unclear, therefore further research is required to understand this.

The middle to older aged participants demonstrated no significant differences in $\dot{V}O_{2peak}$ between the SPV and sCPET protocols. It is likely that the effect of the protocol is reduced in the older group due to their inability to increase Q in response to the increased work rates, as seen in the young group. Indeed, previous research has suggested that Q plateaus at around ~80% of peak PO (Mortensen et al., 2005), and even though in the young group there were no significant differences in Q between the final two stages of the SPV ($P > 0.05$), the pattern of response is not the same as in the sCPET. It is not clear why this differential response has been observed between test protocols. However, interestingly the Q response is similar between protocols in the older group. It is suggested that there are age-related changes which occur in relation to cardiac function in healthy individuals,

in particular these include increased left ventricular wall thickness, changes in diastolic filling, impaired left ventricular ejection fraction, and changes in HR (Lakatta & Levy 2003). All of these changes are known to influence cardiac function (Lakatta & Levy 2003). In particular, diastolic filling time is suggested to be the primary cause of the plateauing that occurs in SV above a certain exercise level (Higginbotham et al., 1986; Vella & Robergs 2005), and with diastolic filling rate progressively slowing with age (Lakatta & Levy 2003), this could be the key reason why the middle to older aged group did not achieve a significantly higher Q and therefore $\dot{V}O_{2peak}$ as seen in the young group. Even though there were no differences in Q in the old group between the two tests, the middle to older aged participants still achieved a higher PO in the SPV vs. the sCPET.

Previous literature has shown the SPV to produce higher $\dot{V}_E$ values when compared to a standard $\dot{V}O_{2peak}$ protocol in young population (Astorino et al., 2015; Faulkner et al., 2015; Hogg et al., 2014; Mauger et al., 2013). Interestingly, studies that demonstrate no difference in $\dot{V}O_{2peak}$ between the SPV and sCPET protocols also failed to find differences in $\dot{V}_E$ (Chidnok et al., 2013; Straub et al., 2014). The greater $\dot{V}_E$ in the young group seen in the current, and previous studies (Astorino et al., 2015; Hogg et al., 2014; Faulkner et al., 2015; Mauger et al., 2013), is likely due to the "all-out" effort required during the final stage (RPE 20) of the test. End-test lactate values (see Table 5.1) suggest that this "all-out" effort results in a greater level of metabolic stress than experienced in sCPET testing. The greater level of acidosis and metabolic buffering would therefore increase the ventilatory response during high intensity exercise (Milani, Lavie, Mehra & Ventura 2006). However, Mauger and Sculthorpe (2012) observed no differences in $\dot{V}_E$ between the tests, although a higher $\dot{V}O_{2peak}$ was still achieved in the SPV. Therefore, it is still

questionable as to whether or not the higher values are predominately a result of an increase in $\dot{V}_E$.

Another speculative, possible contribution to the lack of difference in $\dot{V}O_{2peak}$ for the older group might be a result of the known age-related changes that occur at a muscular level. Research has suggested that there is a reduced muscle oxidative capacity in older populations (Betik & Hepple 2008; Russ & Kent-Braun 2004) due to loss in mitochondrial content and function, and a reduction of muscle volume (Conley, Esselman, Jubriad, Cress, Inglin et al., 2000). This reduced oxidative capacity is likely to affect the a-vO_2 diff, which according to the Fick equation, contributes in the attainment of $\dot{V}O_{2peak}$. Moreover, the distribution of Q may also be altered in older populations. One possibility is that due to the reduced lung performance associated with normal age-related decline (Chaunchaiyakul, Groeller, Clarke & Taylor 2004; Janssens, Pache & Nicod 1999), there is an increase in the oxygen cost of breathing meaning that more Q is needed to be directed the respiratory muscles to support ventilation during exercise (Proctor, Shen, Dietz, Eickhoff, Lawler et al., 1998) which may limit performance. Indeed a 20-30% decrease in leg blood flow during cycling has been shown in older, compared to younger subjects (Proctor, Shen, Dietz, Eickhoff, Lawler et al., 1998). Thus, despite the higher work rate achieved, age-related reductions in leg muscle blood flow may have limited the extent to which work rate could increase, and therefore oxygen consumption. This is evident as the difference in PO between tests was not as great in the middle to old aged (19 W difference), compared to the young (72 W difference) group.

Interestingly, in contrast to the current findings, Chidnok et al. (2013) did not find a higher $\dot{V}O_{2peak}$, $\dot{V}_E$ or end-test blood lactate concentration from a SPV protocol compared to a sCPET test. However, the differences in the outcomes between this and the current study could be attributed to the SPV test protocol designs. As outlined above, the SPV protocol from the current study requires an "all-out" effort to be maintained for the duration of the final stage. This would require pacing on a moment-to-moment basis, rather than pacing the maximal effort (RPE 20) as the highest work rate they could sustain for the duration of the stage, apparently the requirement in the protocol of Chidnok et al. (2013). This fundamental difference between the two test protocols is the likely the reason for the disparity between the findings of the two studies. Indeed, data from the current study demonstrates a mean decrease in PO in the final stage of 120 W for the young group, and 73 W for the older group. In contrast, data from Chidnok's study demonstrate a mean reduction in PO of just 20 W during the final stage of their SPV protocol. Thus, the final stage "all-out" effort might be what is required in order to stimulate the increase in $\dot{V}_E$, and thus $\dot{V}O_2$.

Even though the mean test time for the sCPET protocol in both age groups was between the 'recommended' 8-12 min duration (Buchfuhrer et al., 1983), there was only 55% in the young group and 45% in the older group who completed the test within this time frame. The remaining participants (n = 10 from young, n = 12 from older group) were either < 8 or > 12 min, which may have influenced the results. Further analysis was completed where participants were sub-grouped in to three categories, those who completed the sCPET in < 8 min, 8-12 min and > 12 min. This analysis demonstrated that in the young group there was a greater increase in $\dot{V}O_{2peak}$ from the SPV compared to the sCPET for those who completed the sCPET in < 8 min (2.66 $ml \cdot kg^{-1} \cdot min^{-1}$; P = 0.37) and

> 12 min (3.13 ml·kg^{-1}·min^{-1}; P = 0.02), compared to those who completed between 8-12 min (1.14 ml·kg^{-1}·min^{-1}; P = 0.13). These findings would suggest that test time is in fact an important factor when obtaining optimal $\dot{V}O_{2peak}$ values as suggested by previous work (Buchfuhrer et al., 1983). As a consequence, differences seen in the current study between protocols could be related to participants not completing the sCPET in the "optimal" time. However, it must be noted that there were only three participants in the < 8 min category compared to the seven in the > 12 min category and twelve in the 8-12 min category. Interestingly, in the older aged group there were no significant differences in $\dot{V}O_{2peak}$ between the SPV and the sCPET for the 8-12 min (n = 10) and > 12 min (n = 11) categories (P > 0.05). There was only one participant that completed the test < 8 min but interestingly this individual achieved a 2.19 ml·kg^{-1}·min^{-1} higher $\dot{V}O_{2peak}$ in the SPV vs. the sCPET.

A limitation of the current study is that different cycle ergometers were used to complete the sCPET and SPV. It has previously been suggested that different ergometers might infer differences in metabolic cost and differences in cardiovascular strain (Reiser, Meyer, Kindermann & Daugs 2000). Indeed, various factors like seat angle (Umberger, Scheuchenzuber & Manos 1998), body positioning (Too 1991) and seat to pedal distance (Too 1993) have been show to influence maximal cycling performance. However, different ergometers were a requirement of the different protocols, as the SPV required participants to freely adjust their PO, and the sCPET required accurate fixing of PO. Indeed, a similar magnitude of differences in $\dot{V}O_{2peak}$ to those of the current study have been found by previous studies who used the same cycle ergometer in both SPV and traditional tests (Astorino et al., 2015; Mauger & Sculthorpe 2012). Like the current study, Chidnok et al., (2013) also used different cycle ergometers when making

comparisons between the SPV and sCPET test and found no significant differences in $\dot{V}O_{2peak}$. The authors acknowledge that the use of non-invasive techniques to measure Q and SV have previously been criticised for their lack or accuracy and reliability when compared against more invasive techniques (e.g. direct Fick method) with the typical error being reported to be around 9% for peak Q and SV (Welsman, Bywater, Farr, Welford & Armstrong 2005), therefore caution must be taken when making conclusions with such measures. There is also movement and respiratory artefact associated with exercise which is suggested to affect the results (Siebenmann, Rasmussen, Sorensen, Zaar, Hvidtfeldt et al., 2015). One study also suggested that the Physioflow, in particular, may overestimate exercising Q by 30-50% (Siebenmann et al., 2015). However, other research has demonstrated that non-invasive devices such as the PhysioFlow are a reliable and clinically acceptable measure of Q and SV in adults during exercise (Charloux, Lonsdorfer-Wolf, Richard, Lampert, Oswald-Mammosser et al., 2000; Richard, Lonsdorfer-Wold, Charloux, Doutreleau, Buchheit et al., 2001). Nevertheless the authors accept that caution must be taken when making conclusions with such measures.

The SPV allows participants to freely adjust both resistance and cadence. Previous research has suggested that large variations in cadence could influence the muscle blood flow and Q response to exercise (Gottshall, Bauer & Fahmer 1996). Thus any differences in cadence between SPV and sCPET protocols may have influenced the current results. However, the study by Gottshall and colleagues (1996) was completed at submaximal steady state exercise, and we are unaware of any studies which presented similar data obtained during maximal incremental exercise. Therefore, it is difficult to determine whether cadence differences were a confounding variable within our study. However, the overall mean cadence from both test protocols were very similar in the young (sCPET 76

rev.min^{-1}; SPV 78 rev.min^{-1}) and identical in the middle to older aged group (77 rev.min^{-1}) and so therefore it is unlikely to have had a substantial influence on the results.

5.6. Conclusion

In agreement with the findings of previous research, the current study demonstrates that the SPV produces higher $\dot{V}O_{2peak}$ values compared to a sCPET protocol in a young healthy adult population. In this population, the data suggests that the higher $\dot{V}O_{2peak}$ in the SPV protocol is likely the result of an increase in the oxygen delivery (increased Q and $\dot{V}_E$), rather than a result of any increase or change in the oxygen extraction at a muscular level. In contrast, no differences in $\dot{V}O_{2peak}$ between the SPV and sCPET protocols were seen in a middle aged to older adult population, despite a higher RER and PO being achieved in the SPV. The reasons for this are unclear, although age-related changes in the physiological response to exercise are a possible explanation for the differences in the response to the SPV protocol between the age groups. It was originally hypothesised that the SPV would produce a higher $\dot{V}O_{2peak}$, oxygen delivery and enhanced oxygen extraction at the working muscles in both the young vs older aged population ($H3_1$, $H4_1$), but due to the lack of differences seen in the older aged group the null hypotheses $H3_0$, and $H4_0$ are accepted. Nonetheless, these findings suggest that the SPV helps participants achieve both a physical and physiological workload that is closer to maximum, when compared to a sCPET protocol. Whilst this is manifested as a higher $\dot{V}O_{2peak}$ in young populations, a similar $\dot{V}O_{2peak}$ is observed in middle to older aged populations. Therefore, this study demonstrates that the SPV is a valid determinant of $\dot{V}O_{2peak}$ in both young and older adults (null hypothesis $H2_0$ can be rejected), and produces a cardiovascular response

closer to maximal. This finding is particularly important for the overall aim of this thesis, as it provides confidence that the SPV be can effectively and safely used in an older population, which reflects the ages of those who undertake preoperative CPET. However, it is acknowledged that specific patient groups with varying degree of limitations to exercise may respond differently to the SPV.

What is already known about this topic

- Some studies have shown the SPV to produce higher $\dot{V}O_{2peak}$ values when compared against sCPET protocols. Although reasons behind this higher $\dot{V}O_{2peak}$ is unclear.
- Previous work has shown that cardiac output is higher in the SPV compared to a sCPET, suggesting that there is an increase in oxygen delivery. It has also been suggested that SPV may enhance oxygen extraction at the working muscles as a result of the self-paced nature and the ability to make slight fluctuations in work rate.
- More of an mechanistic explanation and understanding of the SPV was yet to be identified

What this study adds

- In younger populations, the SPV produces higher $\dot{V}O_{2peak}$ values as a result of an increase in oxygen delivery. However, likely due to age-related differences in the physiological responses to exercise, the middle to older aged group achieved similar $\dot{V}O_{2peak}$ values, regardless of them reaching higher workloads.
- This study shows that the SPV is a valid test of exercise capacity in a healthy middle aged to older adult population.

Chapter 6. Reliability and validity of a self-paced $\dot{V}O_{2peak}$ test in post-MI patients

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Aspects of the following chapter have been included within the following manuscript: Jenkins LA., Mauger A., Fisher, J. and Hopker JG. (2017). Reliability and validity of a self-paced cardiopulmonary exercise test in post-MI patients. International Journal of Sports Medicine, 38(4):300-306.

6.1. Abstract

The SPV has been shown to produce higher $\dot{V}O_{2peak}$ values compared to sCPET, but has not been tested on any clinical population. This study aimed to assess the validity and reliability of the SPV in post Myocardial Infarction (post-MI) patients. Twenty-eight post-MI patients completed one sCPET and two SPV in a randomised, counterbalanced crossover design. The SPV consisted of 5 × 2-min stages where participants were able to self-regulate their effort by using incremental 'clamps' in RPE (11, 13, 15, 17 and 20). The sCPET consisted of a 20 W/min ramp. Results demonstrated the SPV to have a coefficient of variation for $\dot{V}O_{2peak}$ of 8.2%. The limits of agreement were ± 4.22 $ml \cdot kg^{-1} \cdot min^{-1}$, with intraclass correlation coefficient of 0.89. There was a significantly higher $\dot{V}O_{2peak}$ achieved in the SPV (23.07 ± 4.90 $ml \cdot kg^{-1} \cdot min^{-1}$) against the sCPET (21.29 ± 4.93 $ml \cdot kg^{-1} \cdot min^{-1}$). We conclude the SPV is a safe, valid and reliable method for determining exercise capacity in post-MI patients.

