DEVELOPMENT OF NORMAL RANGES FOR CARDIOPULMONARY EXERCISE TESTING PERFORMED USING ARM ERGOMETRY.

Joanna Shakespeare

DClinSci 2021

DEVELOPMENT OF NORMAL RANGES FOR CARDIOPULMONARY EXERCISE TESTING PERFORMED USING ARM ERGOMETRY.

JOANNA SHAKESPEARE

A thesis submitted in partial fulfillment of the requirements of the Manchester Metropolitan University for the award of Doctorate in Clinical Science Manchester Metropolitan University

Department of Life Sciences, Manchester Metropolitan University, in collaboration with the Department of Respiratory Medicine, University Hospitals Coventry and Warwickshire, Coventry.

2021

Abstract

Introduction

The performance of a cardiopulmonary exercise test (CPET) requires an individual to undertake a progressive, maximal exercise test to a symptom limited end point. CPET is standardly performed using a treadmill or cycle ergometer (CE). There is a growing cohort of patients in whom the performance of a CE or treadmill test is not possible. Arm ergometry (AE) is an alternative exercise modality to CE, however, AE achieves lower oxygen uptake ($\dot{V}O_2$) values as it involves smaller muscle groups and generates less cardiovascular stress. Current predicted equations for the interpretation of AE CPET are limited by small sample sizes, gender bias and limited age ranges.

Aims

To develop predicted equations and reference ranges for AE exercise testing and to compare the results of AE CPET to those obtained from CE.

Methods

Maximal CPET to volitional exhaustion was performed in a group of 116 (62 F) healthy volunteers of median age 38 (IQR 19) years, using both AE and CE with randomised testing order and a rest interval of at least 24 hours. Breath by breath gas analysis was performed using the Ultima CPX (Medical Graphics, UK) metabolic cart. Regression analysis was used to develop regression equations for AE $\dot{V}O_2$, work rate, anaerobic threshold and heart rate.

Results

The model with dependent variable AE $\dot{V}O_2$ $ml.min^{-1}$ and independent variables age (years), sex (0 male, 1 female) and weight (kg) fit the population with a $r^2 = 0.542$ and adjusted $r^2 = 0.53$. The equation estimated with this model was 1930.803 - (12.651 x age) – (756.095 x sex) + (10.507 x weight). Equations for peak work rate, anaerobic threshold and heart rate were also developed. Results demonstrated that AE exercise parameters were significantly lower than those obtained from CE.

Conclusions

These findings represent the largest and most diverse set of predicted values and reference ranges for AE CPET parameters in healthy individuals to date.

Implementation of these reference equations will allow AE to be more widely adopted enabling the performance and interpretation of CPET in a wider population.

Dedication

This thesis is dedicated to my husband Nick and our two children Henry and James. Thank you for believing in me and encouraging me to keep going. Thank you for your continual support as without it I would not have been able to do this. I love you all very much xx

Acknowledgements

The completion of this thesis brings an end to the five-year higher specialist scientific training programme (HSST). Over the last five years I have significantly developed both my clinical and research skills, none of which would have been possible without the support of a wide range of friends and professional colleagues.

Dr Asad Ali has been immensely supportive, and I cannot thank him enough for trusting me with his patients and helping me to develop my clinical skills. Asad has been an excellent clinical mentor and supported me through my professional portfolio, enabling me to develop the skills and confidence to lead sleep and ventilation clinics and develop my career pathway post HSST.

I would like to thank my project supervisor Professor David Parr. Thank you for your advice and support during the data collection, write up and submission process for this thesis. Thank you for giving me your time, support, and the encouragement that I needed to successfully complete this project on time.

Special thank you to my exercise testing colleagues Edward Parkes, Natalie O'Reilly, Jason Burge and Iuri Mata for their support with data collection. A thank you also to the staff of Department of Respiratory and Sleep Sciences for their continued dedication and hard work which has enabled me to take time out to complete this work.

Thank you to my friends and colleagues Danielle Fox and Edward Parkes for keeping me sane and supporting me when I needed it. A big thank you to my best friend Orsi Kelly, thank you for believing in me, for encouraging me, listening to me, and coming on my ridiculous running adventures, love you.

Finally, a huge thank you to my family. To my mum and dad for helping me to get to where I am today and encouraging me to always do the best I can. To my husband Nick and our amazing boys Henry and James, thank you as without you all this wouldn't have been possible or worthwhile. Love you all.

Publications

All publications listed are published conference abstracts presented at the European Respiratory Society Congress 2020.

1. Shakespeare J, Parkes E, Parr DG. Comparison of peak heart rate achievable using arm ergometry versus leg ergometry. *European Respiratory Journal* 2020 56: 3197; **DOI:** 10.1183/13993003.congress-2020.3197

2. Shakespeare J, Parr DG. Comparison of oxygen uptake obtained using arm and leg cycle ergometry. *European Respiratory Journal* 2020 56: 3198; **DOI:** 10.1183/13993003.congress-2020.3198

3. Shakespeare J, Parr DG. Comparison of anaerobic threshold obtained using arm and leg cycle ergometry. *European Respiratory Journal* 2020 56: 3199; **DOI:** 10.1183/13993003.congress-2020.3199

4. Shakespeare J, Parkes E, Parr DG. Peak heart rate to assess maximal exercise in arm ergometry. *European Respiratory Journal* 2020 56: 2159; **DOI:** 10.1183/13993003.congress-2020.2159

5. Shakespeare J, Parkes E, Mata, I. Parr DG. Incidence of clinically significant ECG abnormalities in healthy volunteers participating in cardio-pulmonary exercise research. *European Respiratory Journal* 2020 56: 2158; **DOI:** 10.1183/13993003.congress-2020.2158

Declaration

No portion of this work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institution of learning.

Table of Contents

Abbreviations

AAA	Abdominal aortic aneurysm
AT	Anaerobic threshold
ATP	Adenosine triphosphate
BMI	Body mass index
BP	Blood pressure
BW	Body weight
CAD	Coronary artery disease
C(a-v)O_2	Arterial-venous oxygen content
CF	Cystic fibrosis
cm	Centimetres
CO	Cardiac output
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 19
CPET	Cardiopulmonary exercise test
CTEPH	Chronic thromboembolic pulmonary hypertension
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EELV	End expiratory lung volume
EVAR	Endovascular repair
FeO_2	Fractional concentration of expired oxygen
FEV_1	Forced expiratory volume in one second
FiO_2	Fractional concentration of inspired oxygen
FVC	Forced vital capacity
GCP	Good clinical practice
GP	General practitioner
Hb	Haemoglobin
HbO_2	Oxygenated haemoglobin
HDU	High dependency unit

HFpEF	Heart failure preserved ejection fraction
HFrEF	Heart failure reduced ejection fraction
HR	Heart rate
ICC	Intraclass correlation coefficient
ICU	Intensive Care Unit
IFCC	The International Federation for Clinical Chemistry
ILD	Interstitial lung disease
kg	Kilogram
LLN	Lower limit of normal
LOS	Length of stay
METs	Metabolic equivalents
ms	Millisecond
MVV	Maximal voluntary ventilation
NADH	Nicotinamide adenine dinucleotide and hydrogen
NDIR	Non-dispersive infrared
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
O_2	Oxygen
P50	Oxygen tension when Hb is 50% saturated with oxygen
PAH	Pulmonary arterial hypertension
$PETCO_2$	End tidal carbon dioxide
$PETO_2$	End tidal oxygen
RCP	Respiratory compensation point
RER	Respiratory exchange ratio
rpm	Revolutions per minute
SaO_2	Arterial oxygen saturation
SARS-Cov-2	Severe Acute Respiratory Syndrome Coronavirus 2
SBP	Systolic blood pressure
SCD	Sudden cardiac death
SCI	Spinal cord injury
SD	Standard deviation

SpO_2	Oxygen saturation
STPD	Standardised Conditions of Temperature and Pressure, Dry
TCA	Tricarboxylic acid cycle
ULN	Upper limit of normal
VC	Vital capacity
VD	Deadspace
Vi	Volume of inspired gas
$\dot{V}CO_2$	Carbon dioxide output
$\dot{V}E$	Minute ventilation
$\dot{V}E/\dot{V}CO_2$	Ventilatory equivalent for carbon dioxide
$\dot{V}E/\dot{V}O_2$	Ventilatory equivalent for oxygen
$\dot{V}O_2$	Oxygen uptake
VT	Tidal volume
WPW	Wolff-Parkinson-White
WR	Work rate

Table of Figures

Table of Tables

Table 25. Achievement of the standards for high quality reference value studies.142

Chapter 1: Introduction

Cardiopulmonary exercise tests (CPET's) are a clinical investigation used in routine clinical practice for the assessment of exercise capacity. The concept of maximal oxygen uptake ($\dot{V}O_2$ max) was first identified in the 1920's by Hill but it was the work of Taylor, Astrand and Saltin in the 1960's that resulted in the establishment of protocols and physiological indicators for its measurement (Seiler, 2011). For the following two decades, CPET was primarily undertaken for research purposes or within specialised centres only until its first clinical use in the assessment of heart failure in the mid-1980's (Weber et al., 1984; Weber and Janicki, 1985). By the mid-1990's CPET had become a growing area of interest in respiratory medicine due to its non-invasive nature and clinical applicability (Roca et al., 1997).

Cardiopulmonary exercise testing provides an integrated assessment of the response to exercise of the respiratory, cardiovascular, haematopoietic, neuropsychological, and skeletal muscle systems. Standard, static tests of pulmonary and cardiac function, which are performed at rest, cannot determine exercise capacity or causes of exercise limitation (Balady et al., 2010). However, stressing these systems using cardiopulmonary exercise testing can reveal pathologies that are not apparent at rest. Furthermore, exercise capacity is one of the most powerful predictors of cardiovascular and all-cause mortality (Myers et al., 2002; Leeper et al., 2013; Korpelainen et al., 2016). Consequently, cardiopulmonary exercise testing is increasingly being used to provide a holistic assessment of exercise limitation and its causes and is increasingly being used to assess fitness for surgical intervention.

The performance of a cardiopulmonary exercise test (CPET) requires an individual to undertake a progressive, maximal exercise test to a symptom-limited end point. Tests are standardly performed using a treadmill or cycle ergometer. In normal individuals the limiting symptoms will usually be fatigue or breathlessness. Measurement of inspired and expired breath (breath-by-breath analysis) whilst exercising allows the calculation of various indices which can be compared to expected normal values. Concurrent assessment of heart rate and activity, using an

electrocardiogram (ECG), allows an integrative assessment of an array of variables which evaluate the physiological response to exercise and causes for exercise intolerance. Clinical exercise testing is now routinely used for diagnosis of exercise limitation, risk assessment or for monitoring of progression of known disease.

There is a growing cohort of patients in whom the performance of cycle ergometry or treadmill testing is not possible as a consequence of medical conditions leading to impairment of the lower limbs or inability to perform weight bearing exercise. Consequently, the accepted method for determining surgical fitness or estimating prognosis is not available to these individuals, potentially preventing them from accessing life-saving surgery or therapy.

Arm ergometry is an alternative exercise modality, however, the data that has been obtained in healthy, normal populations for the purpose of generating a normal range of exercise indices are limited by the small size and heterogeneity of the study populations (Balady et al., 1990). Findings to date demonstrate that peak oxygen uptake is significantly lower when obtained using arm ergometry (Eston and Brodie, 1986). In addition, during submaximal phases of exercise, exercise parameters are higher for any given work rate when exercising with the arms suggesting a decreased exercise efficiency (Dekerle et al., 2002; Orr et al., 2013). The fitness measures obtained from arm ergometry therefore cannot be assumed to correlate with the accepted methods of treadmill and cycle ergometry. Consequently, the clinical interpretation of maximal exercise indices obtained from arm ergometry may, in the absence of direct comparison of these modalities and a robust normal reference range, be unreliable.

1.1 Cardiopulmonary Exercise Testing – the physiological basis

The ability to perform exercise is critically related to the cardiovascular system's capacity to deliver oxygen to the muscles and the respiratory system's ability to excrete carbon dioxide from the blood via the lungs. Oxygen is required for the metabolic generation of energy (Adenosine Triphosphate or ATP) to enable muscle contraction with energy demand being directly proportional to work output (Wasserman et al., 1999).

1.1.1 ATP generation

Muscle is an excitable organ that transforms chemical energy into mechanical energy (Maréchal, 2020). Within cells energy is provided by oxidation of metabolic fuels. Whilst fat and protein can sometimes be important in the metabolic response to exercise, carbohydrates are the principal substrate for muscle metabolism in the form of glycogen.

There are three distinct yet closely integrated processes that operate together to satisfy the energy requirements of the muscle (Gastin, 2001). These processes include the ATP phosphocreatine system (ATP PC) and glycolysis both of which are anaerobic and the aerobic process of oxidative phosphorylation. Most exercise involves ATP being synthesised through a mix of all three systems with the most dominant system at any time determined by the intensity and duration of the exercise.

The immediate source of energy for muscle contraction comes from the hydrolysis of ATP. ATP exists in very low concentrations in the muscle and therefore additional processes are required to continue energy production and allow muscle contraction to be sustained with ongoing exercise. The first process involves the splitting of phosphocreatine (PCr), which together with the stored ATP in the cell provides the initial 10 to 15 seconds of energy (Figure 1). The second process involves the anaerobic breakdown of carbohydrate, mainly in the form of muscle glycogen, to pyruvic acid and then lactate through glycolysis. As exercise continues the aerobic

systems become depleted (due to the limited stores of ATP, phosphocreatine and glycogen) and the aerobic system becomes increasingly dominant as it can break down more complex fuels such as fats and proteins in addition to glycogen, see Figure 1.

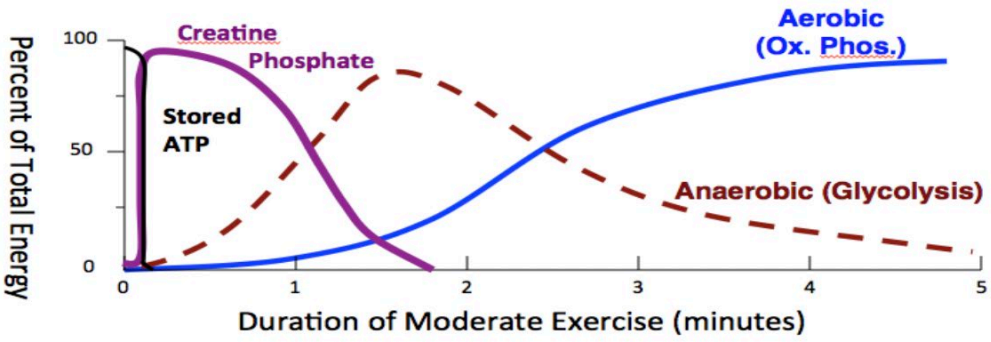


Figure 1 – Energy systems during moderate intensity exercise

During moderate exercise, ATP stored within the muscle is the first source of energy. The creatine phosphate system restores the lost ATP. During the first 1-2 minutes of moderate exercise anaerobic respiration is the main energy source. After 2-3 minutes, aerobic respiration becomes the main source of energy (McCallum, 2017).

1.1.1.1 Phosphocreatine system

Early in exercise, myocyte creatine phosphate and oxygen stores are used for energy production, allowing time for cardiac output and ventilation to increase. The ATP-PC system is stored in all muscle cells and is the bodies simplest and most immediate source of energy (Gastin, 2001). It provides energy through the breakdown of these stored high energy phosphates and supports exercise of maximal intensity but short duration.

1.1.1.2 Glycolysis

During glycolysis glucose molecules are converted through a series of reactions into two molecules of pyruvate, two of NADH and two molecules of ATP. In aerobic

conditions the two molecules of pyruvate enter the TCA cycle to complete oxidation, (see section 1.1.1.3).

When oxygen is not available in sufficient quantity for complete oxidative phosphorylation e.g., during high intensity exercise, important changes occur. The mitochondrial pathways become ineffective, and pyruvate accumulates in the cytosol before being converted to lactate. Lactate effluxes into the plasma where bicarbonate buffering generates carbon dioxide stimulating ventilatory responses to eliminate the additional carbon dioxide.

1.1.1.3 Oxidative Phosphorylation

In aerobic conditions the two molecules of pyruvate enter the TCA cycle to complete oxidation (Figure 2). Pyruvate undergoes oxidative decarboxylation and attaches to coenzyme A to form acetyl-CoA (Figure 2). Acetyl-CoA is also the product of fatty acid ß-oxidation. The main engine for cellular energy production is the electron transport chain, a complex device consisting of lipoproteins that facilitate the flow of electrons which releases energy for the phosphorylation of ADP to ATP (Cooper and Storer, 2001).

Complete combustion of one molecule of glucose leads to the generation of between 30 and 32 molecules of ATP (Mason and Johnson, 2014; Reece et al., 2014). This range is lower than previous estimates of 36 (Cooper and Storer, 2001) as it accounts for the necessary transport of ADP into and ATP out of the mitochondria.

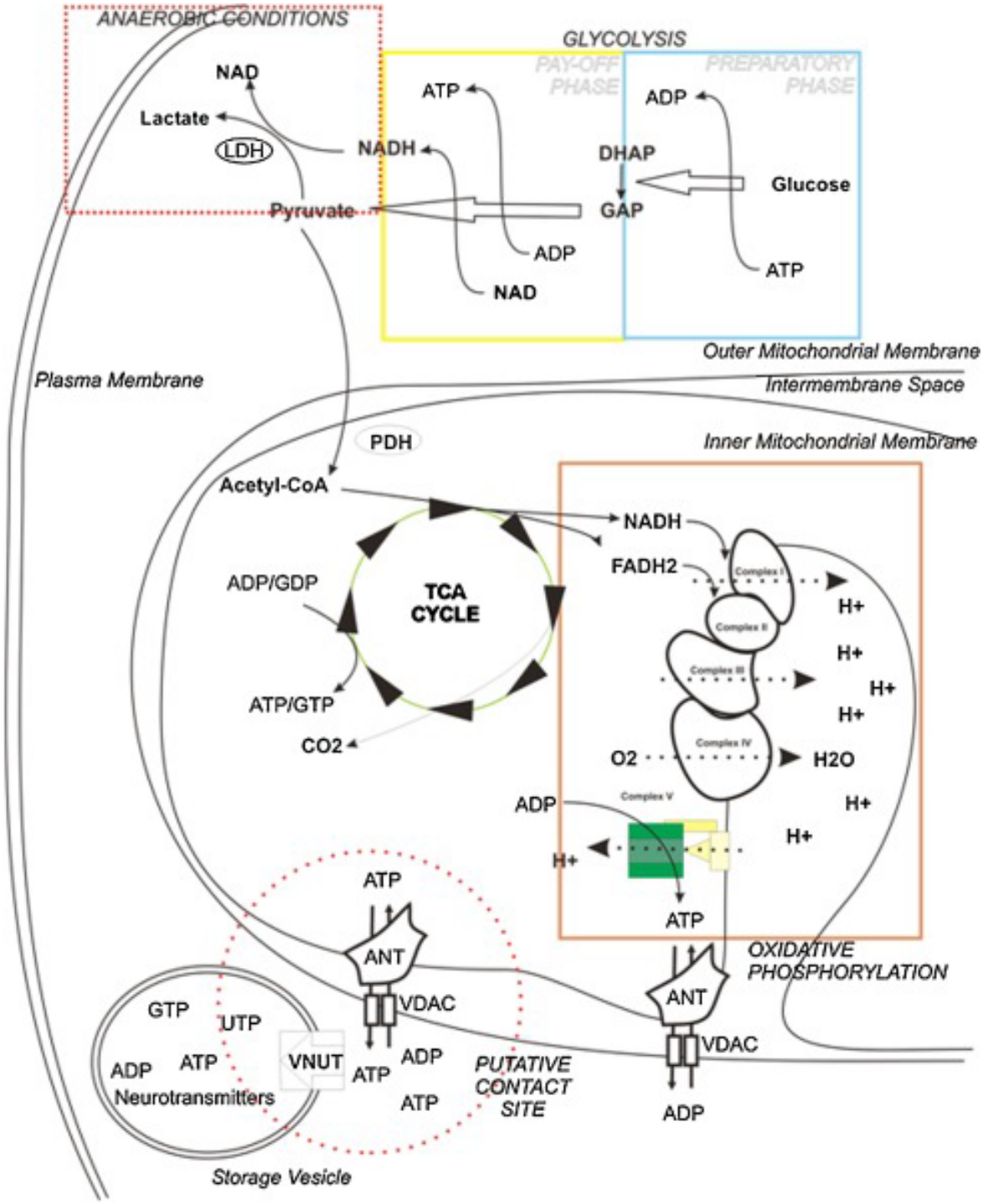


Figure 2 – Summary model of ATP synthesis

Glycolysis is represented in the *yellow* and *blue boxes*, the TCA cycle by the *green circle*, and oxidative phosphorylation in the *orange box*. Reduction of pyruvate to lactate is represented inside the *red dotted rectangle* (Bonora et al., 2012).

1.1.1.4 Coupling of internal and external respiration

To maintain exercise, the increase in oxygen transport from the lungs to the tissues must be rapid, adequate, and sustained. At the same time CO_2, produced by the conversion of substrate to chemical energy, must be continuously removed from the metabolically active tissues and expired to prevent blood acidity from developing. Consequently, the increase in cellular requirements as a result of exercise must be accompanied by appropriate responses of both the cardiovascular and respiratory systems (Figure 3).

The relationship of cardiac output and ventilation to the rate of oxygen consumption and carbon dioxide production respectively, at low and moderate intensity exercise, are such that acidosis is prevented from occurring and lactate is effectively removed. This coupling of the circulatory and ventilatory functions to muscle metabolism is illustrated in Figure 3. As exercise intensity increases to above the anaerobic threshold a combination of aerobic and anaerobic metabolism is utilised to provide sufficient quantities of ATP. This results in a sustained increase in blood lactate which results in an increase in hydrogen ions (H^+). The H^+ are buffered by bicarbonate (HCO_3^-) resulting in the production of water (H_2O) and CO_2. This increase in CO_2 production requires elimination and therefore a significant increase in alveolar ventilation, through increased depth and frequency of breathing, occurs in response.

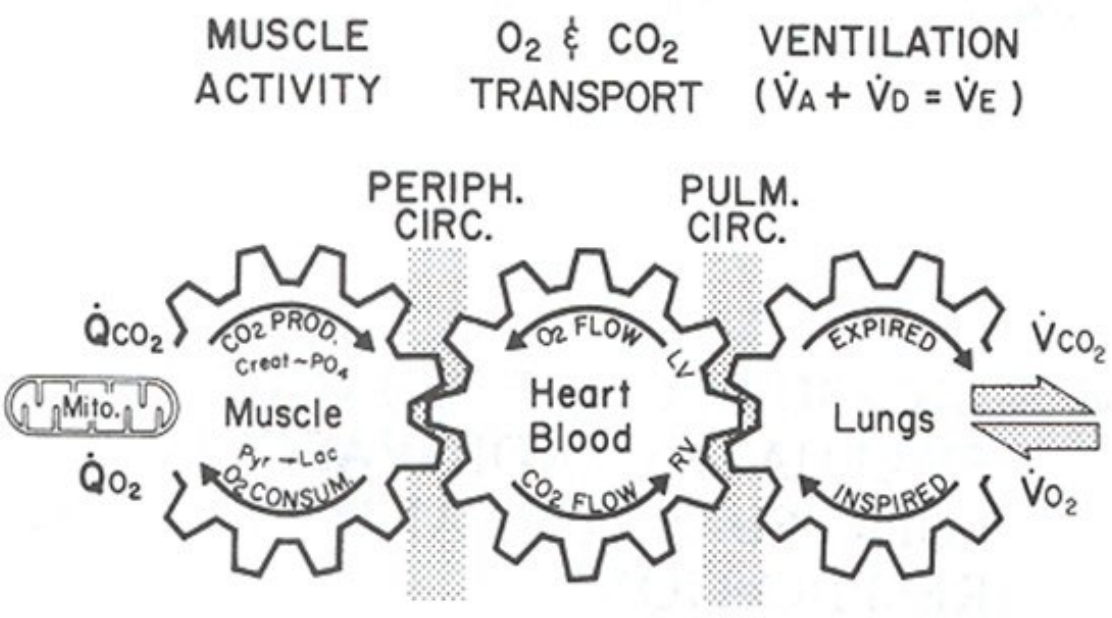


Figure 3 - Coupling of internal and external respiration

Gas transport mechanisms illustrating the coupling of internal and external respiration. Adapted from Wasserman (Wasserman et al., 1999).

Circ = circulation; CO_2 = carbon dioxide; Consum = consumption; Creat = creatine; Lac = lactate; HR = heart rate; Mito = mitochondria; PO_4 = phosphate; O_2 = oxygen; Periph = peripheral; Prod = production; Pulm = pulmonary; Pyr = pyruvate; $\dot{Q}CO_2$ = carbon dioxide production; $\dot{Q}O_2$ = oxygen utilisation; LV = left ventricle; RV = right ventricle; $\dot{V}_A$ = minute alveolar ventilation; $\dot{V}_D$ = minute dead space ventilation; $\dot{V}_E$ = minute ventilation; $\dot{V}CO_2$ = carbon dioxide output; $\dot{V}O_2$ = oxygen uptake. From Principles of Exercise Testing and Interpretation (Wasserman et al., 1999).

1.1.2 Maximal Oxygen Uptake

Maximal oxygen uptake ($\dot{V}O_2$ max) is the maximal volume of oxygen an individual can utilise per unit time during maximal exercise and defines the limits of the cardiopulmonary system. $\dot{V}O_2$ is defined by the Fick Principle:

$$\dot{V}O_2 = CO \times C(a\text{-}v)O_2$$

Where CO = cardiac output (L blood.min-^{1}) and C(a-v)O_2 = the arterial-venous oxygen content difference (mL O_2.L blood-^{1}) (Albouaini et al., 2007). It is determined by cellular oxygen demand up to the maximal rate of oxygen transport.

Oxygen uptake increases linearly with increasing work rate and the slope of this relationship reflects the efficiency of the metabolic conversion of chemical potential energy to mechanical work and to the mechanical efficiency of the musculoskeletal system. As oxygen uptake increases, one or more of the determinants of $\dot{V}O_2$ will approach their limit (stroke volume, heart rate, tissue oxygen extraction) and the $\dot{V}O_2$ work rate relationship will begin to plateau. The determination of a $\dot{V}O_2$ max requires an individual to achieve a plateau in their oxygen uptake and for them to reach their physiological limits. In clinical practice this is hard to achieve and therefore it is usual practice to report the highest attained $\dot{V}O_2$ which is then termed peak $\dot{V}O_2$ (Figure 4). A reduced peak $\dot{V}O_2$ can occur due to many different types of limitations however in a clinical population a normal peak $\dot{V}O_2$ generally excludes exercise impairment and any serious or advanced disease processes.

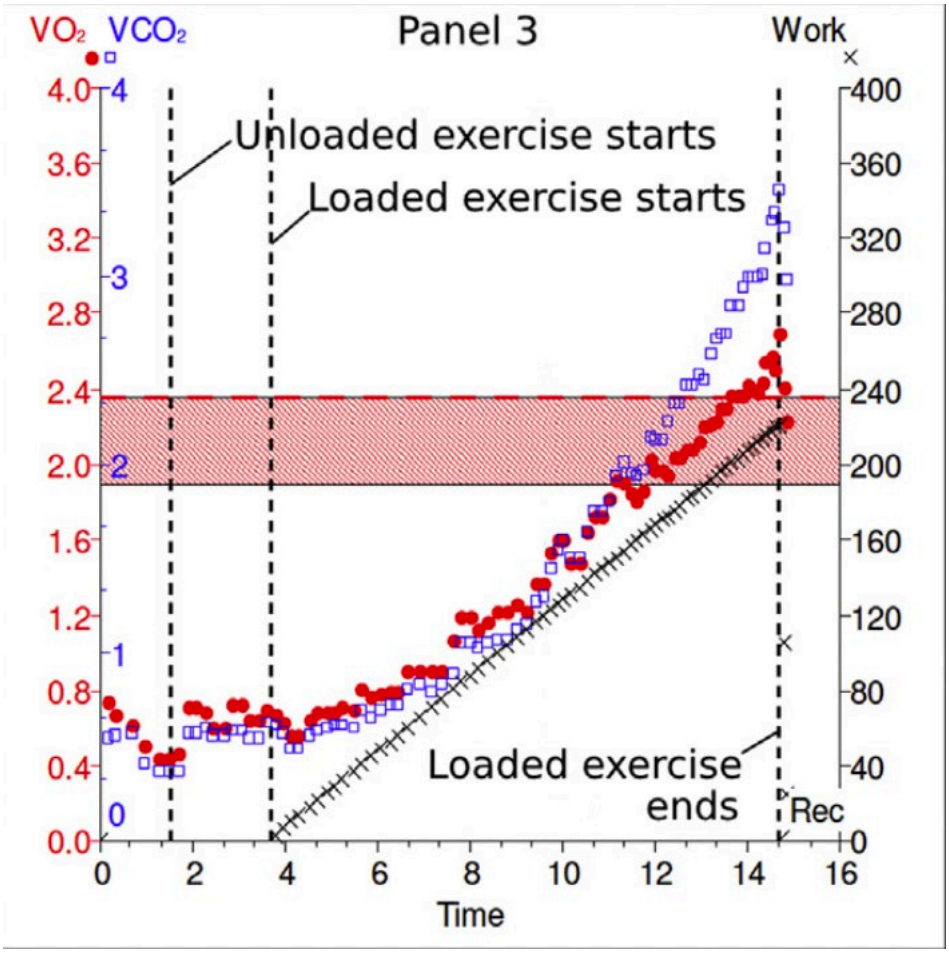


Figure 4 - Oxygen uptake during exercise

Example of the oxygen uptake and carbon dioxide output during an incremental exercise test to peak (Chambers and Wisely, 2019).

1.1.3 Anaerobic Threshold

1.1.3.1 Terminology

During exercise the oxygen consumption above which aerobic energy production is supplemented by anaerobic mechanisms was originally termed the anaerobic threshold by Wasserman and Mcilroy (Wasserman and Mcilroy, 1964). They demonstrated that a change in the gas curve appeared to correspond with an increase in lactate in the blood. It was termed a threshold as at the time it was believed that the body was transitioning to anaerobic metabolism.

During incremental exercise at a certain intensity there is a nonlinear steep increase in ventilation termed the ventilatory anaerobic threshold (VAT). At the same time there is also a nonlinear increase in blood lactate concentration known as the lactate threshold (LT). In addition, there is also a nonlinear increase in CO_2 production and an increase in end tidal O_2, which collectively are termed the anaerobic threshold (AT). The ability of gas exchange variables to detect the onset of acidosis due to the production of excess lactate has been widely assessed with differences between the two found to be nonsignificant (Wasserman, 1986; Davis et al., 1997).

Other terminologies assigned to the anaerobic threshold include the first ventilatory threshold (VT1) (Coso et al., 2009), onset of blood lactate accumulation (OBLA) and the maximal lactate steady state (Hopker et al., 2011).

In sports medicine lactate levels are used to define additional thresholds that are utilised for the prescribing of exercise intensity for exercise training purposes (Jamnick et al., 2020). The first lactate threshold in this setting is LT1 which corresponds to the lowest intensity (watts) at which there is a sustained increase in blood lactate above resting values. If directly monitoring blood lactate this would correspond to a value of approximately 2mmol/L. The second lactate threshold level or LT2 corresponds to the maximal lactate steady state and a lactate value of 4mmol/L and is equivalent to the anaerobic threshold as described earlier.

In reality the terms lactate threshold and anaerobic threshold are used interchangeably. Clinically the term anaerobic threshold has been widely adopted and is the terminology chosen for this study.

1.1.3.2 Anaerobic Threshold Determination

The anaerobic threshold (AT) is the point in an exercise test where the amount of oxygen delivered to the exercising muscles is no longer sufficient to generate the energy required to support continuing exercise. Consequently, anaerobic metabolism is required to supplement aerobic metabolism. The anaerobic generation of energy leads to an increase in the rate of production of lactate which

consequently begins to accumulate, in addition to increased CO_2 production. During a breath-by-breath exercise test, the AT can be determined as the point at which the rate of increase of carbon dioxide output ($\dot{V}CO_2$) exceeds the rate of increase in oxygen uptake ($\dot{V}O_2$). Figure 5 illustrates the V-slope method of determining AT and demonstrates the inflection point in the relationship between $\dot{V}CO_2$ and $\dot{V}O_2$ which is known as the anaerobic threshold.

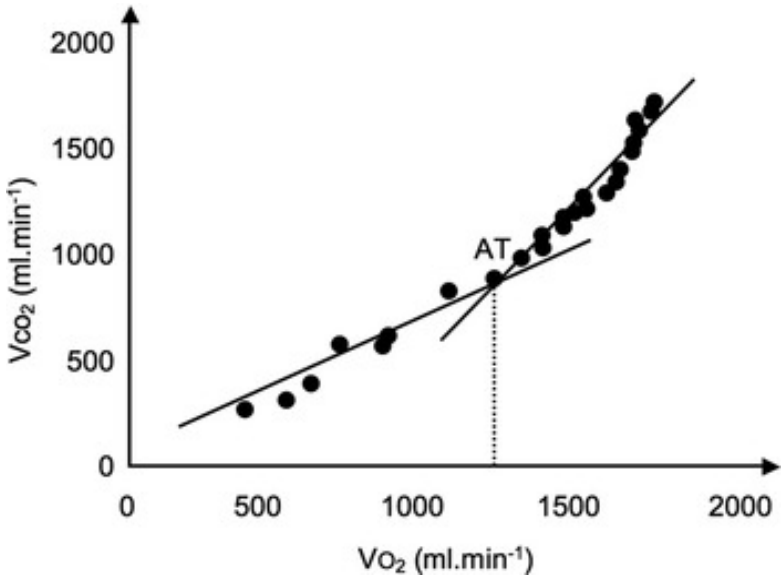


Figure 5 - Determination of anaerobic threshold

Determination of anaerobic threshold (AT) non-invasively using the V-slope method (Yu et al., 2010). The anaerobic threshold is identified by the first point of departure from linearity of carbon dioxide ($\dot{V}CO_2$) output plotted against oxygen uptake ($\dot{V}O_2$). The later inflection relates to the compensation point which occurs in response to falling pH levels, see 1.1.5.

Anaerobic threshold should be interpreted in relation to an individuals predicted $\dot{V}O_2$ max (Cooper and Storer, 2001). In general, an AT of between 40-60% of predicted $\dot{V}O_2$ is seen in normal sedentary individuals and this value can be increased with physical training. AT values <40% of predicted $\dot{V}O_2$ may indicate a cardiovascular or other limitation in oxygen delivery to the tissues (‘ATS/ACCP., 2003).

1.1.4 Ventilation (V̇E)

Minute ventilation (V̇E) is the volume of gas inhaled or exhaled by the lungs per minute. During exercise, V̇E responds to the demands for CO_2 clearance rather than O_2 uptake. Increases in V̇E are required to provide levels of alveolar ventilation appropriately matched to carbon dioxide output and to adequately ventilate the physiological dead space as explained by the equation below:

$$\dot{V}E = 863 \times \dot{V}CO_2/[PaCO_2 \times (1-V_D/V_T)]$$

Where 863 = a constant for correction of gas volumes; V_D/V_T = physiological dead space; $PaCO_2$ = the partial pressure of carbon dioxide in arterial blood (Roca et al., 1997).

Exercise induced increases in V̇E are primarily achieved by increases in tidal volume (V_T) until approximately 60% of vital capacity is achieved. Further increases in V̇E are then achieved by increasing breathing frequency (Figure 6). This breathing pattern minimises work of breathing and dead space ventilation (Molgat-Seon et al., 2020). With symptom-limited exercise, exercise will be terminated prior to maximal ventilation being achieved (usually at 50-70% peak V̇E) with the exception of athletes who can utilise a higher proportion of their ventilatory capacity (Bingisser et al., 1997). Mechanical abnormalities of the respiratory system (airflow obstruction, restrictive lung diseases, respiratory muscle weakness or reduced chest wall compliance) result in a reduced vital capacity and can result in a ventilatory limitation to exercise where peak V̇E reaches maximal V̇E capacity (Figures 6a and 6b).

Figure 6a

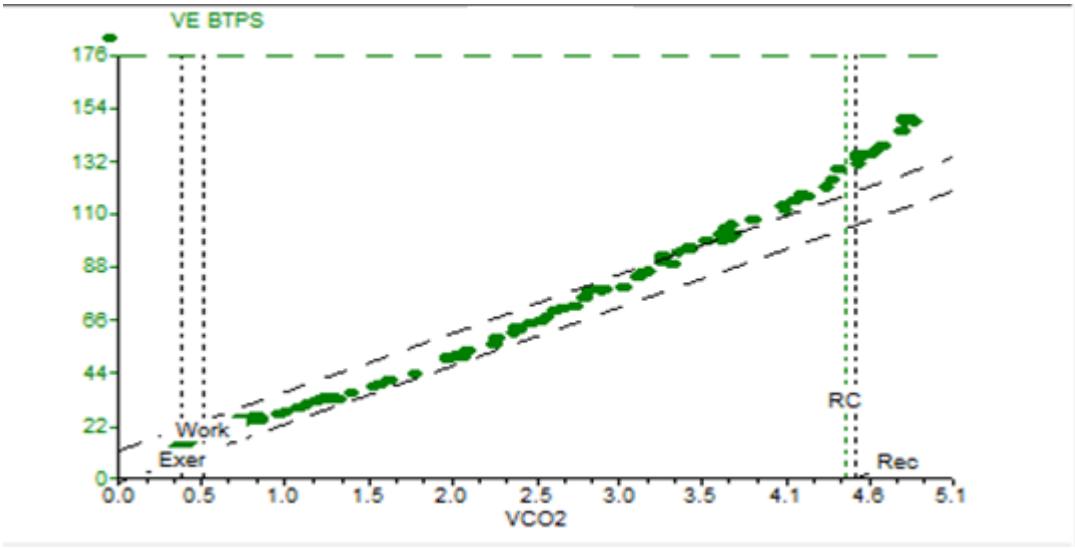


Figure 6b

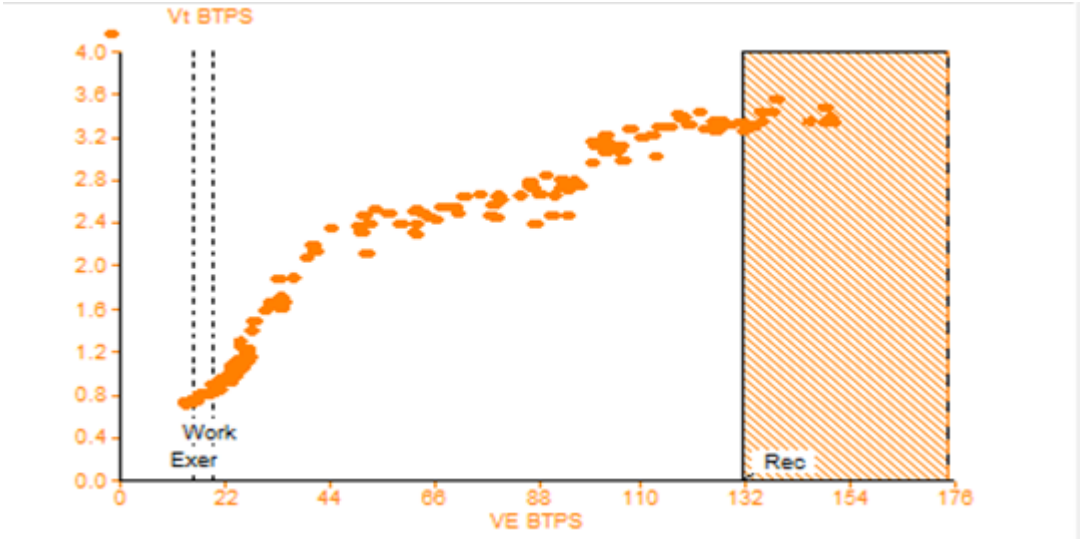


Figure 6 - Ventilation response to incremental exercise

Figure 5a illustrates the linear increase in ventilation during exercise. In this example the subject achieved a peak ventilation of 83% predicted (predicted line represented by green dashed line). Figure 5b illustrates that increases in ventilation early in exercise are achieved by increasing tidal volume (y axis) and this is then followed by increases in breathing frequency. In this example the subject has encroached onto their beathing reserve (orange shaded area) however this relates to their athletic capabilities rather than ventilatory limitation. Image by author.