6.2. Introduction

As previously described, CPET derived parameters have been shown to be strongly correlated with overall health status and mortality, and can therefore provide valuable diagnostic and prognostic information for various patient populations (Albouaini et al., 2007; Buys Cornelissen, Van De Bruaene, Stevens, Coeckelberghs et al., 2011; Kristensen, Knuuti, Saraste, Anker, Botker et al., 2014; Myers et al., 2002). The identification of $\dot{V}O_{2peak}$ from CPET has become a fundamental procedure when assessing cardiorespiratory fitness, monitoring exercise intensity (Bassett & Howley 2000) and when risk stratifying individuals prior to major surgical procedures (Beckles, Spiro, Colice & Rudd 2003). Moreover, exercise testing soon after a Myocardial Infarction (MI) is beneficial as it can provide information on a patient's future risk of a subsequent cardiac event (Davidson & DeBusk 1980) and can be used in individualising exercise rehabilitation programmes (Markiewicz, Houston & DeBusk 1977).

A number of studies have assessed the validity of the SPV in 'healthy populations' (Chidnok et al., 2013; Mauger & Sculthorpe 2012; Mauger et al., 2013; Straub et al., 2014), however no research has investigated whether or not the SPV can be used in clinical populations. Therefore, the aim of this study was to investigate the reliability and validity of the SPV in a stable clinical population (early post-MI patients).

6.3. Methods

6.3.1. Participants

Twenty-eight post-MI patients (2 females, 26 males) undergoing cardiac rehabilitation volunteered to participate (age = 58 ± 8 yr, weight = 89.5 ± 12 kg, stature = 178 ± 8 cm, BMI = 28.2, days from MI event = 57 ± 35). All patients recruited for the study already had their coronary angiogram and any interventions needed following their MI, and were thought to require no further intervention or revascularisation. All patients gave their written informed consent.

6.3.2. Experimental Procedures

All patients were required to complete three exercise tests (a sCPET and two SPV tests) in order to determine the tests' validity and reliability. The order in which the patients completed the tests was in a randomised, counterbalanced crossover design (the repeated SPV was always completed in the third visit). Each test was separated by at least 24 h and all tests were completed at the same time of the day (± 2 h). Participants were asked to refrain from drinking alcohol (24 h abstinence), eating (2 h abstinence), smoking (2 h abstinence), and not to perform any exercise in the 24 h prior to each test. Prior to the main test patients were required to complete a 5-min warm-up at a self-selected intensity during which they were also familiarised with the process of freely adjusting their PO on the cycle ergometer.

6.3.3. SPV protocol

The SPV was completed on an air-braked cycle ergometer (Wattbike Trainer, UK), which allowed patients to continually vary their PO throughout the test. The SPV was conducted

in accordance with the procedures previously outlined in the general methods section (Chapter 3).

6.3.4. Standard CPET protocol

The sCPET was completed on an electro-magnetically braked cycle ergometer (Lode Corival), so that PO for each stage could be fixed according to the test requirements. The test followed a standard incremental ramp design. As previously used with other clinical populations, the test commenced with no resistance and continuously increased by 20 $W \cdot min^{-1}$, standardized across all patients (Brutsche, Spiliopoulos, Bolliger, Licker, Frey et al., 2000, Eindhoven, van den Bosch, Oemrawsingh, Baggen, Kardys et al., 2016, Gitt, Wasserman, Kilkowski, Kleemann, Kilkowski et al., 2002, Kahaly, Wagner, Nieswandt, Mohr-Kahaly & Ryan 1999). The test was stopped when the patient felt like they could no longer continue or maintain more than 60 rpm, despite verbal encouragement.

6.3.5. Physiological Measures

Expired gases, HR, PO and cadence were continuously recorded during the tests. A 12-lead ECG was also recorded through the duration of the test. $\dot{V}O_{2peak}$, AT, peak PO and peak $\dot{V}_E$ were all determined using the methods stated in Chapter 3. The AT was successfully determined in all patients.

6.3.6. Statistical analysis

Test-retest reliability was assessed via the use of 95% LOA using Bland-Altman plots (Bland & Altman 1986), 95% CI of the CV, and ICC (Hopkins 2001) were calculated to

assess the variability of the repeated tests. Differences in $\dot{V}O_{2peak}$, peak PO, AT, peak HR and peak $\dot{V}_E$ were compared from the 1st SPV test to those obtained from the sCPET, using a paired-samples t-test. Complete 2nd SPV test data was not achieved for three of the patients, and so only data from SPV1 has been used in these cases. The reasons for these three missing tests were; one patient had an unrelated illness and was unable to attend their final test within the required timeframe; the other two miscalculated their work rate during the RPE 17 stage causing a premature end to the test. The data of these two patients who did not meet the test requirements for SPV2 has been excluded from the main analysis, but complete data is also presented within the results section.

6.4. Results

The CV for $\dot{V}O_{2peak}$ between SPV1 and SPV2 was 8.2% (95% CI: 6.6-10.9%). Therefore, if a patient achieved a $\dot{V}O_{2peak}$ of 23 $ml \cdot kg^{-1} \cdot min^{-1}$ a typical variation of 1.9 $ml \cdot kg^{-1} \cdot min^{-1}$ would be expected. The ICC was 0.89, this represents a questionable to high level of agreement. The LOA was ± 4.22 $ml \cdot kg^{-1} \cdot min^{-1}$ for the measure of SPV1 and SPV2 (Figure 6.1). If we include the SPV2 data for the two patients who were excluded from the main analysis, the CV becomes 8.4% (95% CI: 6.8-11%), the ICC is unchanged, and the LOA become ± 4.52 $ml \cdot kg^{-1} \cdot min^{-1}$.

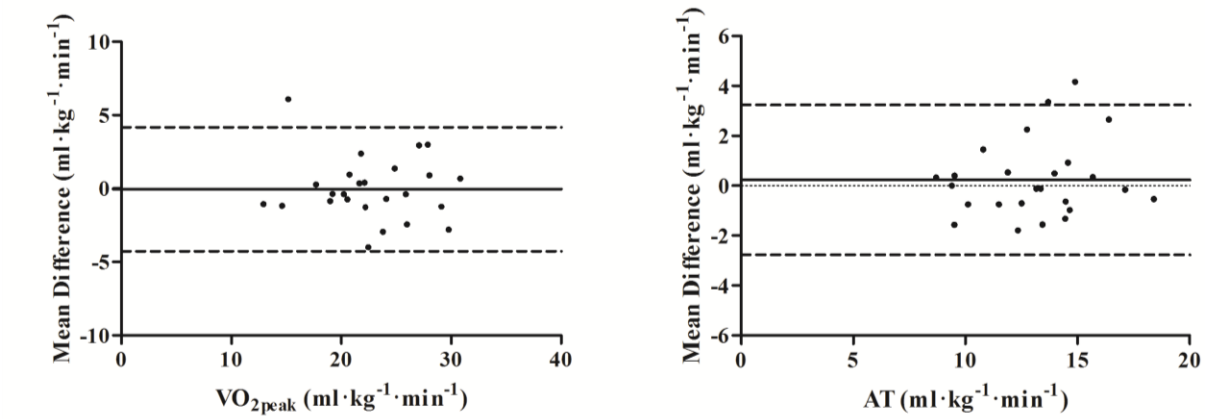

Figure 6.1. Bland-Altman plots of differences in $\dot{V}O_{2peak}$ between SPV1 and SPV2 (left graph); and differences in AT between SPV1 and SPV2 (right graph). The solid horizontal line represents mean difference, whilst the dashed lines represent the 95% LOA.

The CV for AT between SPV1 and SPV2 was 8.4% (95% CI: 6.8-11.2%). The ICC was 0.86. The LOA was ± 3 ml·kg^{-1}·min^{-1} for the measure of SPV1 and SPV2 (Figure 6.1). If we include the SPV2 data for the two patients who were excluded from the main analysis, the CV for AT becomes 8.6% (95% CI: 7-11.4%), the ICC is 0.84, and the LOA remain unchanged. There was a CV of 15.1% (95% CI: 12.1-20.4%) for peak PO, 4.7% (95% CI: 3.8-6.5%) for peak HR, and 11.5% (95% CI: 9.2-15.4%) for peak $\dot{V}_E$. The ICC for these three variables were 0.83 for PO, 0.87 for HR, and 0.85 for $\dot{V}_E$, demonstrating an acceptable to high level of agreement (Vincent 1994, referenced by Atkinson & Nevill 1998).

As shown in Table 6.1, patients achieved a significantly higher $\dot{V}O_{2peak}$ ($P < 0.01$) in the SPV compared with the sCPET. Patients also achieved a significantly higher peak PO, peak HR and peak $\dot{V}_E$ in the SPV than in the sCPET ($P < 0.01$). There were no significant

differences in AT between the SPV and the sCPET ($P > 0.05$). Figure 6.2 shows the $\dot{V}O_2$ response over time, in the two SPVs and sCPET, of a representative patient. When subgrouping the patients into their genders, $\dot{V}O_{2peak}$ was higher in the SPV vs. the sCPET, although there were only two females recruited for this current study.

Table 6.1: Physiological variables over the sCPET, SPV1 and SPV2 in post-MI patients.

	sCPET (n = 28)	**SPV1 (n = 28)**	**SPV2 (n = 25)**
$\dot{V}O_{2peak}$ ($L \cdot min^{-1}$)	1.90 ± 0.50	2.05 ± 0.48*	2.00 ± 0.43
$\dot{V}O_{2peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	21.29 ± 4.93	23.07 ± 4.90*	22.68 ± 4.79
AT ($ml \cdot kg^{-1} \cdot min^{-1}$)	12.63 ± 2.41	13.06 ± 2.39	13.21 ± 2.76
HR (bpm)	129 ± 18	138 ± 14*	136 ± 19
$\dot{V}_E$ ($L \cdot min^{-1}$)	82.0 ± 27.1	94.5 ± 25.9*	91.1 ± 26.2
Peak PO (W)	171 ± 43	209 ± 78*	200 ± 64
TTE (secs)	535 ± 130	600 ± 0*	600 ± 0

*significantly different from the sCPET (< 0.05), data are mean ± SD.

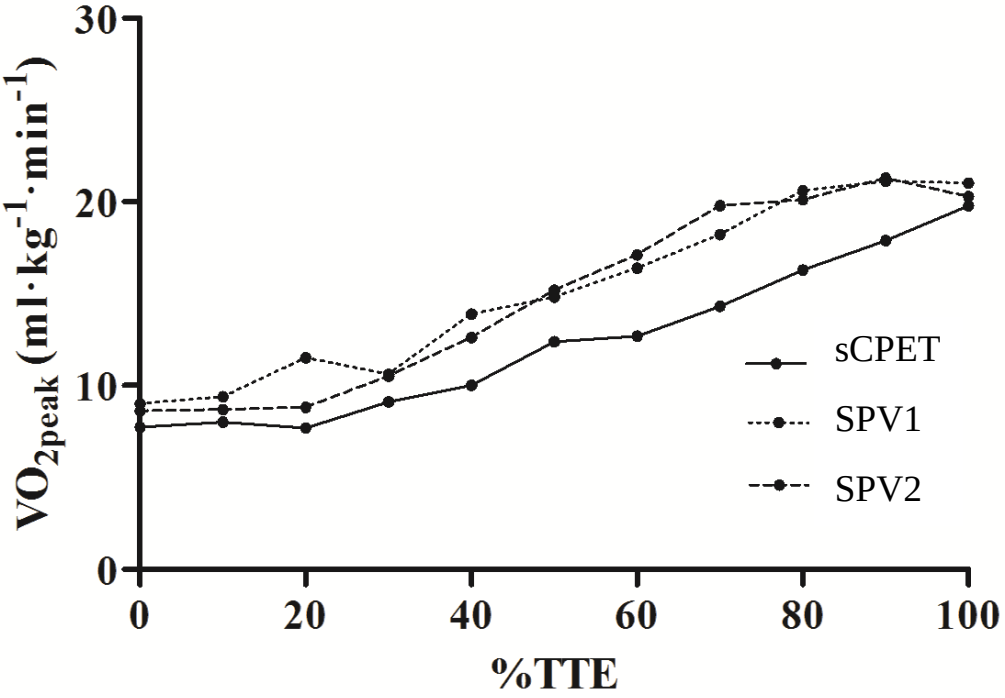

Figure 6.2. $\dot{V}O_2$ response over % of time to exhaustion (TTE) in the sCPET and both SPVs in a representative patient.

Table 6.2 displays PO variability within each stage of both repeated SPVs. In SPV1, it appears that as mean PO increased with each stage of the protocol, the within stage variability also increased, with the highest variability in the final stage. In SPV2, PO variability remained consistent through the first four stages of the test, with a large increase in the final stage.

Table 6.2: Mean PO and the variability within each stage of SPV1 and SPV2 in post-MI patients.

		Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Mean ± SD	**SPV1**	49 ± 2	74 ± 2	103 ± 4	132 ± 8	145 ± 15
	SPV2	42 ± 1	60 ± 2	89 ± 2	125 ± 4	153 ± 16
CV (%)	**SPV1**	3.67 (3.28-4.2)	3.07 (2.75-3.52)	4.78 (4.28-5.48)	5.88 (5.26-6.75)	11.11 (9.9-12.79)
	SPV2	3.34 (2.99-3.83)	3.29 (2.94-3.76)	3.33 (2.98-3.81)	2.96 (2.65-3.38)	16.77 (14.91-19.37)

6.5. Discussion

This is the first study to assess the SPV on a clinical population. The results of the current study demonstrated the SPV to be a valid and reliable indicator of $\dot{V}O_{2peak}$ in post-MI patients. The CV for $\dot{V}O_{2peak}$ in the post-MI patients was 8.2%. In addition, post-MI patients achieved a higher $\dot{V}O_{2peak}$ in the SPV compared to a sCPET protocol, which is in agreement with previous studies on healthy populations (Mauger & Sculthorpe; Mauger et al., 2013). Previously published studies have investigated the reproducibility of physiological variables using sCPET protocols. Froelicher et al. (1974) found that when using three popular maximal exercise treadmill protocols in a healthy population the CV for $\dot{V}O_{2peak}$ ranged from 4.1-5.8%. In addition, one study completed a succession of CPET tests on cardiac failure patients and reported the average CV for $\dot{V}O_{2peak}$ to be 5.7% (Janicki, Gupta, Ferris & McElroy 1990). Other studies have reported "good" test-retest reliability (CV for $\dot{V}O_{2peak}$ = 3.5-6.9%) during cycling MIE tests in patients with various respiratory conditions (Cox et al., 1989; Marciniuk et al., 1993; McKone et al., 1999). CV values from previous research investigating the reliability of traditional protocols are lower than those from the post-MI group of the current study. However, it is difficult to make direct comparisons between studies as different patient populations were used.

Our results demonstrated a CV for AT of 8.4%, which is considered as acceptable for test-retest reliability in clinical populations (Myers, Goldsmith, Keteyian, Brawner, Brazil et al., 2010). Kothmann et al. (2009) found a CV of 10% for AT in Abdominal Aortic Aneurysm (AAA) patients using a sCPET protocol. Identification of AT from CPET has become an increasingly important tool in clinical exercise testing, primarily due to it giving an objective assessment of cardiopulmonary function which does not require high levels of effort (Older et al., 1999). Previous literature has demonstrated AT to be a useful predictor of mortality in patients with chronic heart failure. This information can then be used to help prioritise patients for heart transplantation (Gitt et al., 2002). The identification of AT prior to major surgery has also been shown on a number of occasions to closely correlate with post-operative outcome (Older, Hall & Hader 1999; Wilson, Davies, Yates, Redman & Stone 2010). It is reassuring to see that in the current study there were no differences in AT when comparing it between the SPV and the sCPET ($P > 0.05$), this combined with the reliability results demonstrate that AT can be reliably determined via the SPV, which is of great importance in clinical exercise testing.

As previously mentioned, two post-MI patients were excluded from the main reliability analysis as they did not successfully complete a second SPV due to misjudging the required work rate during stage RPE 17. One of the key benefits associated with the SPV is the fixed test duration, as this aims to ensure that enough exercise data is always obtained, although this was not the case for these two patients which raises questions over its presumed benefit in clinical populations, especially if they are inactive and unfamiliar to exercise. However, it is interesting to note that this miss-pacing occurred on both of

the patients second SPV. It is possible to speculate that from completing the previous two tests (sCPET and SPV1), the patients may have potentially gained confidence in their own ability which may have resulted in them attempting to push harder, but ultimately resulting in them overshooting the work rates. Nevertheless, both patients did provide enough data to demonstrate a valid AT during SPV2.

In agreement with data from a healthy population (Mauger & Sculthorpe 2012), post-MI patients achieved a significantly higher $\dot{V}O_{2peak}$ (+8%) during the SPV compared with the sCPET ($P < 0.01$). Peak HR and $\dot{V}_E$ were also significantly higher in the SPV than in the sCPET ($P < 0.01$), which is in support of previous work (Faulkner et al., 2015; Hogg et al., 2014; Mauger et al., 2013). It is interesting to see that previous studies which failed to find any differences in $\dot{V}O_{2peak}$ between the SPV and a sCPET protocol also found no differences in HR and $\dot{V}_E$ (Chidnok et al., 2013; Straub et al., 2014), potentially leading to the observed differences in $\dot{V}O_{2peak}$. A recently published study (Astorino et al., 2015) found significantly higher maximal HR and cardiac output during the SPV compared to a sCPET protocol (Astorino et al., 2015). Astorino et al. (2015) concluded that the greater cardiac output in the SPV suggests a greater oxygen delivery to the exercising muscles, permitting a higher $\dot{V}O_{2peak}$ to be achieved. These findings suggest that the SPV allows individuals to work to a higher physiological work rate when compared to the sCPET. This may be a result of the nature of self-paced exercise providing a more comfortable experience for patients. Being able to make slight adjustments in effort may minimise fatigue and any peripheral discomfort associated with cycling, particularly in the early stages of the test, which may ultimately lead to a greater work rate being able to be achieved in the final stage (Astorino et al., 2015). In traditional CPET no adjustments in*

effort can be made and the only way to stop any exercise related discomfort would be to stop. With all of this in mind, the current findings suggest that in a clinical population, where cardiac function might be limited, the self-paced nature may in fact provide the patient the opportunity to work harder, producing a greater cardiac output and therefore reaching a higher $\dot{V}O_{2peak}$. However, further research is required to support this speculation.

The mean sCPET time-to-exhaustion was 8 min 55 secs (range = 5 min – 12 min 54 sec) compared to the fixed 10 min of the SPV. Even though the sCPET mean test time falls within those previously recommended times of 8-12 min (Buchfuhrer et al., 1983), only 15 (of 28) participants successfully completed the test within this recommended time. Therefore, the lower $\dot{V}O_{2peak}$ in the sCPET could be attributable to only 54% achieving the recommended test time. For the nine patients who completed the sCPET in < 8 min, there was a 2 $ml \cdot kg^{-1} \cdot min^{-1}$ higher $\dot{V}O_{2peak}$ in the SPV ($P = 0.10$). The fifteen patients who completed the sCPET between 8-12 min, demonstrated a 2.14 $ml \cdot kg^{-1} \cdot min^{-1}$ significantly higher $\dot{V}O_{2peak}$ in the SPV compared to the sCPET ($P < 0.01$). Finally, there were only four patients who completed the sCPET in < 12 min so statistical differences were not tested, although interestingly the $\dot{V}O_{2peak}$ values were very similar between the SPV (26.87 ± 4.53 $ml \cdot kg^{-1} \cdot min^{-1}$) and sCPET ($26.97 \pm 2.79$ $ml \cdot kg^{-1} \cdot min^{-1}$). In this population it appears that slightly longer test times in a sCPET are more beneficial to obtaining higher $\dot{V}O_{2peak}$ values. This is supported by findings from Agostoni et al., (2005), who concluded that $\dot{V}O_{2peak}$ in heart failure patients is lowest when CPET is completed in 5 min, compared to 10 and 15 min. Agostoni et al. demonstrated the highest $\dot{V}O_{2peak}$ values occurred during CPETs of 15 min duration.

A potential limitation of the current study was that we decided to standardize sCPET work rate increments (20W/min) for all patients (Brutsche, Spiliopoulos, Bolliger, Licker, Frey et al., 2000; Eindhoven, van den Bosch, Oemrawsingh, Baggen, Kardys et al., 2016; Kahaly, Wagner, Nieswandt, Mohr-Kahaly & Ryan 1999) instead of doing so on an individual basis (Myers et al., 1991; Myers et al 2002). Individualising work rate increments may have resulted in more patients completing the CPET within the recommended time frame, although the subjectivity of such a choice would not have guaranteed a successful test in all patients. This issue clearly highlights one of the key challenges practitioners face on a day-to-day basis when using CPET with clinical populations. Indeed, if patients are unable to exercise for a sufficient time the utility of test results is severely limited, resulting in a significant waste of finance and time for both patients and health service provider. The SPV eliminates the need to estimate the most appropriate starting intensity and work rate increments as it is based on set levels of perceived exertion. Moreover, the closed loop nature of the SPV ensures that each test lasts 10 min. Thus, a protocol like the SPV may be a more reliable way of acquiring time efficient and useable data than sCPET methods.

The significantly higher PO achieved in the SPV suggests that regardless of the self-paced nature, participants were willing to tolerate significantly higher work rates in the final stage (RPE 20), compared to that demanded by the sCPET. Knowledge of the test end-point in the SPV vs the open-ended sCPET could contribute to the higher tolerance in work rate. Indeed, previous literature has demonstrated that knowledge of exercise duration can improve exercise performance (Mauger, Jones & Williams 2009). It could

also be suggested that the SPV provides patients with a more "comfortable" experience, as they are able to self-adjust their work rate, potentially making the higher perceived work rates more tolerable, especially when the end is proximate. If patients are aware of this prior to testing then they may be more 'willing' to complete the test.

Further analysis demonstrated that during both SPVs, within stage PO variability was greatest at higher work rates. However, variability increased through each stage of SPV1, but in SPV2 PO variability remained fairly consistent through the first four stages, with a large increase in the final stage. This might suggest a slight behaviour change in how the SPV is paced when completed for a 2nd time. Patients demonstrated what might be considered to be a more "cautious" pacing strategy in SPV2. To further support this point, a higher $\dot{V}O_{2peak}$, HR, $\dot{V}E$ and PO was achieved in the first completed SPV compared to SPV2. This pattern was also seen in study 1 (Chapter 4). In Chapter 4 it was suggested that there might be potential behaviour changes associated with completing the SPV, and that participants may protect themselves in repeated tests to avoid any discomfort they experienced in the first test. Thus, familiarisation sessions for the SPV may have a negative impact on subsequent SPV tests and could have been a contributing factor for the discrepancies reported in previously published literature (Astorino et al., 2015; Faulkner et al., 2015; Mauger et al., 2013; Mauger & Sculthorpe 2012; Chidnok et al., 2013; Straub et al., 2013).

As well as the comparative physiological data, it was also important to determine patient views on the different test designs they experienced. Twelve patients stated that they preferred the sCPET, twelve preferred the SPV and four stated that they didn't have a

preference. Some of the common patient reasons for preferring the sCPET was that they found it hard to judge effort when using RPE in the SPV, others stated that they preferred the simplicity of the traditional test and that all they needed to focus on was maintaining their cadence, a few participants also stated that they preferred the sCPET because it felt easier. Common reasons for preferring the SPV were that patients favoured having control over their work rate, that they found the SPV more interesting and more realistic, and that they felt like they had worked harder. Previous research has suggested that an individual's preferred test may result in a higher $\dot{V}O_{2peak}$ being obtained (Hanson et al., 2016; Straub et al., 2014). When separating the patients in current study into groups based upon their preferred test (sCPET or SPV), $\dot{V}O_{2peak}$ was still significantly higher in SPV1 compared to the sCPET ($P < 0.05$). However, there was a bigger difference for those patients who preferred the SPV (2.11 $ml \cdot kg^{-1} \cdot min^{-1}$) to those who preferred the sCPET (1.56 $ml \cdot kg^{-1} \cdot min^{-1}$). Unlike previous findings (Hanson et al., 2016; Straub et al., 2014), it is interesting to note that regardless of preference, this clinical population achieved a higher $\dot{V}O_{2peak}$ in the SPV. Interestingly, those patients who preferred the SPV achieved a similar $\dot{V}O_{2peak}$ in SPV1 compared to SPV2, but those who preferred the sCPET had a lower $\dot{V}O_{2peak}$ in SPV2 compared to SPV1, and not significantly different from the sCPET ($P > 0.05$). It is possible to speculate that those patients who did not prefer the SPV, may have been less willing/motivated to push as hard in SPV2, which resulted in the lower $\dot{V}O_{2peak}$. Participants were also asked which test they felt like they worked harder in, with majority of participants stating it to be the SPV (50%) compared to the sCPET (29%), the remaining 21% said that they felt the tests were equal. Interestingly 71% of participants stated that the SPV made them feel like they had control, with 61% of these stating that they felt this was an important factor to maximal exercise testing. These anecdotal reports suggest that even though the feedback was very diverse, the majority of the participants

felt like they worked harder in the SPV, even though they had control over their own work rate. This again provides some support to the notion that, regardless of the self-paced nature of the exercise, participants were willing to work at higher exercise intensities than encountered during sCPET.

There were no adverse events reported for the current study, providing support for the current evidence base that maximal exercise testing is a safe procedure to perform on cardiac patients (Balady et al., 2010; Kanthan, Tan, Zecchin & Denniss 2012; Roffi, Wenaweser, Windecker, Mehta, Eberli et al., 2003).

It should be noted that a limitation of the current study is that different cycle ergometers were used to complete the sCPET and SPV. It has previously been suggested that different ergometers might infer differences in metabolic cost and differences in cardiovascular strain (Reiser, Meyer, Kindermann & Daugs 2000). Indeed, various factors like seat angle (Umberger, Scheuchenzuber & Manos 1998), body positioning (Too 1991), and seat to pedal distance (Too 1993) have been shown to influence maximal cycling performance. The two different ergometers were necessary to support the demands of the different exercise protocols; the SPV required participants to freely adjust their PO where as the sCPET required PO to be accurately fixed at a given exercise intensity. Even though this limitation means that between test comparisons -should be treated with caution, it does not deter from the findings that the SPV is both a reliable and safe test for use in the clinical population used in this study.

6.6. Conclusion

The results of the current study demonstrate that the SPV has acceptable levels of reliability for determining $\dot{V}O_{2peak}$ in post-MI patients. The SPV also allowed post-MI participants to achieve a significantly higher $\dot{V}O_{2peak}$ than the sCPET. This study suggests that the SPV is a safe, valid and reliable measure of $\dot{V}O_{2peak}$ in a clinical population, and should be considered as an accepted means of testing for exercise capacity. These findings mean that the null hypothesis $H5_0$ stated earlier in this thesis can be rejected, and the alternative hypothesis $H5_1$ can be accepted. Moreover, the defined test duration and self-administered work rates associated with the SPV addresses common issues that clinicians regularly have to overcome, and go some way to ensuring all patients exercise for the recommended duration in order to obtain a valid and reliable CPET. Future research should seek to assess the SPV in other clinical populations and the utility of the SPV versus sCPET to inform clinical decision making on patient treatment.