1.1.5 Ventilatory Equivalents

Ventilatory equivalents are measures of breathing efficiency that relate minute ventilation to oxygen uptake ($\dot{V}E/\dot{V}O_2$) or carbon dioxide output ($\dot{V}E/\dot{V}CO_2$). At rest the ventilatory equivalents are between 30-60 and fall steadily on commencement of exercise to reach a plateau or nadir. The subsequent inflection points for $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ are different (Levett et al., 2018). $\dot{V}E/\dot{V}O_2$ rises first and is a consequence of the dissociation of $\dot{V}E$ to $\dot{V}O_2$ due to increasing carbon dioxide levels as a result of bicarbonate buffering of lactate. Consequently, the $\dot{V}E/\dot{V}O_2$ inflection point can be used to identify anaerobic threshold (Figure 7). Dissociation of $\dot{V}E$ from $\dot{V}CO_2$ does not occur until later and is at the point where buffering can no longer prevent a fall in blood pH, known as the respiratory compensation point (Figure 7).

The plateau value for each parameter is of importance. In normal individuals the plateau is on average 25 for $\dot{V}E/\dot{V}O_2$ and 28 for $\dot{V}E/\dot{V}CO_2$. With increasing physiological dead space due to age, these values increase to on average 30 and 33. Abnormal values suggest that the level of minute ventilation is out of proportion to the exchange of O_2 or CO_2. High values are therefore due to either hyperventilation or increased physiological dead space.

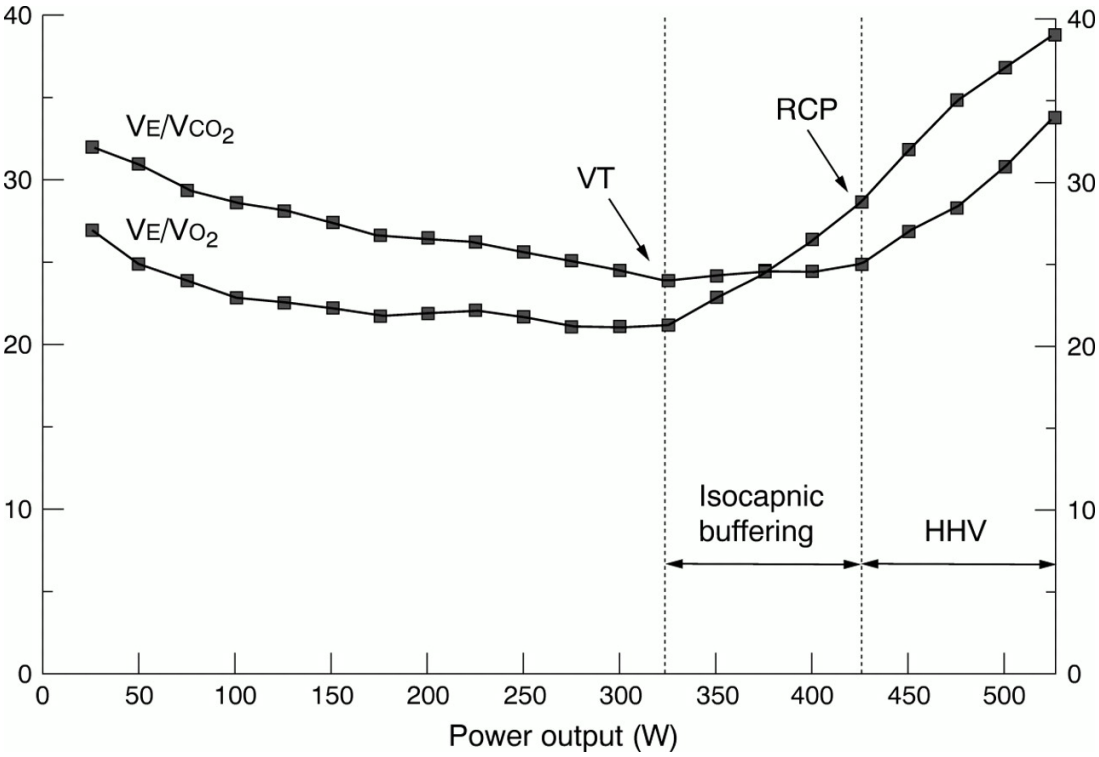


Figure 7 - Response of the ventilatory equivalents for $\dot{V}CO_2$ and $\dot{V}O_2$ to incremental exercise

Graphical representation of the $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slopes and their inflection points. VT represents the anaerobic (ventilatory) threshold, RCP the respiratory compensation point and HHV the hypocapnic hyperventilation range (Chicharro, 2000).

1.1.6 Respiratory Exchange Ratio (RER)

RER is the ratio of the instantaneous measurements of $\dot{V}CO2$ and $\dot{V}O2$ and represents the metabolic exchange of gases in the body's tissues and is dependent on the predominant fuel used for cellular metabolism. At rest the RER is typically 0.7-0.95 due to metabolism of a combination of carbohydrates and fats. At the onset of exercise, RER falls due to the initial more rapid increase in $\dot{V}O2$ relative to $\dot{V}CO2$. However, RER steadily increases with continuing incremental exercise and then rises more rapidly once the anaerobic threshold is reached, as a consequence of the increased CO_2 production from buffering of lactate.

Subject to an exercise test being completed to a symptom limited end point (or the identification of test termination criteria), peak RER can be used as an indicator of maximal effort with an RER of 1.10-1.15 being consistent with a maximal exercise test (‘ATS/ACCP., 2003; American College of Sports Medicine, 2013).

1.1.7 $\dot{V}E/\dot{V}CO_2$ slope

Ventilation can be plotted as a function of $\dot{V}CO_2$ and the slope of this relationship describes ventilatory efficiency i.e., the amount of air that must be ventilated to exhale 1 litre of CO_2. The slope will therefore increase when $PaCO_2$ is reduced by hyperventilation (Figure 8) and when dead space/tidal volume (VD/VT) is high (wasted ventilation). These can relate to respiratory or cardiac diseases that induce ventilation perfusion mismatching. A reduced $\dot{V}E/\dot{V}CO_2$ slope occurs when the $PaCO_2$ set point is raised as in primary alveolar hypoventilation (Arena et al., 2008).

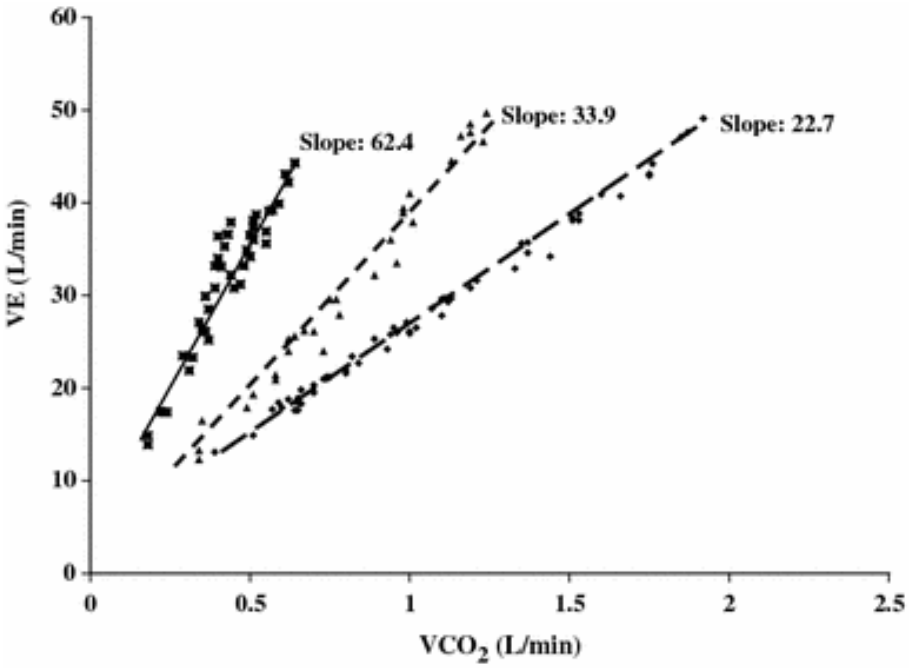


Figure 8 - The relationship between $\dot{V}E$ and $\dot{V}CO_2$ during an incremental exercise test.

The slope of the relationship between $\dot{V}E$ and $\dot{V}CO_2$ describes an individual's ventilatory efficiency. A slope of <30 can be considered normal with increasing slopes indicating inefficient ventilation which may relate to hyperventilation or increased dead space. An increased slope is classically observed in chronic heart failure and pulmonary hypertension (Arena et al., 2008).

1.1.8 Heart rate response

Heart rate increases linearly with work rate and $\dot{V}O_2$ reaching a peak value close to the predicted maximal heart rate. Peak heart rate is age dependent, falling with increasing age independent of cardiorespiratory fitness levels (Ozemek et al., 2017). There are several equations for predicting peak heart rate however the two most commonly used are those of Fox and Tanaka (Fox et al., 1971; Tanaka et al., 2001); see below. Both equations provide equivalent values in those under 40 years of age however the equation of Fox appears to underestimate in older adults (ATS/ACCP., 2003).

1. 220 – age (Fox et al., 1971)
2. 208 – (age x 0.70) (Tanaka et al., 2001)

Achievement of age-predicted normal values for heart rate during exercise reflects maximal or near maximal effort and consequently the achievement of peak $\dot{V}O_2$ however its strict use as an end of test marker is not recommended (ATS/ACCP., 2003). Heart rate reserve at peak exercise is calculated as HRmaxpred – HRpeak and is therefore effectively zero in a normal test. The demonstration of a heart rate reserve in a normal individual would suggest poor effort but would be expected in an individual using β-adrenergic blockade therapy.

1.1.9 Electrocardiogram (ECG)

Exercise ECG is an integral component of a CPET allowing the accurate measurement of heart rate but also allowing the identification of arrythmia and ischaemia that may not have been present at rest. The ST segment of an ECG is the flat section between the end of the S wave and the beginning of the T wave, Figure 9. It represents the time interval between ventricular depolarisation and repolarisation. The most important cause of ST segment abnormality (elevation or depression) is myocardial ischaemia or infarction and ST-segment depression is the most common manifestation of exercise-induced myocardial ischemia (Balady et al., 2010).

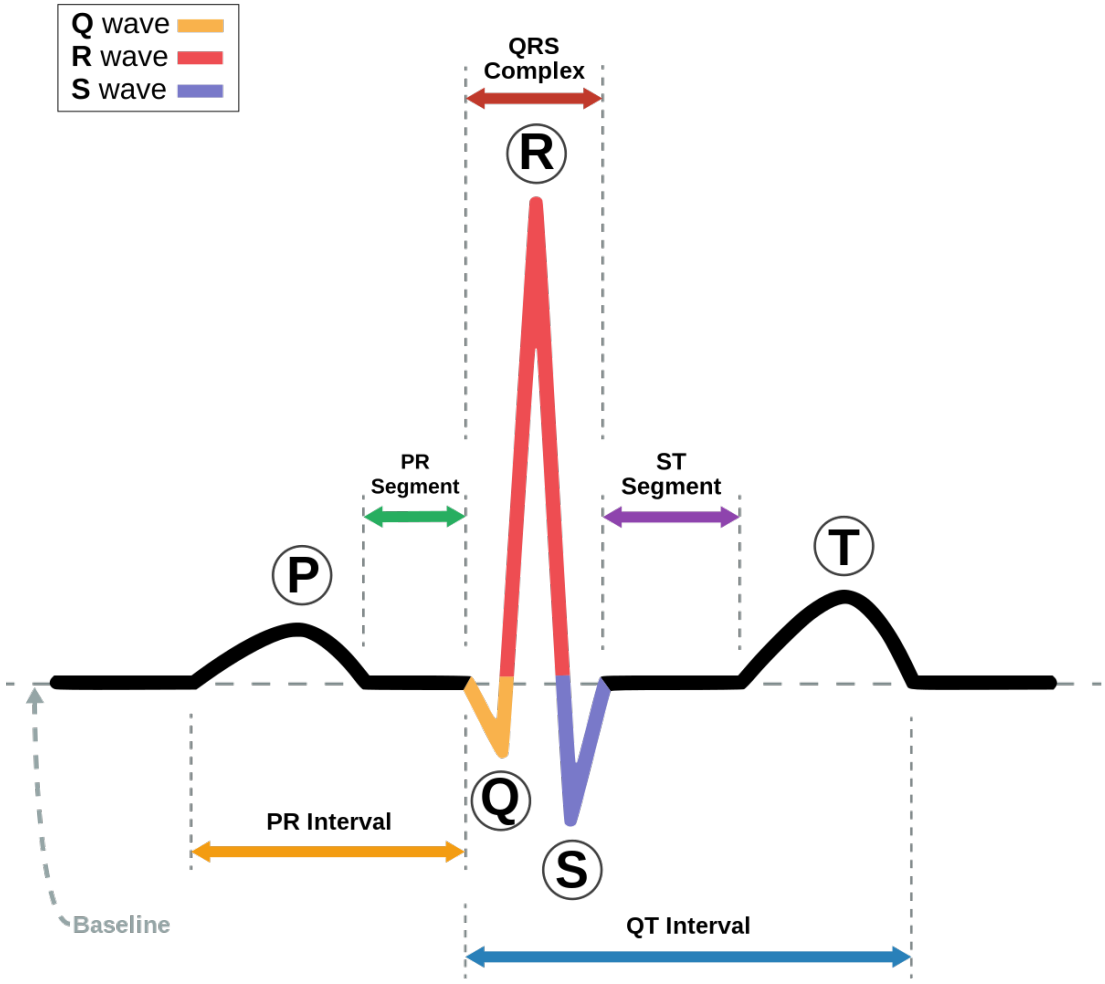


Figure 9 - Schematic representation of a normal ECG

Figure 8 illustrates the normal ECG and its three main components: the P wave, the QRS complex and the T wave. The ST segment represents the flat section between the end of the S wave and start of the T wave (Mesleh et al., 2012).

Epidemiological studies suggest the prevalence of minor (borderline ST depression) ECG changes on cardiopulmonary exercise testing is 10.4% in men and 9.5% in women with the frequency of abnormal findings rising exponentially with age. Major ECG findings have been observed in 6.0% of men and 4.3% of women (De Bacquer, 2000). Other cardiac abnormalities identified on exercise ECG include accessory pathway abnormalities such as Wolff-Parkinson-White syndrome (WPW) with a prevalence of 0.1% in females and 0.08% in males (van der Ende et al., 2017).

ECG evaluation has been effective in the reduction of sudden cardiac death (SCD) in young athletes. However, success is attributed to the detection of ion channel disease and accessory pathways which are evident on resting ECG's (Wilson et al., 2008). In contrast, most middle-aged athletes die from coronary artery disease which is rarely evident on a resting ECG and therefore current recommendations for identifying those at risk rely on the performance of a maximal exercise test (Crawford, 2007). It is however recognised that most abnormal exercise tests in asymptomatic middle-aged athletes represent a false-positive result and have low predictive accuracy (van de Sande et al., 2016).

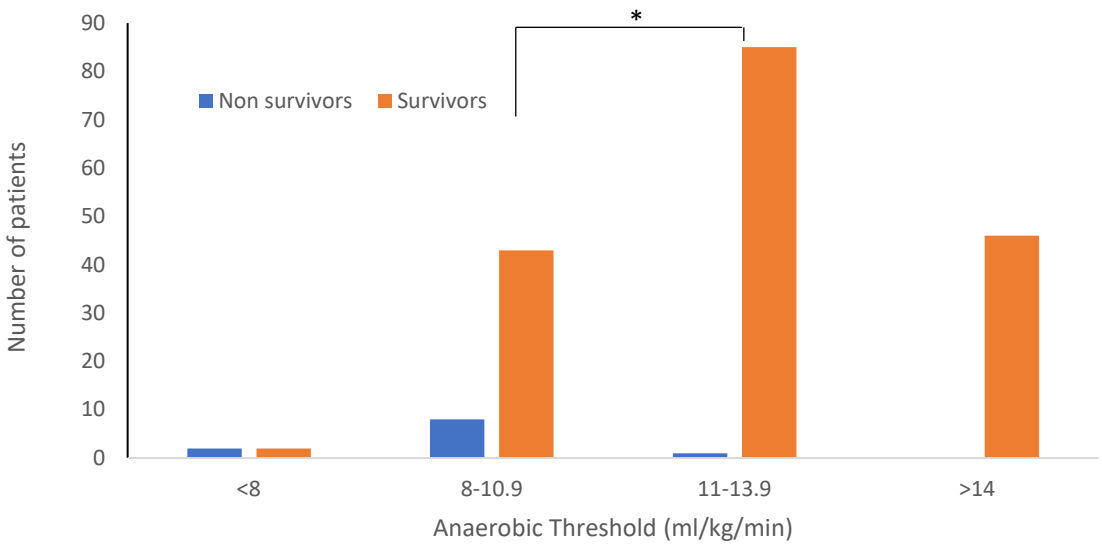
Utility of exercise induced ST segment depression for diagnosing ischaemic heart disease in women has been questioned with studies demonstrating that as many as 62% of females (mean age 54 +/- 7 years) meet the criteria for a positive ECG (Sharma et al., 2018). However, Laukkanen's (2009) study of 1769 men followed up over an 18 year period found that 72 participants died of SCD and that asymptomatic ST depression during exercise increased the hazard ratio suggesting a significant role in the identification of subsequent cardiac related death.

1.2 Clinical Utility of Cardiopulmonary Exercise Testing

The determination of peak oxygen uptake, anaerobic threshold and ventilatory equivalents enables the assessment of an individual's functional status. Exercise testing is being used increasingly in clinical practice to evaluate the level of intolerance to exercise. Often assessment of physiological status is made using investigations performed at rest such as lung function testing, electrocardiograms, and echocardiograms. However, these resting measurements correlate poorly with symptoms that occur during physical activity with the suggestion that organs and systems may fail more easily when under stress (Ferrazza et al., 2009). CPET is often termed the gold standard for assessing exercise intolerance as it provides a global assessment of the integrative responses of the cardiac, respiratory and musculoskeletal systems (Bonini and Fiorenzano, 2017).

1.2.1 Preoperative Assessment

In 1993, Older and colleagues described the novel role of CPET in the assessment and risk stratification of patients requiring major abdominal surgery (Older et al., 1993). Cardiopulmonary exercise testing was used to prospectively evaluate the preoperative fitness of 187 patients (mean age 70 years). Anaerobic threshold (AT) was found to be a strong predictor of post-operative mortality in their patient group (Figure 10). In addition, those with an AT <11 $ml.min^{-1}kg^{-1}$ and ischaemia on the exercise ECG were found to be at the highest risk of postoperative mortality (42%), compared to a mortality rate of 4% for patients with ischaemia but an AT >11 $ml.min^{-1}kg^{-1}$. The relationship between AT and surgical outcome was considered to relate to the parallel of AT to the post-operative situation whereby an increased cardiac output is required to satisfy the increased oxygen demand. Exercise tests for this study were terminated at maximal predicted workload and therefore there was no attempt to assess or identify maximal oxygen uptake.



* = p<0.001

Figure 10 - Anaerobic threshold to assess cardiovascular mortality

Figure 10 illustrates Older's comparison of cardiovascular mortality with anaerobic threshold. [Adapted from: (Older et al., 1993)]

Following the seminal study of 1993, Older performed a three year prospective study utilising the earlier findings to stratify post-operative management (Older et al., 1999). They used the AT cut off 11 $ml.min^{-1}kg^{-1}$ to triage 548 patients post-operatively to Intensive Care Unit (ICU) (AT <11), High Dependency Unit (HDU) (AT >11 with myocardial ischaemia or a $\dot{V}E/\dot{V}O_2$ >35) or ward-based care (AT>11). Twenty one of the 548 patients died post operatively, 19 of these had been classified high risk (AT <11) and managed accordingly. The remaining two patients were triaged to the ward and died of known neoplastic disease and not of post-operative complications.

The use of CPET to evaluate the risk of surgical adverse events and inform post-operative management has increased significantly since Older's original work. Consensus statements by both American (Fleisher et al., 2007) and European (Endorsed by: the European Stroke Organisation (ESO) et al., 2011) societies emphasize the requirement to assess patient's functional capacity prior to non-cardiac surgery however state that patients that demonstrate more than four metabolic equivalents (METS; ability to climb ≥1 flight of stairs without stopping) can proceed safely to surgery without further assessment. A recent large prospective

study of exercise tolerance before surgery found that subjective assessment had 19.2% sensitivity and 94.7% specificity for identifying the inability to attain 4 METs during CPET and therefore should not be used (Wijeysundera et al., 2018). The study also identified previously unknown arrhythmias and myocardial ischaemia in 2% of subjects illustrating the role of CPET in the detection of previously undiagnosed comorbidities. In addition, CPET has been demonstrated to predict all-cause morbidity including respiratory complications which in some cases are more prevalent than cardiac complications (Otto et al., 2020).

Studies now support the use of CPET for risk prediction in a wide range of surgical procedures including; major abdominal, colorectal, urological, hepatobiliary, liver transplantation, bariatric, vascular, thoracic and oesophageal-gastric surgery (Levett et al., 2018). A systematic review of CPET for intra-abdominal surgery identified risk cut off values for CPET variables in a range of surgical interventions which are further outlined below (Moran et al., 2016).

1.2.2.1 Abdominal aortic aneurysm surgery (AAA)

A systematic review of 6 published papers in 2012 concluded that CPET could not be recommended for assessment prior to AAA surgery due to a paucity of evidence for its use (Young et al., 2012). More recently additional evidence suggests that an AT < 10.2 $ml.min^{-1}kg^{-1}$ increases the risk of post-operative mortality and increases length of stay (LOS) in open surgery (Hartley et al., 2012; Prentis, Trenell, et al., 2012; Grant et al., 2015). This is also confirmed by Goodyear et al., (2013) who demonstrated that an AT >11 $ml.min^{-1}kg^{-1}$ improves post-operative survival and decreases LOS in both open and endovascular repair (EVAR). Both Grant et al., (2015) and Hartley et al., (2012) also identify a peak $\dot{V}O_2$ of <15 $ml.min^{-1}kg^{-1}$ as predictive of 90-day mortality ($p<0.05$). Grant et al., (2015) was the only study to assess the role of $\dot{V}E/\dot{V}CO_2$ at AT in predicting mortality and found a threshold of 42 to be significant ($p<0.05$).

1.2.1.2 Colorectal surgery

An AT <11 ml.min^{-1}kg^{-1} has been demonstrated to differentiate mortality at 30, 90 days and 2 years ($p<0.01$). Patients with an AT >11 ml.min^{-1}kg^{-1} also demonstrated a shorter LOS ($p<0.01$) (Lai et al., 2013).

1.2.1.3 Hepatobiliary surgery

A minimum AT of 9.9 ml.min^{-1}kg^{-1} has been shown to predict 90-day survival with an AT ≥ 11.5 ml.min^{-1}kg^{-1} predicting survival at one year (Junejo et al., 2012). Junejo et al., (2014) and Prentis, Manas, et al., (2012) did not demonstrate a relationship between AT and length of stay (LOS) however Bernal et al., (2014) demonstrated that an AT of ≥ 9.2 ml.min^{-1}kg^{-1} reduced LOS by 6 days ($p<0.03$). For both liver resection (Junejo et al., 2012) and pancreaticoduodenectomy (Junejo et al., 2014) the $\dot{V}E/\dot{V}CO_2$ at AT has been found to predict post-operative mortality with cut off values of 34.5 and 41 respectively, significantly increasing risk.

1.2.1.4 Thoracic surgery

Preoperative assessment prior to anatomical resection is essential to ensure that the surgical intervention does not result in long term disability or morbidity. CPET is considered to be the third tier of assessment for thoracic surgery following lung function and walking tests. Risk stratification is limited to peak $\dot{V}O_2$ (measured and % predicted) with an absolute value of <10ml/min/kg or 35% predicted (Brunelli et al., 2013; Roy, 2018) suggesting a high risk of mortality and >15ml/min/kg (Bolliger et al., 1995; *2019 exceptional surveillance of lung cancer: diagnosis and management (NICE guideline NG122)*, 2019) and >20ml/min/kg (Brunelli et al., 2013) considered medium and low risk respectively.

1.2.2 Cardiopulmonary exercise testing in cardiac disease

Reduced exercise capacity is a fundamental symptom of heart failure (Balady et al., 2010). Multiple aspects of the gas transport mechanisms illustrated in are affected by heart failure with the overall result a reduced exercise capacity. The ability to increase $\dot{V}E$ is challenged by abnormal lung mechanics and reduced gas transfer. The

requirement for increased O_2 transport to skeletal muscle is limited by anaemia and an abnormal cardiac output and oxygen utilisation at cellular level is impaired by a decrease in capillary density and mitochondrial content. This is further exacerbated by impaired sympatholysis and a loss of Type I muscle fibres (Malhotra et al., 2016).

Consequently, peak $\dot{V}O_2$ is now recognised as a strong, independent prognostic factor in patients' with heart failure (Albouaini et al., 2007). The HF-ACTION study identified peak $\dot{V}O_2$, %predicted peak $\dot{V}O_2$ and exercise duration time as the strongest predictors of mortality in heart failure patients with reduced ejection fraction (HFrEF) (Ritt et al., 2015). Studies looking at the role of peak $\dot{V}O_2$ in heart failure patients with preserved ejection fraction (HFpEF) also identified peak $\dot{V}O_2$ as the most important predictor of patient mortality (Haykowsky et al., 2011; Dhakal et al., 2015). The cause of a reduced peak $\dot{V}$O2 in both groups of heart failure has been found to be related to both decreased cardiac output (relating to reduced heart rate) and a decreased arterial-venous oxygen difference. Impaired peripheral oxygen extraction has been identified as the predominant limiting factor to exercise in both HFrEF and HFpEF and illustrates that non-cardiac factors play an important role in exercise limitation in these patient groups (Haykowsky et al., 2011; Dhakal et al., 2015).

A peak $\dot{V}O_2$ of ≤14 $ml.min^{-1}kg^{-1}$ was identified by Mancini (1991) as a threshold for consideration for cardiac transplantation due to a significantly reduced 1-year survival when compared to that post transplantation. Jaussaud (2011) questioned the ongoing validity of this threshold as it was developed prior to the beta-blocker era of heart failure management and suggests a cut off of <12 $ml.min^{-1}kg^{-1}$ or <50% predicted in the younger age group or those with obesity. Jaussaud also introduced the role of the $\dot{V}E/\dot{V}CO_2$ slope in the exercise analysis of heart failure. Several studies have identified the $\dot{V}E/\dot{V}CO_2$ slope to be prognostically superior to peak $\dot{V}O_2$ in heart failure patients (Ponikowski et al., 2001; Corrà et al., 2002; Arena et al., 2007). Reasons for this relate to the fact that peak $\dot{V}O_2$ is reliant on patient effort and the contribution of peripheral metabolism as described earlier. In contrast $\dot{V}E/\dot{V}CO_2$ is generally independent of subject effort. Limitations to increasing $\dot{V}E$ in heart failure is related to decreased cardiac output and gas transfer and therefore the $\dot{V}E/\dot{V}CO_2$

slope has a closer reliance on cardiac performance resulting in a greater prognostic accuracy in heart failure (Malhotra et al., 2016).

A summary of the interpretation of CPET variables for the risk stratification of heart failure can be found in Figure 11.

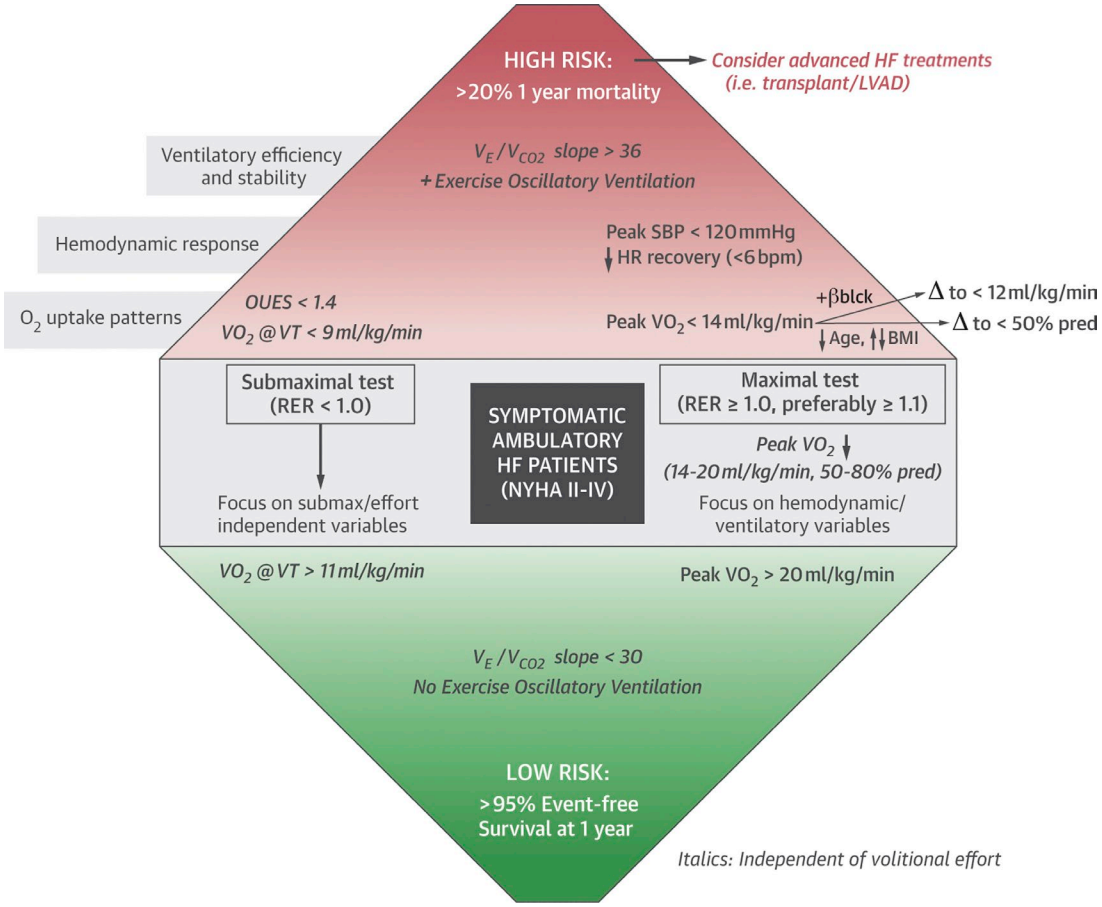


Figure 11 - Interpretation of cardiopulmonary exercise tests in heart failure.

Integrated assessment of CPET variables for risk stratification in heart failure (Malhotra et al., 2016). CPET results identifying heart failure patients at high risk are illustrated in the red area and include interpretation strategies according to subject age, weight, and beta blocker usage.

1.2.3 Respiratory Function

Indications for the performance of CPET in chronic lung disease are summarised in a recent statement by the European Respiratory Society (Radtke et al., 2019) and include:

1. Evaluation of out of proportion exertional dyspnoea/exercise intolerance
2. Preoperative assessment
3. Assessment for pulmonary rehabilitation
4. Functional/disability, prognostic and response to treatment evaluation of patients with COPD, pulmonary arterial hypertension, pulmonary vascular disease, ILD and CF
5. Assessment of exercise induced desaturation

1.2.3.1 Chronic Obstructive Pulmonary Disease (COPD)

The most common symptom experienced by patients with COPD is dyspnoea during physical activity (O'Donnell et al., 2016). Chronic breathlessness, decreased exercise capacity and habitual physical inactivity are inexorably linked and are strong predictors of reduced survival in COPD (Waschki et al., 2011). In COPD, CPET is used as an objective measure of exercise capacity, to identify limitations to exercise and to assess for other causes of exercise intolerance.

Exercise intolerance in these patients is identified by a reduced peak $\dot{V}O_2$ (<80% predicted) and is usually related to an inability to increase ventilation ($\dot{V}E$) sufficiently to maintain gas exchange at higher exercise intensities. This results in a reduced ventilatory reserve at peak exercise (maximal voluntary ventilation (MVV) – peak $\dot{V}E$) consistent with ventilatory limitation (Roca et al., 1997).

Poor ventilatory efficiency has been found to be a key physiological abnormality in symptomatic patients with largely preserved lung function parameters (mild COPD). The physiological basis for this stems from the increased physiological dead space seen in COPD which results in an increased $\dot{V}E/\dot{V}CO_2$. A high $\dot{V}E/\dot{V}CO_2$ nadir is linked to earlier attainment of dynamic mechanical constraints e.g., inspiratory reserve

volume, which explains the increased exertional dyspnoea and decreased exercise tolerance in patients with only mild COPD (O'Donnell et al., 2016).

1.2.3.2 Interstitial Lung Disease (ILD)

CPET is becoming an increasingly useful tool in the assessment of exertional dyspnoea and the determination of prognosis in patients with ILD (Bonini and Fiorenzano, 2017). Exertional dyspnoea and exercise intolerance is multifactorial in ILD. Vital capacity (VC) and lung compliance are decreased limiting the ability to increase $\dot{V}E$ with increasing exercise and increasing the mechanical and metabolic cost of breathing for a given $\dot{V}E$. Increases in ventilation, as with healthy individuals, are initially achieved by increasing VT however this plateau's much earlier in ILD. Further increases in ventilation are then achieved by dramatically increasing breathing frequency. Typically, this leads to a decreased ventilatory reserve at peak exercise consistent with ventilatory limitation. This pattern of breathing also contributes to the abnormally high VD/VT ratio seen in ILD.

Exercise induced arterial oxygen desaturation is common in ILD due to impaired gas exchange with a desaturation ≥10% related to an increase in mortality (Lama et al., 2003; Vainshelboim et al., 2016). Damage to the pulmonary capillary bed can lead to pulmonary vascular remodeling which can lead to cardiovascular limitation to exercise. Cardiac output may be limited by a reduced stroke volume at higher exercise intensities and this can be identified by a decreased oxygen pulse and inability to achieve maximal predicted heart rate (however early test termination due to symptoms may also impact peak heart rate achievement) (Molgat-Seon et al., 2020).

Pulmonary capillary destruction also impairs circulation along with hypoxic pulmonary vasoconstriction and can contribute to the evolution of pulmonary hypertension. Inadequate pulmonary blood flow increases dead space and therefore both $\dot{V}E/\dot{V}CO_2$ and VD/VT are increased and become useful indicators of possible concomitant pulmonary hypertension in ILD (Bonini and Fiorenzano, 2017).

Peripheral muscle dysfunction (e.g. reduced force-generating capacity or weakness and reduced muscular endurance and/or contractile fatigue (Wickerson et al., 2016)) is also emerging as an important contributing factor to exercise limitation in patients with ILD that may have important implications for morbidity and mortality (Bonini and Fiorenzano, 2017). The use of CPET to identify peripheral muscle dysfunction that may have previously gone unaddressed (Cintrão Samouco et al., 2018) is warranted as it is potentially remediable through stimulation of angiogenesis with exercise/rehabilitation (Hendrickse and Degens, 2019).

Peak $\dot{V}O_2$ is a strong predictor of prognosis in ILD with a value of <8.3ml.kg^{-1}.min^{-1} (Vainshelboim et al., 2016) or <65% predicted peak $\dot{V}O_2$ (Wallaert et al., 2011) associated with lower survival at three years. The combination of $\dot{V}E/\dot{V}CO_2$ slope and peak $\dot{V}O_2$ correlates strongly with survival (Triantafillidou et al., 2013) with a slope of >45 independently associated with lower survival at 3 years (Wallaert et al., 2011).

1.2.3.3 Pulmonary arterial hypertension

CPET variables have been demonstrated to provide high diagnostic accuracy for pulmonary arterial hypertension (PAH) in patients with dyspnoea of unknown origin. In those with a reduced peak $\dot{V}O_2$, a combination of an increased $\dot{V}E/\dot{V}CO_2$ slope and a reduced end tidal CO_2 ($PETCO_2$) is highly suggestive of PAH (Farina, 2017). In patients with PAH and chronic thromboembolic pulmonary hypertension (CTEPH) a peak $\dot{V}O_2$ <10.4 mL.min^{-1}.kg^{-1} suggests a 1.5-fold increase in mortality at 24 months. Where the $\dot{V}E/\dot{V}CO_2$ at AT is >55, this increases to a 7.8-fold increase (Schwaiblmair, 2012).