What is already known about this topic

- The SPV is a valid test of exercise capacity in healthy young and older aged individuals, although it had not been tested on any clinical population.

What this study adds

- This study shows that the SPV can be used as a valid CPET in post-MI patients. Repeated tests showed the SPV to have acceptable levels of reliability for the key CPET derived variables.

Impact on clinical practice

- With the defined test duration and self-administered work rates, the SPV may address common issues that clinicians regularly face, for example it takes away the need to choose the most appropriate work rate increments. The fixed test length may also improve the efficiency of running busy clinics. Finally a test which will always acquire 10 minutes of exercise data may reduce the risk of obtaining invalid data from tests which do not last long enough.

Chapter 7. The use of self-paced CPET protocol in preoperative assessment and its ability to predict postoperative outcome in patients undergoing major elective surgery

7.1. Abstract

CPET has become an essential tool used in preoperative assessment, although the standard protocol used has been scrutinised over the years. The SPV attempts to overcome some of those issues associated with sCPET. This study aimed to determine if the SPV can assess patient's preoperative risk similar to sCPET and if exercise variables obtained from the test can accurately predict post-operative outcome. Fifty patients with cardiovascular related co-morbidities completed one sCPET and one SPV in a randomised, counterbalanced crossover design, although only thirty of those patients went ahead with surgery. After surgery patients were monitored for incidence of morbidity on postoperative days 3 and 5, length of hospital stay, and incidence of mortality in the 30 days after surgery. The fifty patients achieved a significantly higher $\dot{V}O_{2peak}$, HR, $\dot{V}_E$, peak PO and TTE in the SPV compared to the sCPET ($P < 0.05$). Logistic regression analysis demonstrated that for the thirty patients who had surgery, none of the CPET variables were associated with postoperative morbidity at either day 3 or 5 ($P > 0.05$). Although when combining postoperative morbidity at days 3 and 5, logistic regression analysis showed that oxygen pulse at AT obtained from the SPV was significantly related to postoperative complications ($P < 0.05$). Receiver operator characteristic (ROC) curve analysis demonstrated oxygen pulse at AT to provide an AUC of 0.72 a.u. (95%CI 0.51 to 0.92), with an optimal cut-off point of 8.5 $ml \cdot beat^{-1}$ which provided 72.7% sensitivity and 71.4% specificity. To conclude the SPV was able to assess preoperative fitness comparable to the sCPET. Although, none of the CPET variables were associated with postoperative morbidity which is a likely result of the small sample size.

7.2. Introduction

As described earlier in this thesis, CPET is an increasingly popular tool used in preoperative assessment (Smith et al., 2009), this is because it provides an objective assessment of a patient's ability to cope with the metabolic demands of major surgery (Hopker et al., 2011). Major surgery is suggested to place high amount of stress on a patient's cardiopulmonary reserve (Forshaw et al., 2008), which increases the requirement for oxygen (Lees et al., 2009). To match this elevated demand, increases in cardiac output and/or oxygen extraction need to occur (Forshaw et al., 2004), failure to do so results in oxygen debt and therefore tissue hypoxia. Ultimately, an inability to meet the demands of major surgery can lead to systemic inflammation, organ dysfunction and ultimately death (Lees et al., 2009). Therefore, using a dynamic test that can objectively assess a patient's ability to deal with increased oxygen demands is seen as a valid approach to risk stratify patients preoperatively. Specific CPET derived variables have been demonstrated to be strong predictors of postoperative outcome, in particular $\dot{V}O_{2peak}$, AT and $\dot{V}_E/\dot{V}CO_2$ at AT have been associated with postoperative outcome (Junejo et al., 2012; West et al., 2014; West et al., 2016). As previously mentioned, there are some disadvantages associated with traditional methods to CPET, which the SPV attempts to overcome.

The SPV has now been shown to be a valid test of exercise capacity in both healthy (Astorino et al., 2015; Faulkner et al., 2015; Mauger and Sculthorpe 2012; Mauger et al., 2013) and clinical populations (Chapter 6). The benefit of such a test in a clinical setting is that regardless of fitness levels, all patients are exercised for 10 min, this may reduce

the risk of acquiring unusable data from tests that do not last long enough. The test also takes away the need of practitioners having to decide on the most suitable work rate increments to ensure an optimal test which lasts for the recommended time period. The nature of SPV may also been deemed as a more 'patient-friendly' test, due to the self-administered work rates and ability to adjust this throughout. Therefore, the aim of the current study is to determine if the SPV can assess a patient's preoperative risk similar to sCPET and if key exercise variables obtained from the test can accurately predict post-operative outcome, like the sCPET has previously been shown to do.

7.3. Methods

7.3.1. Patients

Sixty-four patients with cardiovascular related co-morbidities, who were considered for any elective surgery at East Kent Hospitals University NHS Foundation Trust, volunteered to participate in the study. Patients were excluded if they were unable to successfully complete both CPET, and excluded from the outcome analysis if they did not end up having surgery. All patients gave their written informed consent after reading the participant information sheet.

7.3.2. Experimental Design

All patients recruited for the study were required to complete two exercise tests, a sCPET and the SPV in a randomised, counter-balanced crossover design. Tests were separated

by 2-7 days to allow the patient full recovery, and were completed at the same time of day (± 2 h). Prior to each test patients were asked to refrain from drinking alcohol (24 h abstinence), eating (2 h abstinence), smoking (2 h abstinence), and instructed not to perform any exhaustive exercise in the 24 h prior to each test.

7.3.3. SPV

The SPV was completed on an air-braked cycle ergometer (Wattbike Trainer, UK), which allowed patients to continually vary their PO throughout the test. The SPV was conducted in accordance with the procedures outlined in Chapter 3. Patients were able to view their cadence and PO throughout the test, they also received feedback on elapsed time particularly when approaching the end of each stage. Verbal encouragement was given, particularly in the latter stages of the test.

7.3.4. sCPET

The sCPET was completed on an electro-magnetically braked cycle ergometer (Lode Corival), so that PO for each stage could be fixed according to the test requirements. The test followed a standard incremental ramp design, where PO gradually increased at a continuous rate whilst cadence was kept constant (60-80 rpm). The test commenced with a 2 min rest period, followed by a 3 min unloaded pedalling phase, which then continues straight into the ramp protocol. The protocol consisted of increments of either 5, 10, 15 or 20 $W \cdot min^{-1}$ which was selected on an individual basis in the attempt to optimise the protocol for each patient. Patients were asked to continue pedalling until they reached volitional exhaustion, or, the test was terminated by the tester when the patient could no

longer keep their cadence at or above 60 rpm for more than 5 s. During the test, patients were asked to rate their RPE every 2 min. Verbal encouragement was given in the latter stages of the test.

7.3.5. Preoperative measurements

Patient characteristics recorded on the first test included age, gender, stature, weight, surgery type, surgical severity, and the Portsmouth physiological and operative severity score (POSSUM; Copeland et al., 1991). Surgical severity was categorised into either minor, moderate, major or major complex which were selected following the guidelines for the POSSUM scoring system. A resting lung function test was also performed to determine forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) (MircoLab Mk8 Spirometer, CareFusion). Resting lung function was conducted in accordance to the recommendations (Miller, Hankinson, Brusasco, Burgos, Casaburi et al., 2005), they were completed in a seated position and repeated at least 3 times. During both CPETs, expired gases were measured. HR, 12-lead ECG (Custo Cardio 130, Germany), blood pressure, pulse oximetry were also continuously recorded during each test. Ventilatory and gas exchange variables derived from expired gases included $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$, $\dot{V}_E/\dot{V}O_2$, $\dot{V}_E/\dot{V}CO_2$, $\dot{V}O_2$/HR, and RER. After the test, $\dot{V}O_{2peak}$, AT, Peak cycling PO and $\dot{V}_E$ were all determined as per the methods stated in chapter 3. Once each test had finished patients postoperative 30 day mortality risk was calculated via the Carlisle mortality calculator (Carlisle, Danjoux, Kerr, Snowden & Swart 2015) which can be accessed through the following link: https://sites.google.com/site/informrisk/home (Carlisle 2016). This calculator uses age, stature, weight, body mass index (BMI), preoperative haemoglobin and creatinine concentrations, previous medical history

(including; MI, heart failure, stroke and peripheral arterial disease), CPET variables (including; ẆO2peak, VO2 at AT, $\dot{V}_E/\dot{V}CO_2$ at AT and peak PO), and the risk for the type of surgery. Inputting the above variables produces an individualised 30 day mortality risk. The AT was successfully determined in both sCPET and SPV protocols in all but one patient. It is likely that this patient's tolerance to exercise in both sCPET and SPV was below their AT.

7.3.6. Postoperative measurements

Patients were monitored for the thirty days after surgery for incidence of morbidity, length of ICU stay, total hospital stay and mortality. Morbidity was determined at days 3 and 5 using the 9 domains defined by the Post-Operative Morbidity Survey (POMS) (Bennett-Guerrero, Welsby, Dunn, Young, Wahl et al., 1999), these days were selected based on previous research (Grocott, Browne, Van der Meulen, Matejowsky, Mutch et al., 2007). All postoperative information was obtained via patient records, nurses/doctors notes, drug charts, fluid charts and discharge summaries.

7.3.7. Statistical Analysis

Continuous variables are either reported as mean and SD for normally distributed data, or median and interquartile range (IQR) for not normally distributed data, distribution was determined via the Shapiro-Wilk test. Categorical variables are presented at frequency (%). Differences in the CPET variables between the two protocols were analysed using a paired samples T-test, or a Wilcoxon signed rank test for not normally distributed data. Receiver operator characteristic (ROC) curves were plotted for $\dot{V}O_{2peak}$,

AT, $\dot{V}_E/\dot{V}CO_2$ at AT, oxygen pulse at AT, and PO to assess their independent ability to discriminate between patients with and without morbidity at the specific postoperative days. Optimal cut-off points were taken as the uppermost left point on the ROC curve, this method was chosen to replicate those previous studies that looked at the predictability of CPET on postoperative outcome (West et al., 2014; West et al., 2016). A variable was considered able to discriminate between patients if the area under the curve (AUC) was > 0.7. Simple univariate logistic regression was used to initially assess the relationship between CPET variables and morbidity, variables with p > 0.250 (West, Asher, Browning, Minto, Swart et al., 2016) were excluded from a multiple logistic regression model. Linearity of the logit of each variable were initially checked to ensure the assumptions of logistic regression were not violated, this was assessed by checking that the interaction between each CPET predictor variable and its log transformation was not significant (> 0.05). Multicollinearity was also checked, to ensure the predictor variables were not too highly correlated, by obtaining the tolerance and VIF statistic from a linear regression analysis (Field 2009).

7.4. Results

Fourteen patients were unable to successfully complete both exercise tests, reasons for this included; unable to pedal due to orthopaedic discomfort, muscular weakness and general discomfort on the cycle ergometer, two patients become ill between tests, there were equipment issues meaning the second test for one patient could not be completed in the recommended time frame, and one patient had a vasovagal episode at submaximal exercise, and was subsequently referred to a cardiologist for further investigations. Out

of the fifty patients who successfully completed both tests, thirty of them had surgery. Table 7.1 presents the patient characteristics, which is then grouped into those with and without postoperative complications at day 3 (with = 11; without 19) and day 5 (with = 7; without 23).

Fifteen patients (50%) experienced in-hospital morbidity at day 3 and/or 5. Eight patient were readmitted to Hospital on a median of 11 days, reasons included; gastrointestinal, infectious, cardiovascular and wound complications. Two out of the eight patients who were readmitted required further surgery. One patient required laparoscopic adhesiolysis and decompression of the small bowel, and one other patient required surgical debridement and evacuation of haematoma. Both of these patients had no further complications after this. One patient died on day 17, this occurred one day after their hospital discharge so there is no information about the cause of death in their health records. However, whilst in hospital this patient did experience various complication (pulmonary, gastrointestinal, cardiovascular, haematological and infectious), and was readmitted after their initial discharge due to wound dehiscence which required further surgery. This particular patient had a $\dot{V}O_{2peak}$ of 11.91 $ml \cdot kg^{-1} \cdot min^{-1}$ and and AT of 9.09 $ml \cdot kg^{-1} \cdot min^{-1}$ in the sCPET, and $\dot{V}O_{2peak}$ of 13.23 $ml \cdot kg^{-1} \cdot min^{-1}$ and AT of 9.63 $ml \cdot kg^{-1} \cdot min^{-1}$ from the SPV. These values are lower than the average values obtained by the patients in this study, but interestingly their surgical risk was only calculated as 0.6% and 0.5%. As there was only one reported death, mortality could not be used as an outcome measure.

Table 7.1. Patient demographics and postoperative morbidity at day 3 and day 5. Note: the patients split into day 3 and 5 are not the same, some patients only had morbidity in one of those days, with only 3 patients having morbidity on both.

	Overall (n = 50)	Patients who had surgery (n = 30)			
		Day 3 Morbidity		Day 5 Morbidity	
		Yes (n = 11)	No (n = 19)	Yes (n = 7)	No (n = 23)
Age	73 ± 8	73 ± 7	73 ± 9	76 ± 9	72 ± 8
Sex					
Male	32 (64%)	5 (45%)	13 (68%)	4 (57%)	14 (61%)
Female	18 (36%)	6 (55%)	6 (32%)	3 (43%)	9 (39%)
Body mass index (kg/m^2)	29 ± 5	30 ± 5	28 ± 4	27 ± 3	29 ± 5
Haemoglobin	13 ± 1.8	12 ± 2	13 ± 2	12 ± 1	13 ± 2.
Creatinine	87 (72-106)	87 (76-127)	83 (70-93)	83 (68-87)	87 (71-107)
FEV_1	2.19 ± 0.66	2.01 ± 0.64	2.34 ± 0.65	1.97 ± 0.66	2.29 ± 0.65
FVC	3.12 ± 0.80	3.00 ± 0.81	3.23 ± 0.87	2.75 ± 1.00	3.26 ± 0.77
Co-morbidity					
Ischaemic heart disease	29 (58%)	7 (64%)	12 (63%)	2 (29%)	17 (74%)
Heart failure	11 (22%)	5 (45%)	1 (5%)	0 (0%)	6 (26%)
Cerebrovascular disease	4 (8%)	0 (0%)	1 (5%)	0 (0%)	1 (4%)
Diabetes	15 (30%)	4 (36%)	7 (37%)	2 (29%)	9 (39%)
Hypertension	24 (48%)	6 (54%)	10 (53%)	7 (100%)	9 (39%)
COPD	5 (10%)	2 (18%)	4 (21%)	1 (14%)	5 (22%)
Surgical risk					
0Minor	2 (4%)	0 (0%)	2 (11%)	0 (0%)	2 (9%)
Moderate	11 (22%)	1 (9%)	3 (16%)	2 (29%)	2 (9%)
Major	28 (56%)	8 (73%)	12 (63%)	4 (57%)	16 (70%)
Major complex	9 (18%)	2 (18%)	2 (11%)	1 (14%)	3 (13%)
P-POSSUM					
Mortality (%)	2 (1-6)	3 (1-8)	2 (1-3)	2 (1-6)	2 (1-6)
Morbidity (%)	40 (24-61)	54 (33-88)	34 (14-48)*^	39 (15-72)	39 (21-61)

*Significantly different from patients with morbidity on the same day. ^Significantly related to morbidity obtained from univariate logistic regression.

7.4.1. Differences between the sCPET and SPV

Differences in the CPET variables between the SPV and sCPET are displayed in table 7.2. Patients achieved a significantly higher $\dot{V}O_{2peak}$ ($L \cdot min^{-1}$ and $ml \cdot kg^{-1} \cdot min^{-1}$), AT, HR, $\dot{V}_E$, $\dot{V}_E/\dot{V}CO_2$ at AT, peak PO and TTE in the SPV compared to the sCPET ($P < 0.05$), and when considering only those patients who had surgery there were differences in $\dot{V}O_{2peak}$, HR, $\dot{V}_E$, peak PO and TTE ($P < 0.05$). Further analysis was completed where males and females were separated. For the thirty-two male patients, there was a significantly higher $\dot{V}O_{2peak}$ in the SPV (16.63 ± 3.83 $ml \cdot kg^{-1} \cdot min^{-1}$) compared to the sCPET (14.97 ± 4.05 $ml \cdot kg^{-1} \cdot min^{-1}$) ($P < 0.01$). Although for the eighteen female patients, there were no significant differences in $\dot{V}O_{2peak}$ between the SPV (13.22 ± 2.87 $ml \cdot kg^{-1} \cdot min^{-1}$) and the sCPET ($12.78 \pm 3.05$ $ml \cdot kg^{-1} \cdot min^{-1}$) ($P = 0.34$).

Table 7.2. Represents the CPET derived variables over both the sCPET and SPV.

	Total (n = 50)			**Patients who had surgery (n = 30)**		
	sCPET	**SPV**	**P-Value**	**sCPET**	**SPV**	**P-Value**
$\dot{V}O_{2peak}$ ($L \cdot min^{-1}$)	1.17 ± 0.35	1.28 ± 0.38*	< 0.01	1.18 ± 0.34	1.27 ± 0.39*	< 0.01
$\dot{V}O_{2peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	14.18 ± 3.84	15.40 ± 3.86*	< 0.01	14.52 ± 3.71	15.49 ± 3.62*	0.018
AT ($ml \cdot kg^{-1} \cdot min^{-1}$)	10.06 ± 1.98	10.49 ± 2.00*	0.017	10.23 ± 2.14	10.60 ± 1.90	0.118
HR (bpm)	123 ± 20	127 ± 20*	< 0.01	124 ± 18	128 ± 17*	0.051
$\dot{V}_E$ ($L \cdot min^{-1}$)	49.9 ± 15.4	56.9 ± 19.1*	< 0.01	49.8 ± 14.9	56.4 ± 19.5*	< 0.01
RER	1.17 ± 0.12	1.18 ± 0.13	0.416	1.16 ± 0.09	1.17 ± 0.13	0.663
$\dot{V}_E/VO_2$	29.1 ± 4.4	29.5 ± 4.8	0.429	29.5 ± 4.2	29.5 ± 4.1	0.974
$\dot{V}_E/\dot{V}CO_2$	31.6 ± 4.0	32.6 ± 5.2*	0.049	32.0 ± 4.1	33.0 ± 4.5	0.103
O_2 pulse at AT ($ml\ beat^{-1}$)	8.8 ± 2.0	9.0 ± 2.1	0.095	8.8 ± 1.8	8.9 ± 1.9	0.793
Peak PO (W)	81 ± 33	99 ± 45*	< 0.01	83 ± 33	98 ± 42*	< 0.01
TTE (secs)	478 ± 131	600 ± 0*	< 0.01	501 ± 129	600 ± 0*	< 0.01
Carlisle Mortality (%)	2.5 ± 2.4	2.6 ± 2.9	0.333	2.1 ± 2.3	2.2 ± 2.1	1.000
Carlisle Mortality adjusted for BMI (%)	1.9 ± 2.2	1.9 ± 2.2	0.793	1.4 ± 2.0	1.6 ± 2.0	0.414

*significantly different to sCPET.

7.4.2. Postoperative Morbidity

ROC curve analysis indicated no CPET variables from either test demonstrated the ability to independently discriminate between patients with and without morbidity at either postoperative day 3, or day 5 (AUC < 0.7). Simple univariate logistic regression analysis indicated that for the sCPET, peak PO and oxygen pulse at AT on postoperative day 3 were suitable for a multivariate regression model ($P < 0.250$), and for day 5 $\dot{V}O_{2peak}$ ($L \cdot min^{-1}$) and peak PO ($P < 0.250$). For SPV, the variables of $\dot{V}O_{2peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$) and oxygen pulse were deemed suitable for a multivariate regression model at day 3, with AT and peak PO for day 5 ($P < 0.250$). A multivariate logistic regression model of those variables which were deemed suitable was not statistically significant for the sCPET at day 3 ($\chi^2(2) = 1.961$, $p = 0.375$) and day 5 ($\chi^2(2) = 3.570$, $p = 0.168$), or SPV at day 3 ($\chi^2(2) = 2.396$, $p = 0.302$) and day 5 ($\chi^2(1) = 1.796$, $p = 0.183$).

When combining postoperative morbidity at day 3 and 5, the proportion of patients with morbidity increased to 50%. Simple logistic regression analysis of this combined data indicated that for the sCPET, $\dot{V}O_{2peak}$ ($L \cdot min^{-1}$), peak PO, and $\dot{V}_E/\dot{V}CO_2$ at AT were suitable for a multivariate regression model ($P < 0.250$), and $\dot{V}O_{2peak}$ ($L \cdot min^{-1}$), peak PO and oxygen pulse at AT were suitable from the SPV ($P < 0.250$). For the sCPET variables, the multivariate regression model was not statistically significant ($\chi^2(3) = 4.740$, $p = 0.192$). For the SPV variables, there was a trend in the model predicting postoperative morbity ($\chi^2(3) = 7.094$, $p = 0.069$), with oxygen pulse at AT being a statistically significant contributor to the model (odds ratio (OR) = 0.328, 95%CI 0.119 to 0.904; $p = 0.031$). This analysis therefore suggests that for every unit decrease in oxygen pulse at

AT, the odds of having postoperative morbidity increased by 3.049. Within this combined data, oxygen pulse at AT from the SPV test, was the only variable to be associated with morbidity according to ROC curve analysis. The oxygen pulse at AT provided an AUC of 0.72 a.u. (95%CI 0.51 to 0.92), with an optimal cut-off point of 8.5 ml·beat^{-1} which provided 72.7% sensitivity and 71.4% specificity (figure 7.1). Oxygen pulse at AT was also dichotomized with the cut-off point of 8.5 ml beat^{-1}, this slightly improved the model fit of the logistic regression model ($\chi^2(3) = 7.488$, $p = 0.058$), and also its independent contribution to the model (OR = 0.030, 95%CI 0.001 to 0.705; p = 0.029).

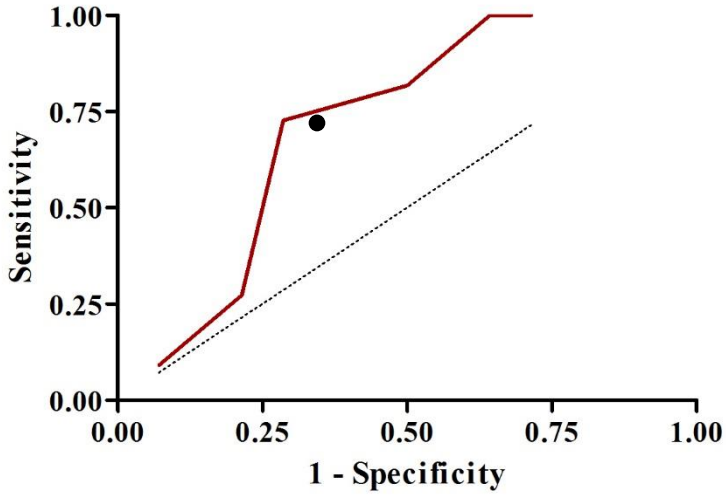

Figure 7.1. Receiver operating characteristic (ROC) curve for oxygen pulse at AT. Black circle indicates the optimal cut-off point obtained by minimizing the distance to the upper left corner. Area under the curve: 0.72 a.u..

There were no significant differences in CPET derived variables between those patients with postoperative morbidity and those without (P > 0.05). Although there was a trend in peak PO from the sCPET (P = 0.052), patients with morbidity achieved a lower peak PO (72 ± 27 W) compared to those without (95 ± 35 W), see table 7.3.

Table 7.3. CPET derived variables between patients with and without morbidity and both day 3 and 5. Differences between the two tests (sCPET vs. SPV), and presence of complication were assessed (no complications vs. complications).

	No complications (n = 15)		**Complications (n = 15)**	
	sCPET	**SPV**	**sCPET**	**SPV**
$\dot{V}O_{2peak}$ ($L \cdot min^{-1}$)	1.28 ± 0.36	1.37 ± 0.38	1.09 ± 0.30	1.17 ± 0.32*
$\dot{V}O_{2peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	15.21 ± 3.81	16.15 ± 3.59	13.83 ± 3.59	14.84 ± 3.66
AT ($ml \cdot kg^{-1} \cdot min^{-1}$)	10.38 ± 2.08	10.87 ± 2.01	10.08 ± 2.27	10.33 ± 1.81
HR (bpm)	123 ± 17	126 ± 15	125 ± 20	130 ± 19
$\dot{V}_E$ ($L \cdot min^{-1}$)	52.9 ± 15.2	58.2 ± 20.6	46.6 ± 14.3	54.7 ± 18.9*
RER	1.16 ± 0.08	1.15 ± 0.10	1.15 ± 0.11	1.19 ± 0.15
$\dot{V}_E/VO_2$	28.6 ± 3.8	29.1 ± 4.7	30.4 ± 4.7	29.8 ± 3.5
$\dot{V}_E/\dot{V}CO_2$	31.1 ± 3.3	32.2 ± 4.6	33.0 ± 3.3	33.8 ± 3.1
O_2 pulse at AT ($ml\ beat^{-1}$)	9.2 ± 2.1	9.6 ± 2.1	8.5 ± 1.3	8.1 ± 1.2
Peak PO (W)	95 ± 35	107 ± 44	72 ± 27	89 ± 40*
TTE (secs)	484 ± 99	600 ± 0*	518 ± 179	600 ± 0
Carlisle Mortality (%)	2.3 ± 2.6	2.2 ± 2.4	2.2 ± 1.6	2.1 ± 1.4
Carlisle Mortality adjusted for BMI (%)	1.7 ± 2.4	1.7 ± 2.4	1.5 ± 1.2	1.5± 1.0

*Significant difference between tests ($P < 0.05$). No significant differences between those with and without complications ($P > 0.05$).

7.4.3. Length of hospital stay

None of the CPET derived variables were correlated with ICU stay, although there were only two patient who required ICU postoperatively. Some CPET variable were associated

with HDU stay; sCPET oxygen pulse at AT was negatively correlated (r = -0.547, p = 0.005), and; SPV $\dot{V}O_{2peak}$ ($L \cdot min^{-1}$) (r = -0.379, p = 0.045) and oxygen pulse at AT (r = -0.489, p = 0.013) was negatively correlated. Total length of hospital stay was negatively correlated with $\dot{V}O_{2peak}$ ($L \cdot min^{-1}$ and $ml \cdot kg^{-1} \cdot min^{-1}$) ($r$ = -0.534, p = 0.002; r = -0.475, p = 0.008), AT (r = -0.363, p = 0.049) and peak PO (r = -0.535, p = 0.002) from the sCPET. $\dot{V}O_{2peak}$ ($L \cdot min^{-1}$) (r = -0.366, p = 0.047) and PO (r = -0.436, p = 0.016) from the SPV were also negatively correlated with total length of hospital stay.