1.2.4 Spinal Cord Injuries

Immobility following spinal cord injury (SCI) can lead to an increase in total and abdominal fat due to neuromuscular limitations and decreases in activity following injury (DiCarlo et al., 1983). This can lead to secondary complications such as diabetes and cardiopulmonary disease (Akkurt et al., 2017). Consequently, physical activity is recommended to combat the effects of weight gain however exercise regimes are limited. Arm ergometry is recognised as a tool for the evaluation of fitness and the

prescription of exercise in subjects with SCI (Drory et al., 1990) leading to significant improvements in peak $\dot{V}O_2$ (Akkurt et al., 2017), endurance capacity (Bougenot et al., 2003) and static seated balance (Williams et al., 2020).

1.3 Arm Ergometry Exercise

The arm ergometer is an arm cycle/arm crank that offers an alternative exercise mode to standard cycle ergometry or treadmill testing. As arm ergometry exercise is performed in the seated position it is a useful form of exercise in those with spinal cord injuries, Figure 12.

Figure 12 - Illustration of the Ergoline 400+ arm ergometer.

The absolute physiological values ($\dot{V}O_2$ and anaerobic threshold) measured using the arms have been demonstrated in previous studies to be lower than those obtained when using the legs (Reybrouck et al., 1975; Eston and Brodie, 1986). The obvious reasons for this are the larger muscle mass of the legs (Wan et al., 2017; Muangkram

et al., 2020) and the mechanical differences of cycle and arm ergometers (Dekerle et al., 2002).

Since 1975, a number of studies have been undertaken looking at the physiological responses to arm exercise. The earliest by Reybrouck et al., (1975) included three subjects and concluded that anaerobic threshold occurred at a lower percentage of peak $\dot{V}O_2$ when using the arm compared to the leg. Two further studies in the 1980's by Eston and Brodie (1986) who studied 19 males (mean age 27.7 years) and Hagan et al,. (1983) who studied 30 participants (15 male) agreed that peak $\dot{V}O_2$ is significantly lower when obtained by arm ergometry. Both studies also found that during the submaximal phases of exercise, $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}E$ and RER were higher for any given work rate on arm ergometry. This suggests a decreased exercise efficiency when using the arms.

Authors have demonstrated that the arm pedal rates chosen can influence measurements with higher pedal rates causing levels of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$ to be raised for any given work rate (Hughes et al., 1982). Unfortunately, the studies by Eston and Brodie, (1986) and Hagan et al., (1983) do not list the pedal speed (rpm) in their methodologies and therefore it is difficult to determine whether this has influenced their findings. Of interest also is that both studies utilized a Schwinn Air Dyne ergometer which is an air resistance bike rather than an electronically braked arm ergometer that has been used in other studies. Electromagnetic bikes create resistance by applying pressure to the flywheel whereas air bikes create resistance as the fan blades of the fly wheel push against air. Consequently, the faster you ride an air bike the more resistance is generated, and this therefore could have contributed to the decreased exercise efficiency.

Orr et al., (2013)compared anaerobic threshold and peak $\dot{V}O_2$ in 15 women randomized to arm or cycle ergometry. Again, this study determined that peak $\dot{V}O_2$ measured using arm ergometry was significantly lower than that measured using a cycle (25 $ml.kg^{-1}.min^{-1}$ versus 40 $ml.kg^{-1}.min^{-1}$ $p<0.0001$). However, they also found a significant correlation between AT on arm and cycle ergometer ($r^2 = 0.60$; $p = 0.0007$)

and suggested that this meant that arm ergometry anaerobic threshold could be used to estimate surgical fitness in the same way as cycle ergometry.

All these studies have demonstrated that anaerobic threshold occurs at a lower oxygen uptake when using arm ergometry compared to cycling. Consequently, absolute values for anaerobic threshold and peak $\dot{V}O_2$ obtained during arm exercise are lower than when determined using the legs (Nikolić and Todorović, 1984; Dekerle et al., 2002). However, the evidence is less clear regarding anaerobic threshold when expressed as a percentage of maximal achieved or peak $\dot{V}O_2$. Sawka (1983) found no difference in anaerobic threshold across exercise modalities with an AT of 50% predicted $\dot{V}O_2$ for both arm and leg exercise in their group of nine males (mean age 28 years). Dekerle et al., (2002) also found no significant difference between AT%$\dot{V}O_2$max; 57.2% versus 54.0% for leg and arm exercise respectively. This is in contrast to the early studies by Reybrouck et al., (1975) and Davis et al., (1976) who found anaerobic threshold as a percentage of peak $\dot{V}O_2$ to be significantly lower for arm ergometry and generally less than 50% peak $\dot{V}O_2$.

The muscles used during an arm ergometry test are predominantly the biceps, triceps, brachial, and deltoid muscles. In contrast, during cycle ergometry the primary muscles used are the quadriceps, hamstrings, calf muscles and gluteus maximus. Therefore, the muscles used when arm cycling are smaller and, compared to the legs which are used for everyday activities such as walking, generally less well conditioned. A smaller muscle needs to develop a greater percentage of its maximal tension which leads to an increase in intracellular metabolites such as H^+, lactate and inorganic phosphate (P_i) resulting in skeletal muscle fatigue earlier than would occur in a larger muscle group (Wan et al., 2017; Muangkram et al., 2020).

In addition to muscle size, the muscles of the arms have a larger percentage of Type II muscle fibres (fast twitch) which have a higher oxygen cost than slow twitch (Ørtenblad et al., 2018), resulting in an increase in anaerobic metabolism which again will result in earlier termination of exercise. It has also been suggested that there is a larger static exercise component during arm ergometry testing due to the

requirement to grip the arm crank (Dekerle et al.,, 2002). This is important as it has been shown that even light static exercise can induce a greater increase in heart rate and blood pressure than dynamic exercise at the same $\dot{V}O_2$ level (Hietanen, 1984).

In the arms, mean oxygen extraction is closely related to the mean *in vivo* P50 value (oxygen tension when heamoglobin is 50% saturated with oxygen) (Calbet et al., 2005). For a given P50 the upper extremities extract less oxygen than the lower extremities, which is associated with a lower oxygen conductance (Calbet et al., 2005). Therefore, for a given oxygen demand, a greater oxygen delivery is needed for exercising arms than leg muscles.

These early studies are consistent in their findings that $\dot{V}O_2$ peak is significantly lower when determined using arm ergometry. This can be explained by the physiology of the muscle groups used for each exercise. There is, however, inconsistency in the literature regarding anaerobic threshold and its relationship to peak $\dot{V}O_2$. Studies to date have been limited by small sample sizes, have used predominantly male subjects, and have lacked a diversity of ages. A more heterogenous study population is important as it has been demonstrated that $\dot{V}O_2$ peak declines with age and is lower in females (Koch et al., 2008).

A systematic review and meta-analysis undertaken in 2016 by Larsen et al., (2016) of studies performed between 1973 and 2014, compared $\dot{V}O_2$ max values obtained from arm and leg ergometry in 41 studies with a total of 581 healthy individuals. A total of 36 groups and 413 subjects reported data for the arm ergometry, leg ergometry difference (AELEdiff) in ml/kg/min with a mean difference of 12.5 ml/kg/min (95% CI: 10.3 to 14.7) or 0.89 l/min (95% CI: 0.78 to 1.00) and a mean ratio of 0.70 (95% CI: 0.66 to 0.75) in favour of leg ergometry. Lower participant mean age and higher aerobic capacity were found to be significantly associated with an increased AELEdiff.

The mean difference in the two techniques I^2 value was 59.9% suggesting that the results of the meta-analysis could be affected by substantial study heterogeneity.

The studies included predominantly male participants (66%) with only 45.3% of studies randomising the order of investigations which may account for this heterogeneity, and these should both be addressed in future studies.

1.3.1 Repeatability

Due to the role of exercise impairment in the assessment of disease and prognosis, it is essential that exercise testing methods are reliable and reproducible in both healthy individuals and across a range of patient cohorts.

Studies looking at test-retest repeatability of cycle ergometry exercise tests in normal healthy subjects have found no significant difference between repeated tests and demonstrated coefficient of variations for peak $\dot{V}O_2$ as low as 4.9% increasing to 10.4% for anaerobic threshold (Decato et al., 2018). Earlier studies looking at repeatability in physically 'trained' versus 'non trained' subjects again found no significant difference between tests reporting coefficient of variations for $\dot{V}O_2$ max of 8 and 13% for trained and untrained subjects respectively (Bingisser et al., 1997).

Cardiopulmonary exercise testing using cycle ergometry has also been demonstrated to be a repeatable and reliable test in a wide range of patient groups including patients with COPD (Barron et al., 2014), pulmonary arterial hypertension (Hansen et al., 1984), heart failure (Meyer et al., 1997; Bensimhon et al., 2008; Barron et al., 2014), valvular heart disease (Lehmann and Kölling, 1996; Barron et al., 2014) and the elderly (Marburger et al., 1998). Peak $\dot{V}O_2$ in particular demonstrates intraclass correlation coefficients (ICC) as high as 0.95 with 95% CI of 0.94-0.97. Parameters of ventilation have also demonstrated repeatability with R values of ≥0.87 for inspiratory capacity and ≥0.92 for ventilation ($\dot{V}E$) (O'Donnell et al., 2009). This high reliability of CPET parameters allows the results of exercise tests to be interpreted with confidence and without the need to perform multiple attempts, which would likely be prohibitive in many patient groups.

Studies looking at the repeatability of CPET parameters when using arm ergometry report similar findings although studies are smaller in number. Leicht (2009) assessed

the repeatability of peak $\dot{V}O_2$ determination using arm ergometry in a group of 15 females (mean age 27 years). No statistical differences were found between the peak $\dot{V}O_2$ performed on each test with a mean peak $\dot{V}O_2$ 2.69 (0.57) and 2.70 (0.58) L/min and ICC 0.87. Bulthuis (2010) also looked at the repeatability of arm ergometry but for submaximal exercise tests. Repeatability was assessed by comparing the mean heart rate during the 5th and 6th minutes of each arm ergometry test. Fifteen subjects (11 females, mean age 21 years) performed two studies with an ICC of 0.76 (95% CI: 0.41-0.92, $p<0.001$) again confirming good test to retest reliability.

Repeatability of arm ergometry has also been assessed in selected patient groups. Durrand (2018) performed repeated arm ergometry tests in a group of 16 subjects (mean age 69.7 +/- 6.7 years) with abdominal aortic aneurysms (mean aneurysm size 3.7 +/- 0.7 cm). No statistically significant difference was found, with a mean peak $\dot{V}O_2$ on first and second test of 13.76 (3.00) and 13.80 (2.84) $ml.kg^{-1}.min^{-1}$ respectively and ICC (95% CI) of 0.87 (0.86-0.88) for peak $\dot{V}O_2$ and 0.65 (0.61-0.69) for anaerobic threshold.

Gorman et al., (2014) evaluated the repeatability of arm ergometry in a group of 21 subjects (19 males, mean age 51.1 ± 13.7 years) with spinal cord injury. Peak $\dot{V}O_2$ was not found to be different across the two tests (16.3 +/- 6.4 and 16.7 +/- 4.9 $ml^{-1}kg^{-1}min^{-1}$). The authors defined high reliability as a correlation of >0.85 and therefore the significant correlation of $r = 0.95$; $p<0.01$ confirmed repeatability.

Evidence confirms the repeatability and reliability of cardiopulmonary exercise testing parameters regardless of exercise modality used. The findings illustrate that cardiopulmonary exercise test outcome variables do not demonstrate a significant learning effect and therefore single investigations are suitable for clinical decision making and for the purpose of research studies.

1.3.2 Heart rate response

Smaller or less conditioned muscles may limit exercise before the heart and lungs are maximally stressed (Sawka et al., 1983). The lower peak $\dot{V}O_2$ observed during arm

exercise testing suggests that arm ergometry CPET stresses the cardiorespiratory system less than leg cycling. Several studies have compared the peak heart rate achieved during maximal cardiopulmonary exercise tests using arm ergometry and leg ergometry. Table 1 summarises the findings which demonstrate that peak heart rate achieved during leg exercising is, in the majority of studies, significantly higher than that achieved during arm exercise. The standardised mean difference was calculated for each study as the mean difference/standard deviation. Given the within subject nature of these comparisons the standard deviation of this difference was adjusted using the method described in chapter 16.4.6.1 of the Cochrane Handbook using an imputed r-value of 0.5 (Higgins and Green, 2011). The standardised mean differences demonstrate that peak heart rate obtained by leg ergometry is higher than that achieved using arm ergometry in all studies however this effect is only small in the studies by Dekerle et al., (2002) and Leicht et al., (2009).

Table 1. Summary of the literature comparing peak heart rate on arm ergometry with that determined using leg ergometry.

	Peak Heart Rate (bpm)			
	Arm (SD)	**Leg (SD)**	**SMD**	**Subject Group**
Orr (Orr et al., 2013)	164 (23)	181 (6)*	0.82	15 Females, mean age 23.5 years
Dekerle (Dekerle et al., 2002)	187 (7.6)	189 (8.8)	0.19	20 Males, mean age 22 years
Mitropoulos (Mitropoulos et al., 2017)	142 (15.6)	151 (14.9)*	0.54	6 Males, 6 Females, mean age 55 years
Muraki (Muraki et al., 2004)	166 (12.9)	178 (7.9)*	1.12	27 Females, mean age 19.9 years
Leicht (Leicht et al., 2009)	141 (9)	150 (12)*	0.28	12 Males, mean age 25 years
Kang (Kang et al., 1997)	170 (16.9)	180 (14.3)*	0.62	8 Males, mean age 21 years
Pogliaghi (Pogliaghi et al., 2006)	149 (19)	158 (13)	0.54	18 Males, mean age 69 years

* = $p<0.05$; SMD = standardised mean difference using Cohen's *d* effect size small = 0.2; medium = 0.5; large = 0.8; very large = 1.3 (Sullivan and Feinn, 2012).

The majority of studies comparing heart rate response across the two modalities have been undertaken in the younger population (<25 years of age) and with single gender groups. All except one of the studies in the younger population demonstrated that peak heart rate achieved using arm ergometry is statistically significantly lower than that achieved using the legs. Peak heart rate is between 2 and 13 bpm lower during arm than leg ergometry. The peak heart rate values achieved in the study by Leicht et al., (2009) appear lower than those from other studies of similar age groups.

This is because for this study subjects undertook intensity matched exercise at 60% of a previously determined peak $\dot{V}O_2$ for both modalities and therefore is not maximal heart rate.

Two studies compared heart rate response in the older age range (>55 years). Mitropoulos et al., (2017) found a significant difference between peak heart rate on arm and leg in contrast to Pogliaghi's group (Pogliaghi et al., 2006). The Pogliaghi group was larger and consisted only of males whereas the Mitropoulos group was 50% female. Balady et al., (1990) studied a group of males and females with ages ranging between 20 and 59 years of age and found that males reached a greater peak heart rate than women (170 ± 20 versus 158 ± 18, $p<0.001$). This suggests that the significant difference in the Mitropoulos group may relate to gender bias. However, the effect size demonstrated in the all-female studies of Orr et al., (2013) and Muraki et al., (2004) are the largest suggesting that there is currently insufficient evidence to determine if peak heart rate across the modalities is influenced by increasing age or by gender.

The consensus is that peak heart rate is significantly greater when leg cycling than arm cycling. This higher peak heart rate could be explained by the greater muscle mass in the lower limbs that stresses the cardiovascular system more than the upper limb musculature. Achieving a peak heart rate of >85% predicted is a criterion for demonstrating that a maximal exercise test has been performed. However, the heart rate predicted equations commonly in use today were developed using studies of lower body exercise. The standard equations for predicting maximal heart rate are the Fox (Fox et al., 1971) 220 - age and the Tanaka (Tanaka et al., 2001) 208 – 0.7 x age equations. If arm ergometry does not stress the cardiovascular system to the same degree, then these predicted equations have the potential to overestimate maximal predicted heart rate on an arm exercise test and limit the ability to achieve a maximal test criterion. Hill et al., (2016) demonstrated that traditional formulae for predicting peak heart rate overpredicted during arm cycling and that equations from lower body exercise modes cannot be used interchangeably with upper body exercise modes.

The Fox et al., (1971) equation is of limited value in the older population as the majority of subjects included were <55 years of age. This is evident in the Tanaka et al., (2001) paper where greater differences between the two equations were noted in the older population, with Fox et al., (1971) underestimating peak heart rate when compared to Tanaka et al., (2001) in those aged over 60 years. As a result of these discrepancies when performing arm ergometry exercise, Hill et al., (2016) recommends that the 220 - age predicted equation is adjusted by subtracting 10 bpm for older adults or if using the Tanaka et al., (2001) equation, 20 bpm. In the younger age group Hill et al., (2016) suggests subtracting 15 bpm from the Tanaka et al., (2001) and 20 bpm from the Fox et al., (1971) equations. Hill et al., (2016) has demonstrated the limitations of the traditional equations, however the proposal to adjust these equations is significantly limited by specifics such as definitions of older and younger populations. These studies identify a need to develop a specific equation for predicting peak heart rate using arm exercise testing modes.

One of the important indications for performing a cardiopulmonary exercise test, and also a safety criterion for terminating testing, is the detection of cardiac events. If arm ergometry does not illicit the same heart rate response, then there is a concern that it may not identify cardiac changes induced by strenuous exercise. Studies by Hanson et al., (1988), Ilias et al., (2009) and Chan et al., (2013) suggest that despite not maximally stressing the cardiorespiratory system, arm ergometry exercise testing is sufficient to identify compromised cardiorespiratory function. Ilias et al., (2009) used arm ergometry to predict all-cause mortality in 359 patients and found its prognostic value consistent with that reported for treadmill or leg cycle. Martin et al., (2015) reports arm exercise to be equivalent to pharmacological myocardial perfusion imaging in predicting cardiovascular mortality whilst not exposing the patient to radiation and being considerably less expensive.

1.3.3 Crank speed

In 1983 Sawka et al., (1983) hypothesised that when a small active muscle mass is used, the development of a higher proportion of its maximal tension is required to

achieve a given power output. This increase in tension could exceed perfusion pressure resulting in a decrease in oxygen delivery to the muscle and an earlier transition from aerobic to anaerobic metabolism. Sawka's et al., (1983) theory was that if a given workload is completed using a faster crank speed, lower muscle tension would be produced resulting in better muscle perfusion and delayed muscle fatigue. He reviewed the impact of test protocol on measurement outcomes, looking at the impact of continuous versus intermittent protocols and also the influence of crank speed and concluded that a combination of a continuous design and a crank rate of 70 rpm provided the most effective protocol to elicit peak $\dot{V}O_2$ values.

Findings from an early study by Bartsokas et al., (1989) evaluating the impact of varying crank speed, contrast with more recent evidence. Their study used crank speeds from 50 to 80 rpm (in increments of 10) and looked at its impact on peak $\dot{V}O_2$, maximal heart rate and maximal dyspnoea. They performed multiple, 1 min, 10-watt incremental exercise tests in a group of 22 (11 male) subjects mean age 32 years. Their results suggested that crank frequency between 50-80 rpm has no influence on peak $\dot{V}O_2$, maximum heart rate or maximal dyspnoea scores.

More recently, studies have again reviewed the impact of chosen arm crank speed on performance with speeds varying from 50 to 90 revolutions per minute (rpm). Price et al., (2007) describes how for a given power output during arm crank ergometry, a decrease in cadence requires greater force generation and ranges of motion when compared with faster cadences. In their study, 10 male subjects (mean age 30.4 ± 5.4 years) performed incremental exercise tests to volitional exhaustion at randomly assigned crank speeds of 50, 70 and 90 rpm. Results demonstrated that peak oxygen uptake was significantly lower at 50 rpm (2.79 ± 0.45 l/min^{-1}) when compared to 70 rpm (3.16 ± 0.58 l/min^{-1}) and 90 rpm (3.24 ± 0.49 l/min^{-1}); $p<0.05$. Total exercise time and peak power output were greater at 70 rpm (745 ± 166 s and 160 ± 30 watts) than either 50 (657 ± 113 s and 144 ± 19 watts) or 90 rpm (685 ± 147 s and 150 ± 26 watts), $p<0.05$ suggesting that 70 rpm is the optimal crank speed.