7.5. Discussion

The main findings of this study suggests that the SPV produces significantly higher $\dot{V}O_{2peak}$, $\dot{V}_E$, HR and peak PO values when compared against the sCPET ($P < 0.05$), these findings support previous work using self-paced protocols (Astorino et al., 2015; Mauger and Sculthorpe 2012; Mauger et al., 2013). None of the CPET derived variables from either test were associated with days 3 or 5 postoperative morbidity, although when combining both days oxygen pulse at AT obtained from the SPV was associated with postoperative morbidity ($P < 0.05$), suggesting an optimal cut-off point of 8.5 ml $beat^{-1}$. This suggests that a greater sample size was indeed needed to provide a statistical significance, and perhaps a larger sample size may be found some more statistical significances. A sample size of one hundred patients was originally planned, which was based upon the work of Nagamatsu, Shima, Yamana, Fujita, Shirouzu et al., 2001, although due to the allocated time frame and resources available this was unable to be met.

CPET derived variables from both sCPET and SPV protocols failed to demonstrate an ability to predict postoperative outcome at either day 3 or 5. These findings are in contrast to previous research, that have suggested V̇O2peak and AT are predictors of post-operative outcome (Junejo et al., 2012; West et al., 2014; West et al., 2016). A recent multi-centre study has found $\dot{V}O_{2peak}$ and AT predict the risk of postoperative complications in patients having major elective colorectal surgery (West et al., 2016). Other research has identified the predictive ability of CPET in a variety of other major surgery types such as lung resection (Walsh, Morice, Putnam, Nesbitt, McMurtrey et al., 1994) and bariatric surgery (McCullough, Gallagher, deJong, Sandberg, Trivax et al., 2006). In particular, patients with a $\dot{V}O_{2peak}$ of > 20 $ml \cdot kg^{-1} \cdot min^{-1}$ have no increased risk of postoperative complications, whereas a $\dot{V}O_{2peak}$ of < 15 $ml \cdot kg^{-1} \cdot min^{-1}$ is perceived as an increased risk, with a $\dot{V}O_{2peak}$ of < 10 $ml \cdot kg^{-1} \cdot min^{-1}$ being a very high risk for postoperative complications (Beckles et al., 2003). It has also been suggested that patients with an AT of < 11 $ml \cdot kg^{-1} \cdot min^{-1}$ are at increased risk of postoperative complications and should be admitted to ICU after surgery (Older et al., 1993; Older et al., 1999). It is likely that the current study failed to demonstrate the same predictive ability of CPET as a result of the low sample size. A sample size calculation based on the odds ratios achieved from the univariate logistic regression for $\dot{V}O_{2peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$) and the probability of morbidity occurring at day 3 (37%), suggested 94 patients would be needed for the sCPET, and 40 for the SPV to achieve a statistical significance of < 0.05 and a power of 0.95. This lower sample needed for the SPV would suggest that there is less variability when looking at the predictability of $\dot{V}O_{2peak}$ on postoperative morbidity compared to $\dot{V}O_{2peak}$ from the sCPET. Indeed, not all studies have found CPET to be related to outcome (Forshaw, Strauss, Davies, Wilson, Lams et al., 2008; Nugent, Riley, Megarry,

O'Reilly, MacMahon et al., 1998), although it was concluded by Nugent et al. (1998) that a major limitation of their study was the small sample size (n = 30), which is comparable to that of the current study. In addition, it may be that CPET is not as useful predictor of outcome in all surgery types. Previous research has shown no predictive ability of CPET derived variables on postoperative outcome in surgeries such as oesophagectomy (Forshaw et al., 2008). It is possible that the suitability of CPET as a predictor for outcome may have influenced the current study findings, particularly as a wide range of surgeries were included, with 20% of these being either minor or moderate risk procedures which were classified using the POSSUM scoring system (Copeland et al., 1991). However, Forshaw et al. (2008) did find a significant difference in $\dot{V}O_{2peak}$ between patients with postoperative complications and those without ($P < 0.05$), again suggesting the lack of sample size might have reduced the predictive power of the CPET.

To increase the total sample size, morbidity cases were combined from days 3 and 5. The resultant statistical analysis demonstrated oxygen pulse at AT obtained from the SPV was associated with postoperative morbidity, suggesting an optimal cut-off point of 8.5 ml $beat^{-1}$. Previous research has also demonstrated that oxygen pulse at AT is able to discriminate patients with and without postoperative complications with an optimal cut-off point of 8.7 (West et al., 2016). However, oxygen pulse at AT has not always been shown to predict postoperative complications (West, Lythgoe, Barben, Noble, Kemp et al., 2014), with some studies not even including it as a predictor (Junejo et al., 2012; Prentis, Trenell, Vasdev, French, Dines et al., 2013). It is interesting to see that only oxygen pulse at AT from the SPV was the only CPET variable related to postoperative morbidity in the current study. Though not significant, oxygen pulse was lower in the SPV compared to the sCPET in those patients with days 3 and 5 morbidity, and because

there were no differences in $\dot{V}O_2$ at AT between the tests, this suggests that HR at the point of AT may have been enhanced to account for the lower oxygen pulse achieved in the SPV. Therefore it may well be that the self-paced nature provides an altered oxygen pulse response, although this is highly speculative with further research needed to investigate this further.

Unsurprisingly, total length of hospital stay was significantly different between those with postoperative morbidity (7 ± 5 days) compared to those without (3 ± 3 days) ($P < 0.05$). More interestingly, length of hospital stay was correlated with $\dot{V}O_{2peak}$, AT, and peak PO from the sCPET, and $\dot{V}O_{2peak}$ and peak PO from the SPV ($P < 0.05$). However, these results should be interpreted with caution as there are many contributing factors which influence a patient's length of hospital stay that may not necessarily be related to postoperative morbidity (Prentis et al., 2013). For example, a patient's hospital stay may be prolonged due issues such as lack of transport, insufficient care at their home or even what day of the week the surgery took place.

The significantly higher $\dot{V}O_{2peak}$ from the SPV seen in the current study, support those studies which also compared the SPV with sCPET protocols (Astorino et al., 2015; Mauger and Sculthorpe 2012; Mauger et al., 2013). Astorino and colleagues (2015) suggested that this enhanced $\dot{V}O_{2peak}$ seen in the SPV is a result of an increase in oxygen delivery (Q), which is likely to be in response to the greater work rates achieved. These greater work rates achieved in the final stage are suggested to be a result of participants adequately pacing their effort to minimise fatigue, particularly in the earlier stages of the test, and possibly preserving the use of type II fibres until the final stage (Astorino et al.,

2015). It is difficult to determine if this is the reason for the increase $\dot{V}O_{2peak}$ in the current study due to the lack of other physiological measures taken, although a greater peak PO, HR and $\dot{V}_E$ was achieved in the SPV compared to the sCPET, which suggest a higher physiological work load was achieved. Another potential reason for this difference in $\dot{V}O_{2peak}$ could be related to test time. Current guidelines suggest that for optimal $\dot{V}O_{2peak}$ values to be achieved, an individual must reach volitional exhaustion between 8-12 min (Buchfuhrer et al., 1983), although it is acknowledged that this is not widely supported and may differ between populations. Nevertheless, if you look the current study's mean test time for each patient, only 54% of patients completed the test within this 'recommended' time frame. Whereas all patient's completed 10 min of exercise for the SPV, thus this increased test time may have contributed to the enhanced $\dot{V}O_{2peak}$ achieved from the SPV in the current study. Interestingly when subgrouping patients based on their sCPET test time, a significantly higher $\dot{V}O_{2peak}$ was achieved in the SPV for those who completed the sCPET in < 8 min and between 8-12 min ($P < 0.05$), with the greatest difference in the < 8 min category (2.10 $ml \cdot kg^{-1} \cdot min^{-1}$). There were only two patients who completed the sCPET in > 12 min but interestingly these two patients demonstrated a 2.53 $ml \cdot kg^{-1} \cdot min^{-1}$ higher $\dot{V}O_{2peak}$ in the sCPET compared to the SPV. As previously reported by Agostoni et al. (2005), these findings might suggest that longer tests durations of the sCPET are beneficial to obtaining higher $\dot{V}O_{2peak}$ values in an older clinical population.

An interesting finding of the current study was that there was significant difference in $\dot{V}O_{2peak}$ between the two test protocols in males ($P < 0.01$), but no differences in females ($P = 0.34$). This might suggest that the SPV is more beneficial for male populations, with potential explanations being both physiological and/or psychological. For example, there

are known physiological differences between the sexes in maximal Q and SV, being lower in females (Ogawa, Spina, Martin, Kohrt, Schechtman, Holloszy & Ehsani 1992). Research has also suggested that there is a greater age-related decrease in peak torque at fast velocities in females compared to males, which is predominantly a result of the loss in type II fibres (Lindle, Metter, Lynch, Fleg et al., 1997). From a psychological perspective, previous research has suggested that sedentary middle-aged (45-64 years) males generally have a higher self-efficacy compared to females of a similar age (McAuley, Courneya & Lettunich 1991), where age has been shown to be negatively related to self-efficacy (Wilcox & Storandt 1996). This could be a likely contributing factor to results of the current study, particularly as the mean age of the female cohort was 73 ± 9 years. However, it should be acknowledged that there was a lower sample size for women (n = 18) compared to the male patients (n = 32) in the current study.

Even though statistically different, the mean difference in $\dot{V}O_{2peak}$ from sCPET and SPV was only ~1 $ml \cdot kg^{-1} \cdot min^{-1}$. It is debatable whether this statistical difference is actually clinically meaningful and would alter clinical decision making. Furthermore, when using the Carlisle mortality calculator (Carlisle et al., 2015), there were no differences in estimated postoperative 30-day mortality risk between the SPV and sCPET ($P > 0.05$). Thus, the difference in $\dot{V}O_{2peak}$ observed between the two CPET protocols did not influence risk stratification and thus suggests that the SPV can assess patient postoperative mortality risk, comparable to that of the sCPET. The Carlisle mortality calculator has been previously shown as a valid tool for survival estimates which is comparable to Kaplan-Meier estimates (Carlisle et al., 2015). However, the validity analysis was only completed on patients who were considered for AAA repair, so it is unclear if it can be applied to other surgery types.

7.5.1. Limitations

The current study used the POMS to assess postoperative morbidity (Grocott et al., 2007). The POMS surveys nine domains of postoperative morbidity (pulmonary, infectious, renal, gastrointestinal, cardiovascular, neurological, haematological, wound, and pain), with specific defined criteria for each domain (Grocott et al., 2007). A number of preoperative CPET studies have used POMS to define postoperative morbidity (Junejo et al., 2012; West et al., 2014; West et al., 2016), and it is said to be the only published prospective method for describing short-term morbidity (Grocott et al., 2007). However, a limitation of the POMS is that it does not necessarily capture the severity of postoperative complications. The Dindo-Clavien classification system is a 5 grade system which defines severity of complications (Dindo, Demartines & Clavien 2004). Previous research have used the Dindo-Clavien classification when looking at the predictability of CPET derived variables on postoperative complications (Prentis et al., 2013; West et al., 2014; West et al., 2016). It may have been beneficial to use this severity classification in the current study to determine if CPET variables from the SPV could predict the severity of complications, although the aim of this initial study was to simply determine the presence of morbidity.

Another limitation of the current study is that the POMS scores were not completed by the medical staff whilst patients were in-hospital, rather, scores where collected retrospectively once the patient had been discharged with the information being obtained via patient medical records. Unfortunately, the hospital used for the research study does not use the POMS as a post-operative complication scoring system and so it is not possible

to collate data whilst the patient was in hospital. As a consequence there is a heavy reliance on patient's in-hospital notes being fully completed by the appropriate medical staff. If complications were not mentioned in the patient's notes it had to be assumed that there were no POMS present. Nevertheless, a robust assessment was completed for each patient, where their daily notes, fluid balance charts, pathology results, and medicinal prescription charts were reviewed on each pre-selected postoperative day. An additional POMS limitation was that scores were only recorded on postoperative days 3 and 5. This may have resulted in some complications being missed in the intervening days, although previous studies have used similar methods (Bennett-Guerrero et al., 1999; Grocott et al., 2007; West et al., 2016).

A further limitation was that the CPET results were not blinded from the multidisciplinary team. Therefore perioperative management might have been influenced by the CPET results and ultimately influenced postoperative outcome. This decision was taken due to CPET providing information about a patient's risk that fed into the hospital risk assessment process. Finally, there was a median of 45 (range = 17-67) days between patients first CPET and their surgery. This is comparable to a median of 56 days reported by Hartley, Pichel, Grant, Hickey, Lancaster et al. (2012). However, having the shortest possible time between CPET and surgery will likely enhance its predictive ability as the results will be more indicative of the patient fitness level at the time of surgery. In this regard, some previous research that demonstrated predictability of CPET derived variables on postoperative outcome documented CPET being completed approximately 2 weeks before surgery (Colson, Baglin, Bolsin & Grocott 2012; Junejo et al., 2012; Nagamatsu et al., 2001, Older et al., 1999; Tolchard et al., 2014). Although, it is also important to note that some studies investigating the predictive power of CPET do not

mention the length of time between exercise test and surgery (Forshaw et al., 2008; Nugent et al., 1998; Older et al., 1993; West et al., 2016).