Smith et al's., (2001) study of 20 males (mean age 24.9 ± 5.9 years) used a protocol of four minutes exercise at 30, 50, 70 and 90 watts with the tests repeated at crank speed frequencies of 60, 70 and 80 rpm. As with Price et al., (2007), they found that the higher crank speeds produced the greater values for peak $\dot{V}O_2$. However, whereas Price et al., (2007) found that 70 rpm elicited the greatest value for power and test duration, Smith et al., (2001) found that it was their fastest crank speed (80 rpm) that produced statistically significantly higher values for ventilation and heart rate (both $p<0.05$). This difference in findings may relate to the choice of crank speeds for each study with Price et al., (2007) using 50, 70 and 90 rpm and Smith et al., (2001) 60, 70 and 80 rpm. In addition, differences in their choice of protocol may have influenced these findings with Price et al., (2007) starting at a higher wattage of 50 but shorter duration of only 2 minutes in each stage.

Due to the potential influence of crank speed on performance, studies have evaluated the use of self-selected crank speeds. Both Dekerle et al., (2002) and Weissland et al., (1997) found that when crank speed is decided upon spontaneously, speed increases significantly (Weissland et al., (1997), 74.4 to 81.4 rpm; $p<0.01$) and linearly (Dekerle et al., (2002); $p<0.05$) in relation to power output. However, large variations of pedal rate strategies were found between subjects making it an inappropriate protocol for research studies.

1.4 Reference Ranges for Cardiopulmonary Exercise Testing

The concept of reference values was first introduced in 1969 by Grasbeck and Saris (Grasbeck and Saris, 1969). A reference range provides an indication of the variation of a measurement within healthy individuals (Häggström, 2014). They allow the evaluation of whether a results deviation from the mean is a consequence of random variability or due to underlying pathology.

The International Federation for Clinical Chemistry (IFCC) outline the requirements for the development of reference intervals (Solberg, 2004). Reference intervals are defined as the prediction interval between which 95% of values of a reference group fall into, with 2.5% falling below the lower limit of normal (LLN) and 2.5% being above the upper limit of normal (ULN). For example, the reference interval for haemoglobin A1c (HbA1c) levels are 4-5.9%. We expect 95% of the population (without diabetes) to fall within this interval with values outside of this range highly likely to represent disease.

Pulmonary function varies with age, height, sex and ethnicity and therefore obtained results need to be compared to predicted values and lower and upper limits of normal rather than a single reference interval for all subjects (Quanjer et al., 2012). Studies developing reference values for physiological variables such as CPET parameters utilise regression analysis adjusted for confounding variables such as age, height, and weight. The use of quantile regression allows the calculation of any quantile (%) for a particular variable in addition to the mean (predicted value in addition to ULN and LLN).

1.4.1 Cycle ergometry

Cycle ergometry is an established method for assessing functional capacity and is used in a variety of clinical situations to assess prognosis and make clinical decisions. It is therefore essential that reference values for exercise test parameters are accurate to ensure correct interpretation of the results. Inadequate reference equations impact on differential diagnosis, risk stratification and appropriateness for

surgical and invasive interventions. Waterfall and colleagues (2020) compared the results of 766 paediatric subjects with both Cooper and Weiler-Ravell, (1984) and Bongers et al., (2016) regression equations and found the mean peak $\dot{V}O_2$ percent predicted to be 11% greater when using Cooper and Weiler-Ravell, (1984).

A large number of reference equations for cycle ergometry are available but the majority of these are from studies using small sample sizes, heterogenous exercise protocols, variable normalization strategies and inadequate adjustment for confounding factors, see below (Waterfall et al., 2020). The ATS/ACCP (2003) have published a set of fourteen requirements for the development of an optimal set of reference values. Paap and Takken (2014), in a systematic review of reference values, compared studies to these 14 requirements and considered studies with a score of ≥10 to be high quality, 7-9 moderate quality and ≤6 low quality. The ATS/ACCP's fourteen standards for high quality reference value studies are summarised below in Table 2.

Table 2. The ATS/ACCP's fourteen standards for high quality reference value studies.

1	Subjects' community based.
2	Level of physical activity is reported.
3	Exclusion of different racial groups.
4	Exclusion of smokers in the sample studied.
5	No lack of definition of the confidence limits for individual or specified characteristics.
6	The number of subjects tested is sufficiently equal or larger than the appropriately powered sample size, with a uniform distribution of subjects for sex and groups.
7	Randomisation was applied.
8	A prospective study design.
9	Quality control was applied.
10	Exercise testing protocol and procedures are described.
11	Results are obtained by either breath-by-breath analysis or mixing chamber.
12	CPET result in interval averaged preferably every 30-60 seconds and the peak value reported represents the mean of the last completed stage or of all the data collected during the final stage, but preferably for no less than 30 seconds.
13	Reference equations are validated in population other than those used to generate the existing data.
14	The function that most accurately describes the distribution of the data are used.

The Paap and Takken, (2014) systematic review included 35 studies between 1985 and 2013, with 23/35 for cycle ergometry. Frequently observed weaknesses in the

studies reviewed were lack of power analysis, lack of quality assurance of equipment and validation of reference equations. Females were understudied at only 39% of the total study population. A score of 10-14 was seen in only four of the studies reviewed (one of which was treadmill only) with two of the three cycle ergometry studies including current smokers in their subject group. The remaining high scoring study by Davis et al., (1997) is an early study and utilizes a mixing chamber for measurement of gas exchange which has more recently been superseded by the use of real time gas analysis with the introduction of more rapid gas analysers and computer technology.

The conclusion of Paap and Takken's, (2014) review was that there was no one set of reference values that met all the ATS/ACCP., (2003) criteria and of those with a high-quality score there was no one set of equations that were suitable to be widely adopted. The differences in reference values emphasise the importance of each country/region having its own reference values and that these should be updated regularly. Local decisions regarding which reference values to use could be made by the utilising biological controls (10 males and 10 females) and using the reference values that best represented the local population. The review also found a lack of reference values for parameters such as anaerobic threshold and the $\dot{V}E/\dot{V}CO_2$ slope.

Subsequent to this review a large number of studies were undertaken to develop regression equations for CPET. A further systematic review between March 2014 and February 2019 was published by Takken et al., (2019) and identified 578 potential studies. Of these 578, 29 were considered to be eligible to be included in the review. Table 3 illustrates a range of internationally recognised reference value publications for cycle ergometry identified from this review with the inclusion of an additional slightly earlier study by Gläser et al., (2013). The population and methodology types are summarized along with the exercise parameters that the reference values relate to.

Table 3 - Summary of the reference value equations for cycle ergometry published between 2013 and 2019, adapted from Takken (Takken et al., 2019).

Author	Sex	Age range (years)	Source	Smokers Included	Parameters
Agostini (Agostoni et al., 2017)	260M/240F	18-77	Population based, prospective	Y	$\dot{V}O_2$, CO, HR, SV, CI
Blanchard (Blanchard et al., 2018)	112M/116F	12-17	Population based, prospective	N	$\dot{V}O_2$, O2 pulse, WR, $\dot{V}E$, HR, RER, OUES, $\dot{V}E/\dot{V}CO_2$, HRR
Bongers (Bongers et al., 2016)	114M/100F	8-19	Population based, prospective	NK	WR, HR, RER, $\dot{V}O_2$, $\dot{V}E$, $\dot{V}E/\dot{V}CO_2$, OUES
Buys (Buys et al., 2015)	877M/534F	20-60	Population based, prospective	NK	$\dot{V}O_2$, WR, HR, RER, OUES
Genberg (Genberg et al., 2018)	90M/91F	50	Population based, prospective	Y	WR, $\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$
Gläser (Gläser et al., 2013)	283M/333F	25-85	Population based, prospective	N	WR, $\dot{V}O_2$, AT, RER, SBP, DBP, O_2 pulse, $\dot{V}E$, $\dot{V}E/\dot{V}CO_2$
Kaafarani (Kaafarani et al., 2017)	113M/71F	6-18	Hospital based, retrospective	N	WR, $\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$, SBP
Kaminsky (Kaminsky et al., 2017)	1717M/2777F	20-79	Population based, retrospective	NK	WR, HR, RER

Kokkinos (Kokkinos et al., 2018)	3378M/1722F	20-79	Random, Population based, retrospective	Y	$\dot{V}O_2$
Lintu (Lintu et al., 2015)	71M/69F	9-11	Hospital based, retrospective	NK	WR, $\dot{V}O_2$, $\dot{V}E$, RER, $\dot{V}E/\dot{V}CO_2$, O_2-pulse, HR, SBP
Mylius (Mylius et al., 2019)	3570M/907F	7-65	Population based, retrospective	N	$\dot{V}O_2$
Pistea (Pistea et al., 2016)	58M/41F	>70	Population based, prospective	Y	$\dot{V}O_2$, HR, WR, $\dot{V}E$, $\dot{V}E/\dot{V}CO_2$, $\dot{V}E/\dot{V}O_2$, RER
Rapp (Rapp et al., 2018)	6462M/3628F	21-83	Population based, retrospective	Y	$\dot{V}O_2$, SBP, DBP
Tompouri (Tompuri et al., 2018)	18M/20F	9-11	Hospital based, prospective	NK	WR, $\dot{V}O_2$, RER
Van de Poppe (Van de Poppe et al., 2019)	2868M/595F	20-60	Population based, retrospective	N	WR, $\dot{V}O_2$, HR, RER

Abbreviations: NK = not known; $\dot{V}O_2$ = maximal oxygen uptake; CO = cardiac output; HR = heart rate; SV = stroke volume; CI = cardiac index; WR = work rate; $\dot{V}E$ = maximal ventilation; OUES = oxygen uptake efficiency slope; HRR = heart rate reserve; AT = anaerobic threshold; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Table 3 illustrates the limitations to the current reference values available for cycle ergometry. Many of these internationally recognised equations do not include all of the variables measured during a CPET test. This then unfortunately requires a combination of authors to be used when interpreting a CPET test. As outlined previously the parameters of $\dot{V}O_2$, AT and $\dot{V}E/\dot{V}CO_2$ are utilised in a range of subjects to assess for fitness, assess disease severity and to provide prognostic information. Only the equations developed by Gläser et al., (2013) include all three of these parameters. However, as anaerobic threshold is most often interpreted as a

percentage of predicted peak $\dot{V}O_2$, it could be suggested that an anaerobic threshold predicted equation is not necessary. Lintu et al., (2015); Bongers et al., (2016); Pistea et al., (2016); Kaafarani et al., (2017); Blanchard et al., (2018); and Genberg et al., (2018) all provide predicted equations for the essential parameters of $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ however these studies are significantly limited by the age range that they cover and 4/6 either included current smokers or did not provide evidence that they did not. A third (5/15) of the references listed in Table 3 are for under 18's. Of the adult predicted equations 7/10 cover the age ranges of 20 to 60 years with 5 of these including subjects over 70 years. Table 4 lists the highest quality studies when scored according to the ATS/ACCP., 2003).

Table 4. The ATS/ACCP scores for a selection of the highest scoring cycle ergometry reference equation studies published between 2013 and 2019.

Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
Agostini	1	0	0	0	1	0	0	1	0	1	1	1	0	1	7
Buys	1	0	1	0	1	1	0	1	1	1	1	1	1	1	11
Gläser	1	0	0	1	1	1	1	1	0	1	1	1	1	1	11
Kaminsky	1	0	0	0	1	1	1	0	1	0	1	1	1	1	9
Kokkinos	1	0	0	0	1	1	1	0	1	1	0	1	1	1	9
Mylius	1	0	0	1	1	1	0	0	1	1	1	1	1	1	10
Rapp	1	0	0	1	1	1	0	0	1	1	1	1	0	1	9
Van de Poppe	1	0	0	1	1	1	0	0	1	1	1	1	1	1	10

All studies listed in Table 4 did not report the level of physical activity undertaken by subjects participating (number 2). With the exception of Buys et al., (2015), all other studies failed to exclude different racial groups. The original review by Paap and Takken, (2014) found the use of equipment quality control was limited however Table 4 demonstrates that in more recent studies this has improved with only 2/8 not demonstrating equipment quality control. Of the two highest scoring studies Gläser et al's., (2013) would appear to be preferential with a wider age range, a greater number of parameters included and higher participant number.

Despite reference values for cycle ergometry being developed for over three decades, there is still not one set of equations that fulfill all requirements. Quality can be improved by performing a power analysis, good quality assurance of equipment and methodologies and by validating the reference equation in an independent sub sample (Takken et al., 2019). To date the equations developed by Gläser et al., (2013) would appear to be the most comprehensive and appropriate for a European population.

1.4.2 Arm ergometry

It is essential that the reference values employed are appropriate to the methodology that was used to develop them. Studies over the last three decades have focused predominantly on the development of equations for cycle ergometry with a smaller number looking at treadmill values. As described earlier, results of peak $\dot{V}O_2$ and anaerobic threshold are lower when obtained from arm ergometry exercise. For the interpretation of arm ergometry it is therefore essential that the reference values used are specific to arm ergometry.

Unfortunately, there are currently no recommended reference equations for use with arm ergometry, with much of the arm ergometry literature focusing on its relationship to cycle ergometry instead. A review of the literature has identified studies reporting reference equations for arm ergometry exercise testing, those of Balady et al., (1990), the American College of Sports Medicine (Kenney et al., 1995) and Manfre et al., (1990). The equations are outlined in Table 5.

Table 5. Published regression equations for peak $\dot{V}O_2$ measured using arm ergometry

Reference	Regression Equation
$\dot{V}O_2$ (ml/min) (Kenney et al., 1995)	(kgm/min x 3) + (3.5 x weight kg)
$\dot{V}O_2$ (ml/min) (Balady et al., 1990)	693 – (0.4 x weight kg) + (3 x Watts) + (0.05 x Watts^2)
$\dot{V}O_2$ (L/min) Healthy (Manfre et al., 1990)	0.395 + 0.0177(Watts)
$\dot{V}O_2$ (L/min) Cardiac (Manfre et al., 1990)	0.481 + 0.0124(Watts)

The study by Balady et al., (1990) aimed to assess the physiological response of a range of subjects to arm ergometry exercise and generate a formula from which peak $\dot{V}O_2$ could reliably be predicted. His group of 80 healthy volunteers was split into three age groups: 20-29 years, 30-39 years and 40-59 years, each including ten males and ten females. The output variables measured were work rate (WR), $\dot{V}O_2$ peak and heart rate (HR). Tests were performed on a bicycle adapted for arm ergometry with a 10 watt per 2min protocol performed at 75-80 rpm. Multiple regression analysis was used to derive prediction equations for $\dot{V}O_2$ at each stage (wattage) of exercise.

The Manfre et al., (1990) equations were developed in two groups of subjects. A group of 12 healthy males free from significant risk of coronary artery disease (CAD) and a group of 19 patients diagnosed with CAD. In this study subjects performed a discontinuous arm ergometry protocol at 60rpm, stopping at the end of each 15-watt increment stage to record an ECG.

There is minimal information available regarding the ACSM (Kenney et al., 1995) equation development in the literature however it is known that the subject population included healthy young males and the protocol was 25 watt increments.

All four equations were compared against measured peak $\dot{V}O_2$ in a cohort of patients with coronary artery disease (CAD) by Milani et al., (1996). Milani et al., (1996) performed arm ergometry exercise in a group of 15 male cardiac patients and compared their measured results to all four sets of predicted equations, Figure 13 illustrates the findings. The Milani et al., (1996) cohort performed three-minute exercise stages commencing at 20 watts and increasing by 20 watts at each subsequent stage.

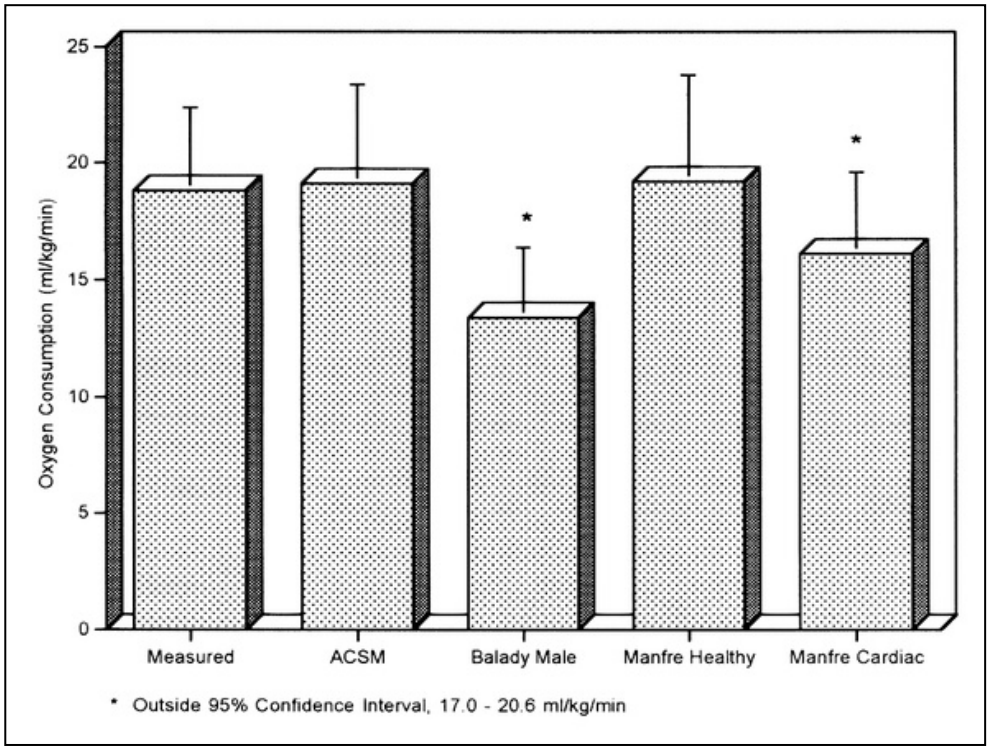


Figure 13 - Comparison of $\dot{V}O_2$ arm ergometry equations

Graphical representation of measured peak $\dot{V}O_2$ in a group of patients with coronary heart disease and the estimated peak $\dot{V}O_2$ from four different arm ergometry equations (Milani, 1996).

Milani et al., (1996) found that at peak exercise, the Balady et al., (1990) and Manfre et al., (1990) Cardiac equations underestimated $\dot{V}O_2$ max from 0.8 ± 0.9 to 2.0 ± 0.8 METS (One metabolic equivalent or METS is defined as the amount of oxygen consumed while sitting at rest and equal to 3.5ml O_2 per kg body weight x min, (Jetté

et al., 1990)). The Balady et al., (1990) equations were derived from a non-conditioned population however still underestimated peak $\dot{V}O_2$ in a CAD population, suggesting that the differences between the two may relate more to the protocol used rather than the patient group. Previously it has been identified that a higher crank speed results in a higher peak $\dot{V}O_2$ however the findings of Milani et al., (1996) contradict this suggesting that the wattage stages and the discontinuous nature of the Manfre et al., (1990) protocol have influenced the measured peak $\dot{V}O_2$.