7.6. Conclusion

The current study demonstrates that none of the CPET derived variables from either test were associated with postoperative morbidity in patients with cardiovascular related co-morbidities. However when combining patients with complications at day 3 and 5, to increase the sample size, oxygen pulse at AT obtained from the SPV was associated with postoperative morbidity. The lack of significance seen in the other CPET derived variables is a likely result of the small sample size and varied surgery types included, nevertheless, previous research has demonstrated the ability of sCPET derived variables to predict postoperative outcome. In addition, results from this study demonstrate that the SPV produces significantly higher $\dot{V}O_{2peak}$, HR, $\dot{V}_E$ and peak PO ($P < 0.05$) in preoperative patients with cardiovascular related co-morbidities. Although it is acknowledged that these differences are likely to lack clinical significance and would not be enough to influence risk stratification or clinical decision making according to the Carlisle mortality calculator (Carlisle et al., 2015). It was hypothesised that the SPV would provide and accurate representation of a patient's cardiovascular fitness, and be a reliable predictor or post-operative outcome ($H6_1$). However, due to the of sample size and statistical significance seen in the predictability of the CPET derived variables lack on post-operative outcome, at this stage the null hypothesis ($H6_0$) must be accepted. Nonetheless the SPV still assessed preoperative fitness comparable to the sCPET, and when combining postoperative morbidity from days 3 and 5 it was only an SPV variable

that was related to outcome. Therefore, the SPV could be considered as an alternative means of testing to the sCPET, particularly as the test takes away the need of practitioners having to choose the right work rate increments, increasing the chances of obtaining useable CPET data. It is clear that clinical CPET provides crucial information for both patients and clinicians, therefore any test which may improve the validity and reliability of this process should be of interest. Further research should assess the SPVs ability to predict postoperative outcome in a larger and more homogeneous sample to determine whether or not it can predict postoperative outcomes comparable to sCPET.

What is already known about this topic

- CPET is more commonly being used in the preoperative assessment of patients going into high risk elective surgery.
- The SPV has now been shown as a valid test for determining key CPET derived variables in a clinical population.

What this study adds

- This study shows that the SPV is able to assess preoperative fitness and risk comparable to a sCPET. Although, likely due to the small sample size, none of the CPET derived variables from either test were associated with postoperative morbidity.
- Even though none of the variables were associated with postoperative outcome, the SPV assessed preoperative fitness comparable to sCPET and with the increasing amount of research showing the benefits of CPET in preoperative assessment, the SPV could be considered as an alternative way of testing.

Impact on clinical practice

- The fixed 10 minutes of the SPV may help improve the general day to day running of busy CPET clinics. The SPV also takes away the need of clinicians having to choose the most appropriate work rate increments to ensure a valid test. The test may also provide potential cost savings as the fixed 10 minutes will reduce to risk of obtaining unusable data from tests that do not last long enough. Increasing the likelihood of acquiring valid CPET data will mean that more patients will benefit and have their perioperative care best tailored to them, which should ultimately improve their postoperative outcome.

Chapter 8. General Discussion

8.1. General discussion

This thesis aimed to assess the ability of a self-paced CPET protocol to determine patient fitness prior to major elective surgery and predict postoperative outcomes. A number of limitations have been highlighted in regard to the general nature of sCPET protocols including: the variable and uncertain test duration, no clear end point to work towards and, individuals having no control over their work rate (Noakes 2008). As CPET is an important component of a patient perioperative care (West et al., 2011), alternative test protocols should be considered if they improve clinical decision-making, the patient experience, and/or general working practice for clinicians. The SPV protocol may provide a viable alternative to sCPET protocols in clinical practice because it ensures all patients exercise for the recommended 10 minutes which will reduce the risk of obtaining invalid CPET data, it takes away the need of clinicians having to choose the most appropriate work rate increments to ensure a valid test, and it also allows patients to have full control over the test and chosen work rates.

The first experimental study of this thesis (Chapter 4) demonstrated the SPV to be a reliable indicator of CPET derived variables in young, healthy participants. Prior to this, there was limited information about the reliability of the SPV. The results from Chapter 4 established the CV for $\dot{V}O_{2peak}$ (4.7%) to be similar to that found by Straub et al. (2014), and also previous findings using sCPET protocols (Froelicher et al., 1974; Janicki et al., 1990). This is important as good test-retest is essential when conducting CPET in clinical environments as often there is only enough time in some clinical pathways for one test to be completed (e.g. cancer pathways). The ability of a CPET to provide an indication of

patient fitness without the need for familiarisation of the protocol is therefore essential. However, it is also important that the test provides a true reflection of a patient's cardiorespiratory fitness. As a consequence Chapter 5 compared the physiological responses from the SPV to a sCPET protocol in both young and old healthy populations. All previous studies investigating the SPV have been conducted on younger individuals, whereas clinical populations tend to be of middle to old age. Results from Chapter 5 demonstrated that young participants achieved a significantly higher $\dot{V}O_{2peak}$ in the SPV vs. the sCPET, which is comparable to previous studies (Astorino et al., 2015; Mauger & Sculthorpe 2012; Mauger et al., 2013). In addition to the higher $\dot{V}O_{2peak}$, the SPV also produced a significantly higher peak $\dot{Q}$, SV, $\dot{V}_E$, RER and PO, with a trend for higher end-exercise lactate values ($P = 0.06$). These findings suggest that a higher physiological work rate was achieved in the SPV compared to the sCPET. In particular, it has previously been established that $\dot{Q}$ is strongly associated with $\dot{V}O_2$, and is a principal limiting factor for $\dot{V}O_{2peak}$ (Bassett & Howley 2000). Therefore as suggested by Astorino and colleagues (2015), the enhanced $\dot{Q}$ response is likely to be the key reason for the increased $\dot{V}O_{2peak}$. In the older adult group there were no significant differences in $\dot{V}O_{2peak}$ or peak $\dot{Q}$ between test protocols. This again may supports the notion that $\dot{Q}$ is a key contributor to $\dot{V}O_{2peak}$. However, interestingly similar to the young group, the older adult SPV data showed significantly higher peak RER and PO values, with a statistical trend for a higher end-exercise lactate ($P = 0.05$) compared to the sCPET. These findings suggested that despite the older group reaching a higher work load and metabolic rate in the SPV, $\dot{Q}$ did not appear to respond in the same way as in the young group. The reasons for this are unclear, although the lack of difference in $\dot{Q}$ may be a result of the normal age-related changes that occur in cardiac function (Lakatta & Levy 2003), preventing $\dot{Q}$ to increase beyond a particular point. Nevertheless, the findings from Chapter 5, combined with

previous research (Astorino et al., 2015; Chidnok et al., 2013; Faulkner et al., 2015; Mauger and Sculthorpe 2012; Mauger et al., 2013; Straub et al., 2014), provides further evidence that the SPV is able to produce similar or superior levels of CPET derived variables. The other important finding from the Chapter 5 study was that the SPV could be safely used in an older population, reflective of the general ages of those patients needing preoperative CPET. Rather than testing a clinical population first, it was deemed safer to use a healthy older adult population as some have suggested the SPV might provide heightened risks for older clinical populations (Eston, Crockett & Jones 2014).

The principle aim of Chapter 6 was to assess the utility of the SPV in a clinical population. Specifically, the study aimed to determine the validity and reliability of the SPV protocol for assessing cardiopulmonary fitness in a stable clinical population (early post-MI patients). Results demonstrated the SPV to reliably produce higher $\dot{V}O_{2peak}$ values, along with significantly higher peak HR, $\dot{V}_E$ and PO values. This is surprising as the older adult group in Chapter 5 demonstrated similar $\dot{V}O_{2peak}$ values between SPV and sCPET protocols, even though mean ages were similar between participants (Chapter 5: 59 ± 6 years; Chapter 6: 58 ± 8 years $\dot{V}O_{2peak}$). A possible explanation might be provided by differences in peak PO between the sCPET and SPV between the two studies; there was a greater difference between SPV and sCPET protocols in the post-MI patients (~35 W) compared to the healthy older population (~19 W). This greater difference in PO between protocols in the post-MI patients is a likely reason why they also display a significantly higher $\dot{V}O_{2peak}$ in study 3 (Chapter 6), and may also be why there is a lack of difference seen in the healthy older group in study 2 (Chapter 5).

The primary aim of Chapter 7 was to assess the ability of the SPV protocol to predict postoperative outcomes in the preoperative assessment of patients having elective surgery, compared to a sCPET protocol. In contrast to previous research (Junejo et al., 2012; West et al., 2014; West et al., 2016), none of the CPET derived variables from either protocol were associated with postoperative morbidity. It is likely this is a result of the low sample size and wide range of surgery types used in the study. Due to the small sample size for morbidity cases, statistical power was increased by combining 3 and 5 day POMS census points. Resultant logistic regression analysis demonstrated that oxygen pulse at AT obtained from the SPV was the only variable to be associated with postoperative morbidity. In addition, ROC curve analysis suggested an optimal cut-off point of 8.5 ml $beat^{-1}$, which is comparable to previous research (West et al., 2016). The reasons for this finding, and why oxygen pulse at AT was only significant from the SPV protocol is unclear. Additional research would be needed to investigate this further.

As with earlier chapters in this thesis, results from Chapter 7 demonstrated the SPV produced a significantly higher $\dot{V}O_{2peak}$, $\dot{V}_E$, HR and peak PO values when compared to the sCPET. However, it is acknowledged that the average difference of ~1 $ml \cdot kg^{-1} \cdot min^{-1}$ from chapter 7 and ~2 $ml \cdot kg^{-1} \cdot min^{-1}$ from Chapter 6 is not likely to be a clinically meaningful difference. To support this, the study outlined in Chapter 7 found no differences in the Carlisle 30-day mortality score (Carlisle et al., 2015), which suggests that the observed difference in $\dot{V}O_{2peak}$ would not influence risk stratification and thus clinical decision making. Therefore, it can be concluded from that the SPV has the capability of assessing patient's fitness, comparable to a sCPET.

Previous research has suggested that the SPV may reduce the physiological demand of an incremental exercise test in comparison to a sCPET (Lander et al., 2009); a possible reason for the higher $\dot{V}O_{2peak}$ being achieved by participants. However, data from the current thesis suggests the contrary; data from the three experimental chapters that compared physiological parameters between SPV and sCPET protocols (Chapter 5, 6 & 7), all suggest that there is an enhanced physiological workload achieved in the SPV. Specifically, a higher HR, VE, and RER was found in all three comparative studies (Chapter 5, 6 &7), and higher Q, SV and blood lactate seen in study 2 (Chapter 5). Therefore, it seems that the SPV simply provides individuals with the opportunity to work at high work rates which in turn drive $\dot{V}O_2$ to a greater level. Even though the SPV is completely self-paced, participants were generally willing to work at higher intensities than seen in the sCPET. This could be a result of the defined test duration and the participants knowing the test was going to end within a defined time period may have motivated them to work harder in the final stage. It is also possible that the continuous fluctuation in PO and adequate pacing in the earlier stages of the test may have contributed in minimising early fatigue, leading to a greater work rate being achieved in the final stage of the SPV.

Throughout this thesis there has been a reoccurring discussion concerning optimal CPET test duration. Current guidelines suggest that a CPET should last between 8-12 minutes (American Thoracic Society/American College of Chest Physicians 2003), which was based on the work by Buchfuhrer et al. (1983). For this test duration to be achieved, the test administrator must select the most appropriate starting intensity and work rate increments to ensure exhaustion within the 8-12 min period to prevent obtaining invalid CPET data. However, that results of this thesis (Chapter 5, 6 & 7) suggest that guideline

may not be appropriate in all populations. Specifically, in studies 2, 3 and 4 (Chapter 5, 6 & 7) sub-analysis was completed to consider individuals who completed the sCPET in the 'recommended' time of 8-12 min, compared to those who did not (> 8 min; > 12 min). In the young healthy group from study 2, there was a higher $\dot{V}O_{2peak}$ achieved in the SPV (compared to the sCPET) by participants who completed the sCPET outside of the 8-12 min (> 8 min; > 12 min). There was no difference in $\dot{V}O_{2peak}$ for those who completed the sCPET within the 8-12 min time period, supporting findings of previous work (Buchfuhrer et al., 1983). However, it is important to note that only 3 participants completed the test in < 8 min. Interestingly, in both clinical studies (Chapter 5 & 6) $\dot{V}O_{2peak}$ was higher in the SPV compared to the sCPET for patients who completed the sCPET in < 8 min and 8-12 min. There were only four patients from study 3, and two patients from study 4, who completed the sCPET in > 12 min but, $\dot{V}O_{2peak}$ was higher in the sCPET in all individuals. These findings support previous research (Agostoni et al., 2005), in suggestting longer CPET durations might be beneficial for clinical populations. However, further research is required to establish optimal CPET durations for a variety of different populations (Midgley et al., 2008). Selecting the most appropriate work rate increments for each individual is essential to ensure that valid CPET data is obtained. If selected work rates are too hard for the patient they are likely to stop early giving invalid and limited CPET information. Conversely, if the increments are too low, the patient may not drive $\dot{V}O_2$ sufficiently to obtain a true $\dot{V}O_{2peak}$ prior to the development of significant peripheral fatigue. The SPV provides all patients the opportunity to exercise for 10 min, therefore increasing the likelihood of obtaining more valid and useable CPET data.

There are potential benefits associated with using the SPV in a clinical environment. For example, there could be potential health service cost savings, the standardised 10 min test

may reduce the risk of having unusable data from tests that do not last long enough. If unusable data is obtained then the test may need to be repeated, or have patient preoperative risk being calculated using traditional, less direct methods which may under- or over-predict risk. In turn this may increase costs associated with postoperative care needed for that patient. The fixed test duration is also likely to improve the efficiency of busy CPET clinics and ensure allocated appointment timeslots are adhered to. From a clinician's perspective, the SPV removes the need to estimate the most appropriate starting intensity and increment rates, which will ensure a maximal stress is applied to the cardiorespiratory system within the 10 min test duration. From a patient perspective, the SPV provides an individual with control over the exercise intensity, so that they can freely regulate their work rate throughout the test. The patient also has knowledge of test duration which may help motivate them to complete the full 10 min duration of the test. Finally, by providing useable and valid CPET data the SPV will ensure that the most appropriate perioperative care is provided for the patient, which will ultimately assist in improving their postoperative outcome.