The ACSM (Kenney et al., 1995) and Manfre et al., (1990) Healthy accurately estimated $\dot{V}O_2$ for 47% of patients with CAD. However, they were unable to accurately estimate $\dot{V}O_2$ for more than 27% of the patient population. It is counterintuitive that the equations developed in younger and healthier subject populations better predicted the peak $\dot{V}O_2$ of a group of 60-year-olds with CAD. This suggests a greater limitation of the ACSM (Kenney et al., 1995) and Manfre et al., (1990) equations than it does accuracy of these equations to predict normality in a 'normal' population.

The available arm ergometry equations to predict cardiopulmonary exercise testing outcomes are significantly limited in number, sample size, heterogeneity and protocol standardisation. There is clearly a need to develop reference values for arm ergometry if arm ergometry is to be more widely adopted. Any equations that are developed must fulfil the ATS/ACCP (ATS/ACCP.,2003) requirements for high quality reference values with an expectation that they achieve a quality score of ≥10.

Chapter 2: Aims and Objectives

2.1 Aims

The aim of the study was to assess the physiological responses of adult males and females (free from underlying cardiac or respiratory disease) to arm ergometry exercise testing and to use this data to generate a local set of regression equations for CPET variables for use in the interpretation of arm ergometry exercise.

2.2 Secondary Aim

The secondary aim was to compare the results of arm ergometry CPET to results obtained from cycle ergometry testing performed in the same subject group and determine the relationship between key indices.

Chapter 3: Methodology

3.1 Ethics

Ethical approval for this study was granted by the Health Research Authority, Wales REC 7 (REC Reference 17/WA/0284; IRAS Project ID 226248) and Manchester Metropolitan University EthOS (Reference 2020-17764-15222).

3.2 Participant Recruitment

Volunteers were all healthy staff of University Hospitals Coventry and Warwickshire NHS Trust. They were identified through advertisements using the Trusts available communications which included the Trust's weekly electronic communications publication, the Intranet, and all user emails. The study was explained to volunteers both verbally and through the provision of a participant information sheet (see Appendix A). Consent was taken prior to undertaking the first exercise test and no sooner than 24 hours after being provided with the participant information sheet (see Appendix B).

3.2.1 Inclusion criteria

- Adults both male and female
- Ability to undertake arm and leg exercise without any impediment
- Not taking prescribed medication likely to affect exercise performance i.e., beta blockers
- Able to understand the performance of an exercise test
- Ability to provide consent
- Working age (18-69 years)
- No known underlying cardiac or respiratory disease
- No identified contraindication to performing physiology led cardiopulmonary exercise

3.2.2 Exclusion criteria

- Female subjects that are knowingly pregnant or believe they may be pregnant
- Having an impediment preventing them from performing arm or cycle ergometry
- Taking prescribed medication likely to affect exercise performance
- Unable to understand the performance of an exercise test
- Unable to provide informed consent
- Aged less than 18 years
- Aged more than 69 years
- Having a known underlying cardiac or respiratory disease

The first participant was recruited on 6th November 2017. In March 2020 all research activity was stood down by UHCW NHS Trust due to the nationwide restrictions arising from the COVID-19 pandemic. Permission to recommence this project was received on 19th August 2020 however two additional periods of redeployment in November 2020 and January/February 2021 resulted in temporary cessation of research activity. The final participant completed their exercise tests on 6th July 2021.

3.3 Participants

A total of 120 participants were recruited to the study. Race was self-reported by study participants and race categories (White, Black, Asian) were defined by the lead investigator based on Office for National Statistics (ONS) definitions (Office for National Statistics, 2019). Race data was collected as recommended by the ATS/ACCP (2003) standards for the development of high quality reference values.

3.4 Pre-participation Screening

Prior to participation, individuals were assessed for any potential health risks associated with exercise by completing the PAR-Q & You questionnaire (Thomas et al., 1992), consistent with the recommendations of the ACSM guidelines for cardiovascular disease risk stratification (Kenney et al., 1995). The questionnaire assesses safety or possible risks from exercising based on an individual's health

history, current symptoms, and risk factors. Individuals who answered yes to any of the questions were required to obtain medical clearance prior to participating. A copy of the questionnaire can be found in Appendix C.

After health screening, anthropometric measurements of height (cm) and weight (kg) and calculation of body mass index (kg/m^2) were made according to established procedures (Best and Shepherd, 2020).

Baseline physiological measurements of spirometry, ECG and blood pressure were performed to assess for any evidence of underlying respiratory or cardiac disease. Participants with normal baseline spirometry, ECG and blood pressure were eligible to take part in the study. If baseline physiological measurements prevented a volunteer from entering the study, they would be directed to book a consultation with their General Practitioner (GP) and a copy of their investigation results provided.

3.4.1 Activity Questionnaire

Following successful screening, participants were requested to complete the Recent Physical Activity Questionnaire (RPAQ) (MRC Epidemiology Unit, 2006) to quantify their level of physical activity. The RPAQ is a self-completion questionnaire that enquires about activity across four domains (leisure time, occupation, commuting and home life) during the previous four weeks. An initial assessment of reliability and validity of the questionnaire demonstrated moderate-high reliability and also validity in accurately assessing vigorous activity and estimating total energy expenditure (Besson et al., 2010). An example of the questionnaire can be seen in Appendix D.

3.5 Exercise Equipment

3.5.1 Cycle ergometer

Cycle ergometry exercise was performed using the Ergoselect 200 (Ergoline, Germany) electronically braked cycle ergometer. Electromagnetically braked cycle ergometers allow direct quantification of the work rate performed and can be computer controlled allowing the work rate to be incremented continuously (Palange

et al., 2018). Work rate can be controlled effectively independent of any pedal frequency (cadence) between 40 and 80 rpm (Lanooy and Bonjer, 1956). However large changes in cadence can result in detectable changes in physiological responses e.g., $\dot{V}O_2$ for a given work rate and therefore it is preferable to keep cadence as constant as possible within an exercise study and across visits (Casaburi et al., 1978). Maintaining a constant pedal rate within 50-70 rpm provides the most efficient range in which the lowest oxygen uptake is produced at a given load (Cooper and Storer, 2001). A cadence of 60 rpm ± 5% was used for the purpose of this study.

Appropriate adjustment of the saddle height is also important for reproducible test results and subject comfort (Cooper and Storer, 2001). Incorrect saddle positioning leads to a higher oxygen consumption and higher heart rate to achieve an equivalent mechanical efficiency (Stefanov and Kolev, 2016). Saddle height was adjusted according to the heel method whereby, when the pedal is at its lowest position, the knee is slightly bent (5-15° knee flexion).

3.5.2 Arm ergometer

Arm ergometry exercise was performed using the Ergoselect 400+ (Ergoline, Germany) electronically braked arm ergometer. To ensure consistency across the modalities a cadence of 60 rpm ± 5% was also used for the arm ergometry protocol. Seat height was not adjustable on the arm ergometer bike and instead the arm crank was adjusted to ensure that the arm was slightly bent at the elbow during furthest extension as per knee flexion for cycle ergometry (Pina et al., 1995).

3.5.3 Metabolic Cart

Ready availability of online digital computer analysis of physiological measurements has enabled the accurate measurement of breath by breath calculation of $\dot{V}O_2$ and $\dot{V}CO_2$ values (ATS/ACCP., 2003). Measurements of gas exchange were analysed using the breath-by-breath analysis system Ultima CPX (Medical Graphics, UK). Breath-by-breath systems utilise each individual breath, computing its volume and gas composition. This is accomplished by sampling the inspired and expired flow signals

at high frequency (50-125Hz, (Palange et al., 2018)) and integrating to give volume changes throughout the breath cycle. Inspired and expired gas concentrations must be sampled simultaneously with the same frequency and carefully time aligned with the volumes (Cooper and Storer, 2001). In order to accomplish this, there is a requirement for precise flow transducers and rapidly responding gas analysers. It is important to recognise that the confidence with which these metabolic indicators can be calculated depends on the combined measurement errors for each of the determined variables. Calibration plays an essential role in ensuring that all sensors are accurate, preventing errors that can become additive and therefore large (see 3.9 Calibration and Quality Assurance).

3.5.4 Flow Transducers

Measurements of flow were made using a prevent® flow sensor, Figure 14. The prevent® is a bidirectional flow sensor using the pitot tube principle. The pitot principle is that the pressure of gas flowing against a small tube is related to the gas's density and velocity. Flow is determined by the equation:

Flow = Pressure difference/Resistance

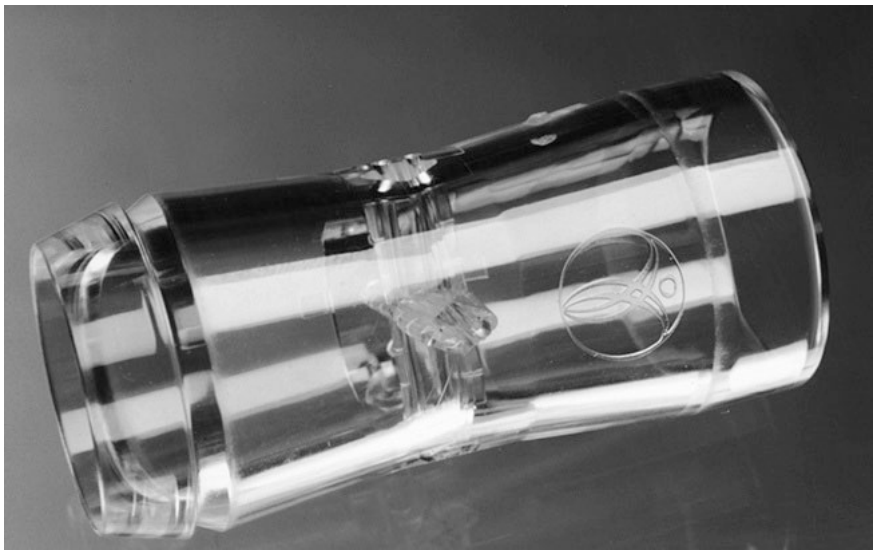


Figure 14 - preVent® flow measuring device

A series of small tubes inside the flow sensor allow the determination of bidirectional flow and also act as a resistance (resistance <1.5 cmH_2O). A pressure transducer is attached either side of the resistance allowing the measurement of pressure change and the subsequent calculation of flow according to the equation above. The preVent® device allows the measurement of flow up to ± 18 L/s with an accuracy of ± 3% or 50ml whichever is the greater. Computerised systems enable the flow signal to be integrated and produce measurements of volume. As this type of flow measuring device is affected by gas density, software correction for different gas compositions e.g., oxygen and carbon dioxide is necessary and calibration of the gas analysers prior to each test allows this correction factor to be identified and applied.

3.5.5 Gas Analysers

The Ultima CPX system utilises rapid responding oxygen and carbon dioxide analysers for the determination of breath-by-breath gas analysis data.

The oxygen analyser is an electro-galvanic oxygen sensor with the structure outlined in Figure 15. An electro-galvanic fuel cell is an electrochemical device which consumes a fuel to produce an electrical output by a chemical reaction. Oxygen enters the sensor through the membrane where it comes into contact with the cathode and is immediately reduced to hydroxyl ions which migrate through the electrolyte to the lead anode. At the anode, the hydroxyl ions react, oxidising the lead to lead oxide. As these two processes occur, a current is generated proportional to the oxygen concentration. The analyser measures oxygen concentrations from 0-100% with an accuracy of ± 1% and a response time (10-90%) <180 ms as per ATS/ACCP recommendations (Wijeysundera et al., 2018).

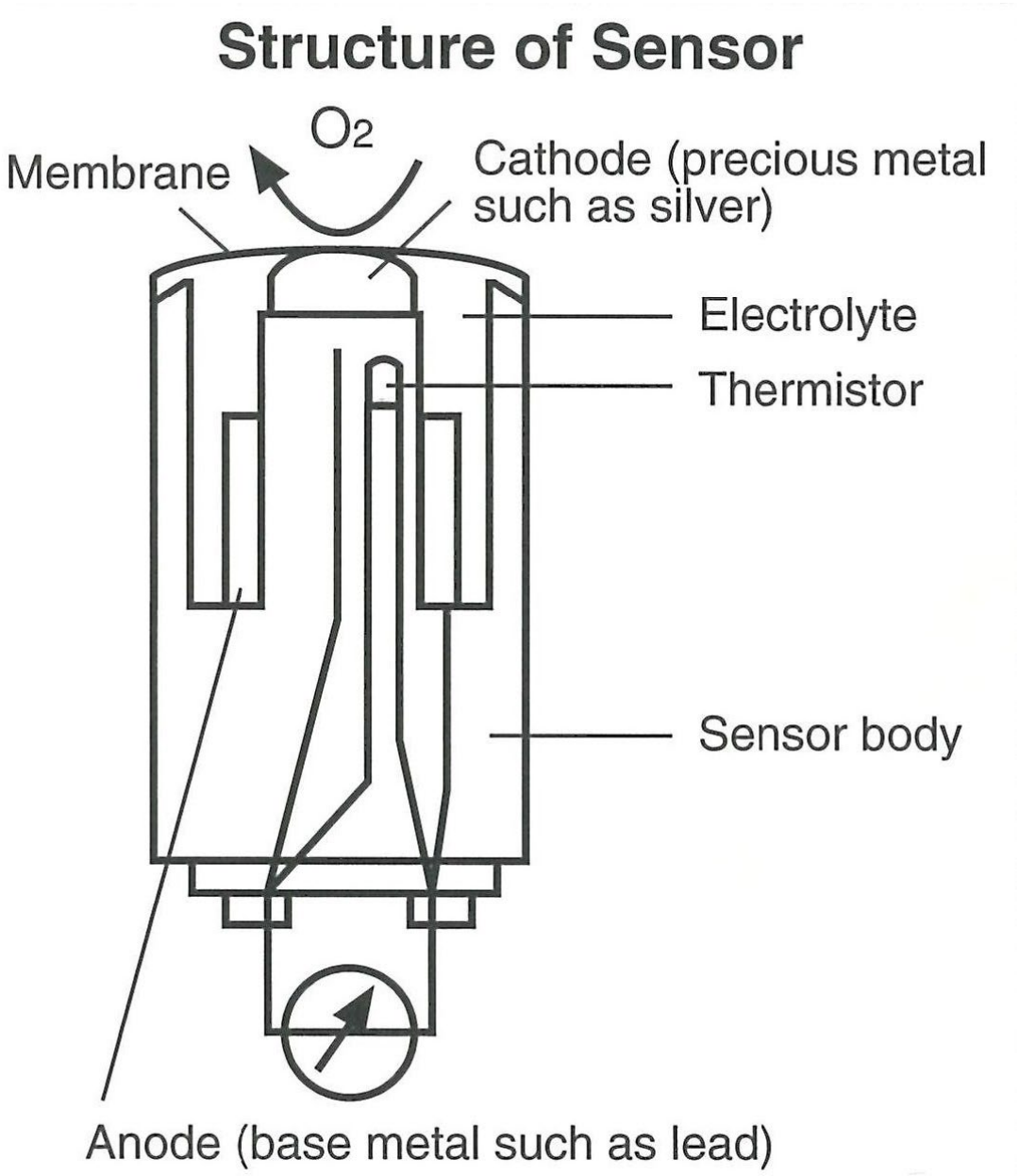


Figure 15 - Structure of an electro-galvanic oxygen analyser

Diagram illustrating the structure of an electro-galvanic oxygen analyser (GASTEC Corporation, n.d.)

The CO_2 analyser is a non-dispersive infrared (NDIR) gas analyser as illustrated in Figure 16. NDIR analysers use infrared light absorption to determine the concentration of CO_2 molecules in the sample. The difference between the amount of light radiated by the infrared lamp and the amount received by the detector is measured. The difference is due to light being absorbed by the CO_2 molecules in the

sample and therefore is directly proportional to the concentration of CO_2 in the sample. The analyser measures CO_2 concentrations in the range 0-15% with an accuracy of ± 1% and a response time (10-90%) <180 ms as per ATS/ACCP recommendations (Wijeysundera et al., 2018).

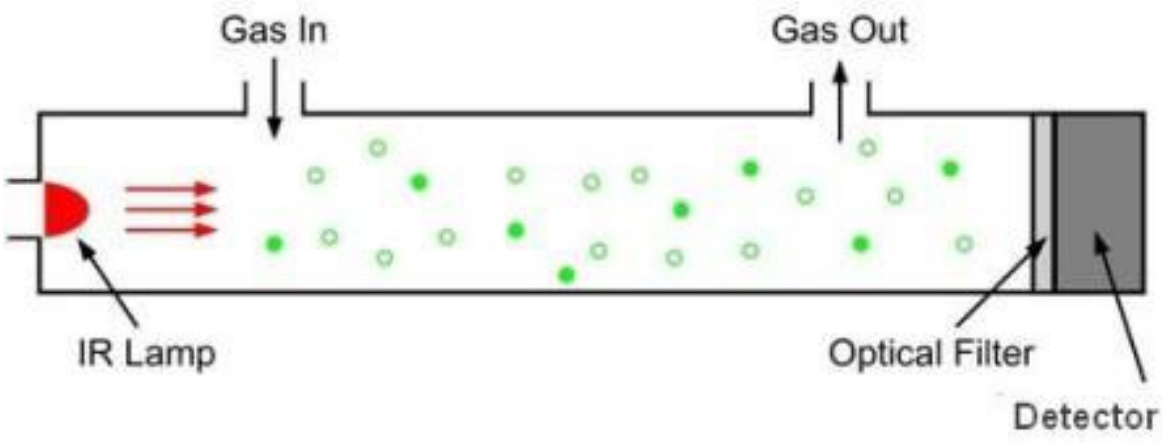


Figure 16 - Structure of a non-dispersive infrared (NDIR) gas analyser

Diagram illustrating the structure of an NDIR gas analyser (CO2Meter.com, n.d.:2)

3.6 Gas Exchange Measurements

Oxygen uptake ($\dot{V}O_2$) and carbon dioxide output ($\dot{V}CO_2$) represent the difference between the volume of gas inhaled (O_2 and CO_2, respectively) and the volume exhaled per unit time. The measurement of $\dot{V}O_2$ is based on the equation:

$$\dot{V}O_2 = [(\dot{V}I \times FIO_2) - (\dot{V}E \times FEO_2)] / t$$

$\dot{V}_I$ and $\dot{V}_E$ represent the volumes of inhaled and exhaled gas, respectively, and t is the time period of the gas volume measurement. FIO_2 and FEO_2 represent the O_2 concentration in the inhaled and exhaled gas, respectively.

The measurement of $\dot{V}CO_2$ is simpler because $FICO_2$ in room air is essentially zero therefore the equation reads:

$$\dot{V}CO_2 = [\dot{V}E \times FECO_2] / t$$

These calculations must accommodate water vapour, barometric pressure and ambient temperature variations in order to obtain standard conditions of temperature and pressure, dry (STPD) values (Palange et al., 2018). Compensation for the delay between the time at which the gas is sampled at the mouth and the time at which the gas concentration is measured within the gas analysers is necessary. This is undertaken prior to the calculation of $\dot{V}O_2$ and $\dot{V}CO_2$ using time delays determined in the pre-test calibrations.

Breath by breath changes in end expiratory lung volume (EELV) will violate the algorithm where $\dot{V}O_2$ must be measured using expired gas, whereby substantial error can be introduced with each breath in which EELV changes (Beaver et al., 1981). These effects can be minimised by averaging over time and the averaging method of the running average of 5 of 7 breaths was utilised (Sherrill and Swanson, 1989; Wijeysundera et al., 2018).