8.2. General Limitations

As stated earlier within this thesis, the CPET duration is an important factor that need to be considered in order to obtain valid $\dot{V}O_{2\ peak}$ data. Guidelines suggest that a CPET should last between 8-12 min (American Thoracic Society/American College of Chest Physicians 2003; Buchfuhrer et al., 1983). However, this duration was not achieved by all participants; in fact there was only 50% of patients in studies 2 and 4, and 54% in study 3, who achieved this recommended time frame. Clearly, having only approximately

half of the participants in each study (Chapter 5, 6 & 7) complete the sCPET within the 'recommended' optimal window of 8-12 minutes is a major limitation. Thus, conclusions made in this thesis need to be taken with caution as it could be suggested that optimal CPET data was not obtained in those who did not reach volitional exhaustion between 8-12 minutes.

The sCPET protocols used in this thesis were devised in an attempt to minimise the risk of participants exercising for durations outside of the 'recommended' time window. For example, in study 3 (Chapter 6) work rate was standardized using a 20 $W \cdot min^{-1}$ ramp for all patients, based upon previous research completed on clinical populations (Brutsche et al., 2000; Eindhoven et al., 2016; Gitt et al., 2002; Kahaly et al., 1999), although individualising work rate increments may have resulted in more patients completing the sCPET in the optimal time. Individualised work rate increments (from a preselected range) were used in studies 2 and 4 (Chapter 5 & 7) based on the individuals physical activity level (i.e. ability to walk up a flight of stairs). This was decided as the most suitable approach for both of these studies (Chapter 5 & 7) due to a diverse range of participant characteristics and physical activity levels. However, the individualisation of work rate increments still did not increase the number of participants completing the sCPET in the 'recommended' time. Some previous research has used equations based on height, weight and age estimate the most appropriate work rate increments (Agnew 2010; Smith et al., 2009), although these do not take into account important variables such as disease state or training status, and so were not deemed to be suitable methods for the study populations. These issues highlight one of the disadvantages associated with sCPET methods, and why a test such as the SPV may be favourable for clinicians.

Due to the nature of the fixed exercise intensity in the sCPET and variable intensity in the SPV, the same cycle ergometer could not be used across both protocols. Therefore, the experimental studies documented in Chapters 5, 6 & 7 had to use of different ergometers to complete the sCPET and SPV protocols. Previous research has suggested that using different ergometers may cause differences in the metabolic cost and cardiovascular strain of exercise (Reiser, Meyer, Kindermann & Daugs 2000). However, it is questionable as to whether the differences in resistance offered by electromagnetic (Lode) vs. air resistance (Wattbike) would be able explain the physiological effects seen between protocols in the experimental chapters of this thesis. Factors such as seat angle (Umberger et al., 1998) and body position (Too 1991) have also been shown to influence maximal exercise performance. Therefore, the use of different ergometers may have contributed to some of the differences seen in the CPET derived variables between the sCPET and SPV, which must be taken into considering when interpreting the findings from this thesis. However, ergometer set-up was replicated as closely as possible between ergometers used with each experimental study to attempt to reduce the impact of seat angle and body position.

8.3. Future directions

It is clear that the findings from this thesis contribute to the current body of literature surrounding the SPV protocol, although these findings have highlighted specific areas that warrant further research. Firstly, it is evident from Chapter 5 that there are potential

mechanistic differences associated with the SPV protocol, compared to sCPET. Although as a result of some methodological limitations, further investigation would be needed to provide a clearer understanding of the physiological responses to the SPV. Indeed those findings of Chapter 5 combined with those found by Astorino et al. (2015) certainly suggest an enhancement in Q, but due to the lack of accuracy and reliability associated with non-invasive techniques to measure Q (Welsman et al., 2005), further research should seek to use more accurate invasive techniques during the SPV. This would hopefully provide a clearer insight into the underlining response to the SPV, and whether the test is truly appropriate in testing maximal levels in all clinical populations.

Secondly, the patients used in Chapter 6 were early post-MI, therefore it is unclear whether the SPV can be used to the same effect in other specific clinical populations (e.g. respiratory disorders). Indeed, the physiological responses to CPET has been suggested to be altered depending on the disease state (Palange et al., 2007). Therefore, future research should assess the ability of the SPV to accurately determine CPET derived variables in various other clinical populations.

Finally, as a result of the lack of significance seen in Chapter 7, future research should assess the SPVs ability to predict postoperative outcome in a much larger sample size and with making the sample more homogeneous i.e. using a specific population and including only one particular surgery type that has previously been shown to benefit from the use of preoperative CPET. This would likely improve the statistical power and determine whether or not the CPET derived variables obtained from the SPV can accurately predict postoperative outcomes comparable to sCPET.

8.4. Conclusion

The overall aim of this thesis was to assess the ability of a self-paced CPET protocol to determine patient fitness prior to elective surgery and its ability to predict postoperative outcomes. Each experimental chapter aimed to support this overall aim. The main findings from this thesis are that the SPV is a valid and reliable test for assessing exercise capacity in cardiovascular patients. These preliminary findings indicate that the SPV could be considered as an alternative means of assessing patient cardiorespiratory fitness, particularly as it reduces the chance of obtaining unusable CPET data from tests that do not last long enough. In addition, the SPV removes the need for clinicians to have to select the most appropriate work rate increments, it allows patients to have full control over the test, and the fixed test duration may help to improve the efficiency of running busy CPET clinics. There are clear benefits for using the SPV in a clinical environment, although it is evident that further research is necessary to assess its ability to predict postoperative outcome in a much larger sample of patients.

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Appendices

Appendix A – Ethical Approval for Clinical Studies (Chapter 6 & 7)

East Kent Hospitals University NHS
NHS Foundation Trust

Please reply Research & Development Directorate
Post Graduate Centre
Buckland Hospital
Coombe Valley Road
Dover Kent.
CT17 OHD

Telephone: 01304 222561
Fax: 01304 222690
E-mail: art.ationu@nhs.net

08/05/2013

Dr Jane Fisher
Consultant Cardiologist
William Harvey Hospital
Kennington Road
Willesborough
Ashford
Kent
TN24 0LZ

Dear Dr Jane Fisher

The use of a self-paced VO2max protocol for assessing maximal oxygen uptake in pre-and postoperative patient care

R&D Ref	2010/CARDIO/01
REC Ref	12/LO/1737

Documents received

REC Favourable Opinion Letter	12/12/2012
Protocol – v. 1.0	10/09/2012
Participant Information Letter – Phase I – v. 1.0 (revised wording)	09/10/2012
Participant Information Letter – Phase II – v. 1.0 (revised wording)	09/10/2012
Participant Consent Form – v. 1.0	10/09/2012
GP/Consultant Information Sheets – v. 1.0	10/09/2012
Questionnaire – pre-screening Health Questionnaire – v. 1.0	10/09/2012

Thank you for submitting the above referenced protocol to the R&D Department. I am pleased to confirm that your study has now been granted NHS Permission by the Trust provided that you comply with the conditions of Trust R&D NHS Permission which are attached.

You are advised to study this letter and the attached Conditions of Trust NHS Permission carefully.

NB - Commencement of the above trial is confirmation of your compliance to these Trust NHS Permission Conditions

All research undertaken within the NHS requires both management NHS Permission from R&D offices, NHS Research Ethics Committee favourable opinion and any other applicable regulatory approvals. Research may not commence at any NHS site until these have been obtained.

You must ensure that you are fully aware of your responsibilities and that your activities are conducted in line with the Local Research Governance Framework for Health and Social Care 2nd Edition, Research Ethics Committee conditions, The Medicines for Human Use (Clinical Trial) Regulations 2004 and Amendment Regulations 2006.

Pharmaceutical clinical trials involving an investigational medicinal product shall be conducted in accordance with the conditions and principles of International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH GCP)

Investigators of other research should be conducting their activities to similar standards and good clinical practice systems.

Safety Reporting

Researchers should follow the safety reporting requirements of the protocol and study sponsor, Trust R&D SOP9, - Serious Adverse Event Reporting, and the Trust Policy for the Management of incidents http://www.ekhuft.nhs.uk/staff/systems/datix-incident-reporting/. All staff are responsible for reporting adverse incidents, whether or not related to research in accordance with the above.

Amendments

The study sponsor is responsible for ensuring that amendments are submitted, as applicable, to the REC and the MHRA, and for ensuring that amendments are notified to PIs and the R&D Department. The sponsor is responsible for providing any updated documentation and regulatory approvals to the PI/research team.

Principal Investigators must ensure that amendments are not implemented until all applicable regulatory approvals and R&D acceptances are in place (unless an urgent safety measure).

Further guidance and examples of substantial and non-substantial amendments can be found on the NRES website www.nres.nhs.uk

Service Support Departments – Medical Records, Radiology, Pathology, Pharmacy

Principal Investigators participating in a CTIMP are responsible for identifying trial patients in the study on all referral requests to service support departments such as Pathology, Radiology, Pharmacy and medical records are marked for retention. This will enable the necessary archiving in compliance with the Medicines for Human Use (Clinical Trials) Regulations [SI 2004 1031] & Amendment Regulations 2006 [SI 2006 1928].

Principal Investigators are required to regularly provide relevant support departments with a list of patients recruited into studies.

Service Support Departments (SSDs), (if supporting the study) should be notified immediately of any amendments to the study and provided with a current version of the protocol.

Monitoring
The sponsor is responsible for ensuring studies are appropriately monitored, particularly CTIMPs

The R&D Department may conduct on-site monitoring visits on a risk-based basis.

All Principal Investigators will have access to the R&D Database – Reda - to upload study documents and study information. As a condition of Trust NHS Permission Investigators are required to use the Reda database to provide regular updates to R&D on their studies,

Accrual
It is a condition of NHS Permission that PIs regularly provide accrual figures by uploading this information to Reda database. Failure to provide such information may result in the withdrawal of Trust NHS Permission.

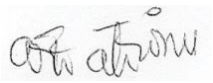
End of Study Reports
Researchers must submit End of Study reports to R&D when all study activity, including recruitment, follow-up etc, has ended.

Training
For all interventional studies, including CTIMPs, medical devices etc, you agree to attend Good Clinical Practice training and updates. The PI is responsible for ensuring that the research team are competent and appropriately qualified to carry out their research roles, and have received appropriate GCP training. The PI is also responsible for ensuring the research team have trial specific training, particularly in completing CRFs and reporting of SAEs.

Delegation logs
Principal Investigators are responsible for ensuring that an up to date delegation log for the study is maintained detailing the roles and responsibilities delegated to research team members.

Breach of NHS Permission conditions
Failure to comply with these conditions or failure to provide the information when requested will result in the study being suspended and may lead to Trust approval being withdrawn.

Yours sincerely



Dr Art Ationu (BSc, MSc, PhD, PG Dip, CBiol, MIBiol, CSci, FIBMS)
R&D Manager

Appendix B – Ethical Approval for Study 1 (Chapter 4)

School of Sport & Exercise Sciences
Research Ethics and Advisory Group (REAG)
University of Kent at Medway
Chatham Maritime
Kent
ME4 4AG

Ethics Reference: Prop 79_2012_13

Date: 4th September 2013

Dear Ms Lauren Jenkins,

Re: Reliability of a novel self-paced VO2max test.

I am now delighted to confirm that SSES REAG has approved your research study (REF No. Prop 79_2012_13) and you are now permitted to recruit participants and commence testing.

If there is the need to amend any aspect of your research, please ensure you inform SSES REAG by completing a request for amendment form and submitting all revised paperwork (participant information sheet, questionnaires, etc.).

If there should happen to be any adverse event during your study, please also ensure SSES REAG is kept informed.

I hope you have a successful study.

With kindest regards,

Steve Meadows

(Chair SSES REAG)

Appendix C – Ethical Approval for Study 2 (Chapter 5)

University of Kent

School of Sport & Exercise Sciences
Research Ethics and Advisory Group (REAG)
University of Kent at Medway
Chatham Maritime
Kent
ME4 4AG

Ethics Reference:
Prop123_2013_14

Date: 24 April 2014

Dear Miss Lauren Jenkins,

Re: Differences in the physiological responses between a self-paced and a standard incremental ramp VO2max test

I am now delighted to confirm that SSES REAG has approved your research study (REF No. Prop123_2013_14) and you are now permitted to recruit participants and commence testing.

If there is the need to amend any aspect of your research, please ensure you inform SSES REAG by completing a request for amendment form and submitting all revised paperwork (participant information sheet, questionnaires, etc.).

If there should happen to be any adverse event during your study, please also ensure SSES REAG is kept informed.

I hope you have a successful study.

With kindest regards,

Steve Meadows

(Chair SSES REAG)

Appendix D – RPE scale instructions

Rate of Perceived Exertion (RPE)

The Rate of Perceived Exertion (RPE) scale is a subjective rating of exercise intensity, based on how hard you feel like your body, as a whole, is working. It is based on physical sensations that you may experience during the exercise, including an increase in your heart rate, breathing rate, sweating, and feelings of muscle fatigue/tiredness. Try not to concern yourself with just one of these sensations, try to focus on your total feeling of exertion. Try to evaluate your feelings of exertion as honestly as possible, as it is your own personal feeling of effort, not compared to other peoples.

6	No exertion at all – sitting down	
7	Very, very light (Rest)	
8		
9	Very light - gentle walking, very low effort	
10		50%
11	Fairly light - does not require much effort	
12		60%
13	Somewhat hard - steady pace which requires slightly more effort	
14		70%
15	Hard (heavy) - hard and tiring but can continue	
16		80%
17	Very hard - very strenuous, can continue but you really have to push yourself and you are very tired.	
18		90%
19	Very, very hard –extremely strenuous, for some people it feels like the most exertion they have ever experienced.	
20	Maximal exertion	100%