3.7 ECG

Continuous ECG monitoring is a necessity in a clinical CPET providing essential information on heart rate and detecting myocardial ischaemia and arrythmias with high sensitivity and specificity (Fletcher et al., 1995). Adverse events and death during CPET are rare; reported as 1-5 per 10,000 and 0.5 per 10,000 respectively; however continuous monitoring with 12 lead ECG waveforms is essential for the duration of the test and into recovery (Balady et al., 2010).

The instrument should meet the specifications set by the American Heart Association on frequency, speed and sensitivity (Bailey et al., 1990). The Mortara ECG system (Mortara, model X12^{+}, Milwaukee, WI, USA) has a frequency bandwidth of 0.5 to 150Hz, sensitivity of 10 mm.mV^{-1} and a speed of 25 mm.s^{-1}.

Silver-silver chloride electrodes are recommended as the most dependable for minimising motion artifact. Lightweight shielded cables lessen motion artifact and in

addition the cable systems arises from a central box that can be worn around the waist further stabilising the ECG signal (Pina et al., 1995).

The most critical point of the electrode amplifier recording system is the interface between the electrode and the skin and therefore effective skin preparation is essential. The areas for electrode placement should firstly be shaved if necessary and then rubbed with fine sandpaper. Removal of the superficial layer of skin significantly reduces its resistance, decreasing the signal to noise ratio (Fletcher et al., 1995).

The standard 12-lead ECG placement of electrodes on the arms and legs is not possible when performing exercise, a modified placement was first described by Mason and Likar (1966) and is illustrated in Figure 17. Differences between this method and the traditional can be minimised by placing the arm electrodes as close to the shoulder as possible and the leg electrodes below the umbilicus (Fletcher et al., 1995).

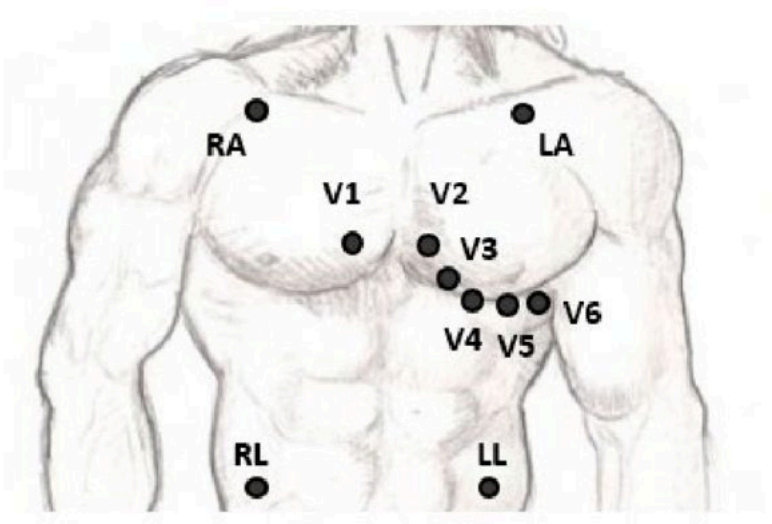


Figure 17 - Illustration of 12 lead ECG placement for exercise testing

Electrode placement for a 12-lead ECG configuration suitable for exercise testing as first described by (Mason and Likar, 1966). The picture identifies the position of the electrodes for the right arm (RA), the left arm (LA), the left leg (LL) and the right leg (RL) as well as the chest electrodes V1-V6 (Kalra et al., 2018).

3.8 Blood Pressure and Pulse Oximetry

Measurements of non-invasive blood pressure and oxygen saturation were made using a Tango M2 stress test monitor (SunTech Medical, Morrisville, NC), an automated blood pressure system designed specifically for use during exercise.

3.8.1 Blood pressure

The oscillometric method uses pressure oscillations within the sphygmomanometer cuff to determine systolic and diastolic blood pressure. With each arterial pulse there is a small increase and decrease in the volume of the limb where the pressure is measured (usually the arm). This causes a rise and fall in pressure within the encircling cuff which is detected by a solid-state transducer. The pressure in the cuff is initially inflated to a level that causes arterial blood flow to the arm to stop, the pressure is then gradually released. As the pressure in the cuff falls below the pressure of the peak of the arterial pulse, the transducer detects a small pressure wave, which reflects the difference between the pressure in the cuff and that in the artery. As the cuff pressure further decreases these pressure differences become greater until the cuff begins to fall away from the limb and less of the volume pulsation is detected. Using an algorithm that combines the average volume change and rate of change in pressure waves the blood pressure device estimates systolic and diastolic blood pressure (Babbs, 2012), see Figure 18.

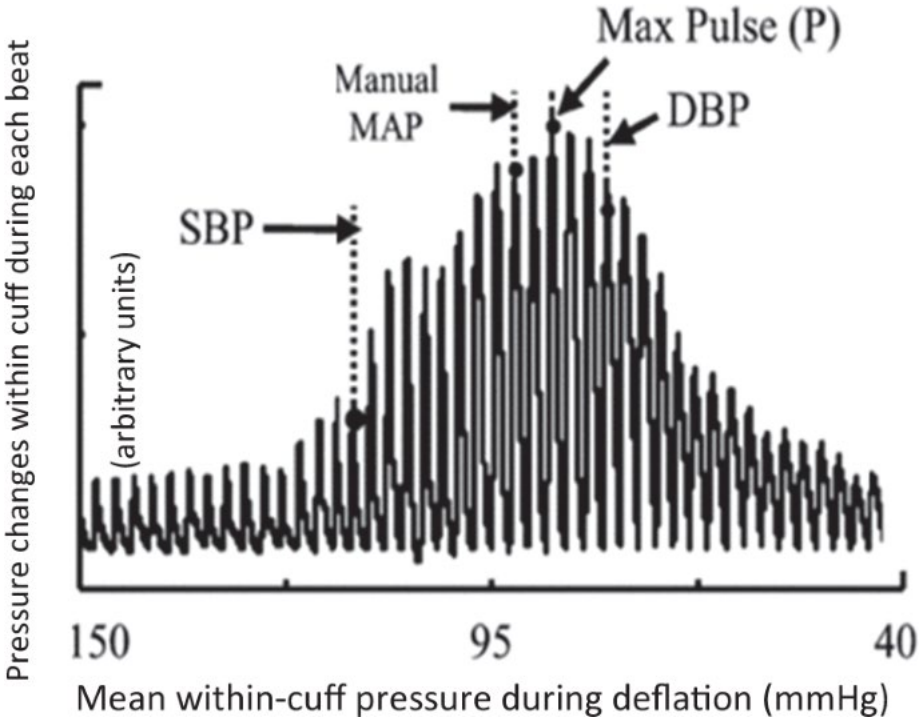


Figure 18 - Illustration of the cuff pressure changes used to calculate blood pressure

(on behalf of the British and Irish Hypertension Society's Blood Pressure Measurement Working Party and Lewis, 2019)

Pulse detection by oscillometric machines relies on the amount of change in the volume of the arm with each pulse and on the regularity and rate of these pulses. Therefore, irregular pulses and movement of the arm will affect the pressure changes in the cuff leading to inaccurate pressure calculations. This principle is seen in rhythm disorders such as atrial fibrillation where frequent extra systoles result in a smaller volume than regular beats. In addition bradycardia (heart rate <50 bpm) my lead to too few beats being detected to permit an accurate estimate of blood pressure (on behalf of the British and Irish Hypertension Society's Blood Pressure Measurement Working Party and Lewis, 2019). Auscultation is recognised as the gold standard method for determining blood pressure, however, oscillometric measurements are quicker and easier to obtain during exercise. It should be recognised that comparison of the two methods suggests that the oscillometric method yields higher readings of up to 10mmHg for systolic pressure and 5mmHg for diastolic (Park et al., 2001).

3.8.2 Pulse oximetry

Pulse oximetry is an in-direct, non-invasive, accurate and safe method of measuring oxygen saturations (SpO_2). Pulse oximeters are designed to measure SpO_2 by measuring the absorption of specific wavelengths of light in oxygenated haemoglobin (HbO_2) as compared to that of deoxygenated haemoglobin (Hb). Oximeter probes contain light-emitting diodes (LED's) which shine light of two wavelengths, red (660nm) and infrared (940nm), from one side of the probe, generally a finger probe, to a photodetector on the opposite side. Pulsatile arterial blood during systole causes an influx of HbO_2 to the tissue, absorbing more infrared light and allowing less light to reach the photodetector, see Figure 19. The oxygen saturation of the blood therefore determines the degree of light absorption. The result is processed into a digital display of oxygen saturation on the oximeter screen, which is symbolised as SpO_2.

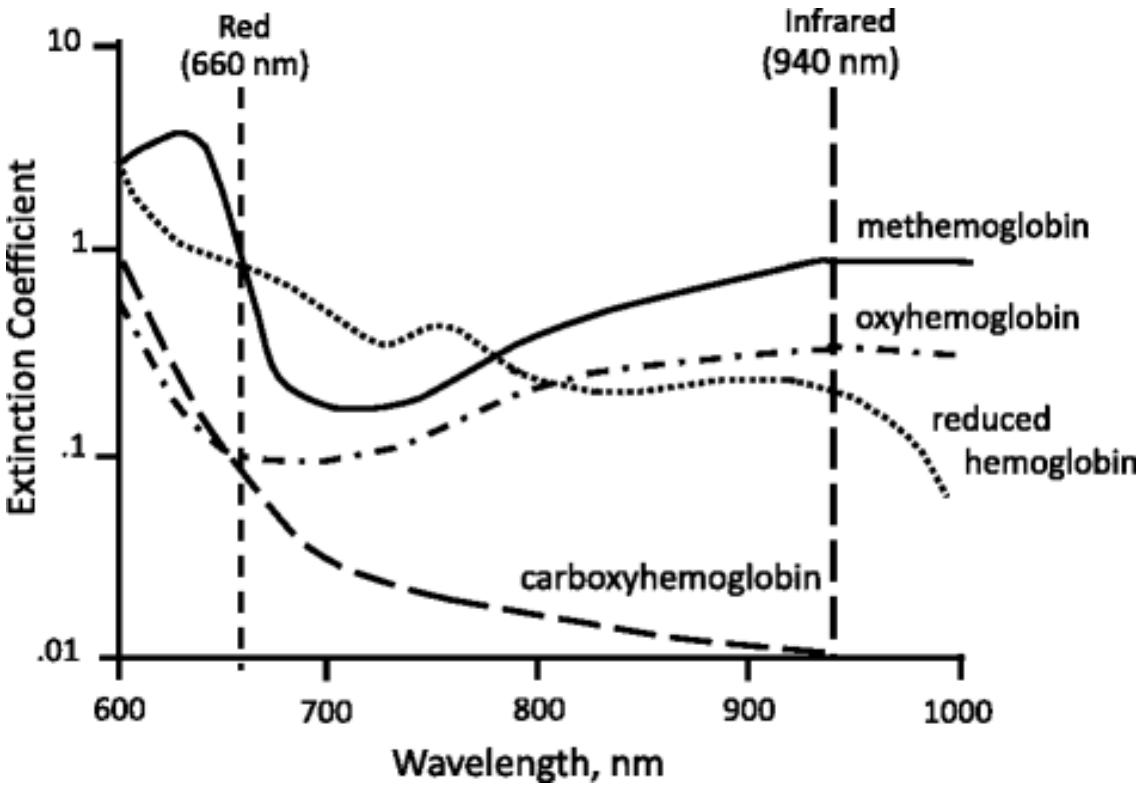


Figure 19 - Measurement of light absorption.

Transmitted light absorbance of four haemoglobin species: oxyhaemoglobin, reduced haemoglobin, carboxyhaemoglobin and methaemoglobin (Jubran, 2015).

The accuracy of a pulse oximeter is determined by the differences between SpO_2 measured on oximetry and oxygen saturation measured from an arterial blood gas (SaO_2) performed at the same time. Manufacturers claim an accuracy of 2% with a standard deviation (SD) of the differences between 2-3% (Jubran, 2015). There is evidence however that suggests that this measurement error is as high as 4% (Nitzan et al., 2014). The accuracy of oximetry readings is influenced by the strength of arterial pulse, body movements, colour interferences, venous pulsations, and several physical factors. Measured saturations also fluctuate significantly with ventilation changes related to coughing, talking, breath holding and physical activity. Although easy to perform, pulse oximetry requires clinical skills training to ensure accurate readings are obtained (Fluck et al., 2003). Evidence suggests that clinicians are not always aware of the limitations of pulse oximetry and that motion artefact and poor signal quality result in inaccurate readings (Jubran, 2015).

3.9 Calibration and Quality Assurance

The accuracy and reproducibility of the values obtained during cardiopulmonary exercise testing are dependent on scrupulous calibration and quality control procedures (Levett et al., 2018).

3.9.1 Calibration

Daily and immediately prior to each test, calibration of the flow sensor and gas analysers was performed. The calibration was corrected for current room temperature, barometric pressure and humidity using a 'weather station' positioned next to the equipment. The flow sensor was calibrated for volume using a calibrated 3 litre syringe across a physiological range of flow rates (<2 to >8 $L.s^{-1}$ (Porszasz et al., 2018)). Agreement in measured volumes within ± 3% indicated adequate performance (ATS/ACCP., 2003; Sylvester et al., 2020). Gas analysers were calibrated using precision analysed gas mixtures at two points which corresponded to inhaled (21% oxygen, balance nitrogen) and exhaled (5% carbon dioxide, 12% oxygen, balance nitrogen) gas compositions. Due to the transport delay associated with gas being received by the gas analysers, the flow and gas concentration signals need to be time aligned. It is essential that this 'phase delay' is measured prior to each test and not assumed as small errors can equate to large measurement inaccuracies (ATS/ACCP., 2003; Levett et al., 2018). This delay is measured using a solenoid which allows an abrupt switch between the two gas concentrations with the time delay between the solenoid activation and the detection of the change in gas concentration being equal to the phase delay and is deemed acceptable if it is <180ms.

3.9.2 Quality assurance

Quality assurance for CPET using normal healthy volunteers has been demonstrated to be an effective quality control measure (Revill and Morgan, 2000). It allows the system to be validated whilst performing the test in its entirety and therefore represents an assessment across its working range and ensures accuracy of the measured variables as well as the measurement sensors. Quality assurance requires a volunteer to perform a constant work rate test at two different workloads with

these workloads equating to sub anaerobic threshold work rates (Levett et al., 2018). The test should be performed at regular intervals that reflect the level of equipment usage or at least monthly (Cooper and Storer, 2001). Exercise is undertaken at each workload for a minimum of six minutes to ensure a steady state, data for $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$ are averaged over the final two minutes. This data is then stored in a database for each individual per work rate as their expected normal values. Subsequent tests are compared to the expected normal with values outside of the 95% confidence interval suggestive of an equipment fault that requires further investigation.

Two healthy volunteers took part in a programme of CPET quality assurance to ensure equipment accuracy and early identification of faults. One participant performed quality assurance using the arm ergometer at two work rates previously identified to be sub anaerobic threshold (20 and 40 watts). The second performed quality assurance of the cycle ergometer at 25 watts and 50 watts, again identified as sub anaerobic threshold.

Initial quality assurance data from ten tests were averaged to generate a normal range for each individual at each work rate. This data is summarised in Table 6 and Table 7 and illustrates the expected value and coefficient of variation for the three variables $\dot{V}CO_2$, $\dot{V}O_2$ and $\dot{V}E$ per participant.

Table 6. Quality assurance data for arm ergometry

	20 Watts			**40 Watts**		
	$\dot{V}O_2$	**$\dot{V}CO_2$**	**$\dot{V}E$**	**$\dot{V}O2$**	**$\dot{V}CO2$**	**$\dot{V}E$**
Subject 1	496.64 (3.63)	450.25 (7.47)	16.78 (4.15)	779.62 (3.07)	762.43 (6.70)	25.59 (5.62)

Data expressed as mean (coefficient of variation)

Table 7. Quality assurance data for cycle ergometry

	25 Watts			50 Watts		
	$\dot{V}O_2$	**$\dot{V}CO_2$**	**$\dot{V}E$**	**$\dot{V}O2$**	**$\dot{V}CO2$**	**$\dot{V}E$**
Subject 2	639.07 (4.04)	579.48 (7.87)	16.82 (4.95)	871.62 (4.41)	787.80 (6.30)	21.29 (7.03)

Data expressed as mean (coefficient of variation)

Following the identification of a normal range, subsequent quality assurance values are plotted to ensure that all data is within the expected normal values. Where data exceeds the normal expected range, equipment will be recalibrated, and the gas analyser calibration log interrogated for evidence of analyser drift. Service engineers will be contacted to evaluate the system and ensure correct functioning before further investigations are undertaken. Examples of quality assurance graphs for arm ergometry can be seen in Figure 20 and Figure 21 and for cycle ergometry in Figure 22 and Figure 23.

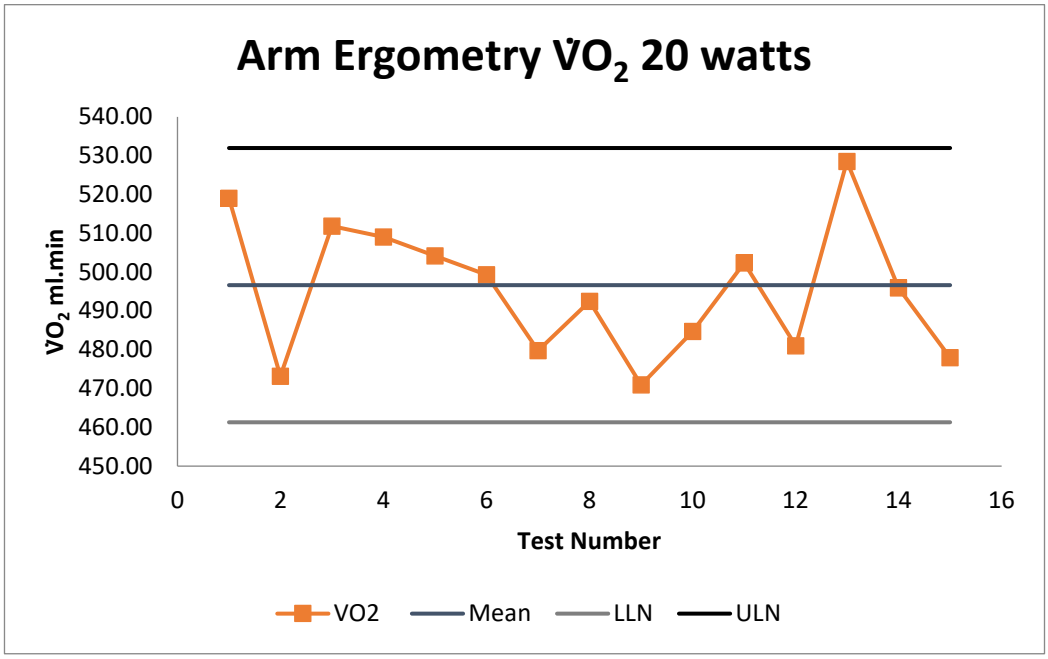


Figure 20 - Arm ergometry quality assurance VO_2

Quality assurance data for $\dot{V}O_2$ (mL/min) during steady state arm ergometry exercise testing at 20 watts. Abbreviations: LLN = lower limit of normal; ULN = upper limit of normal.

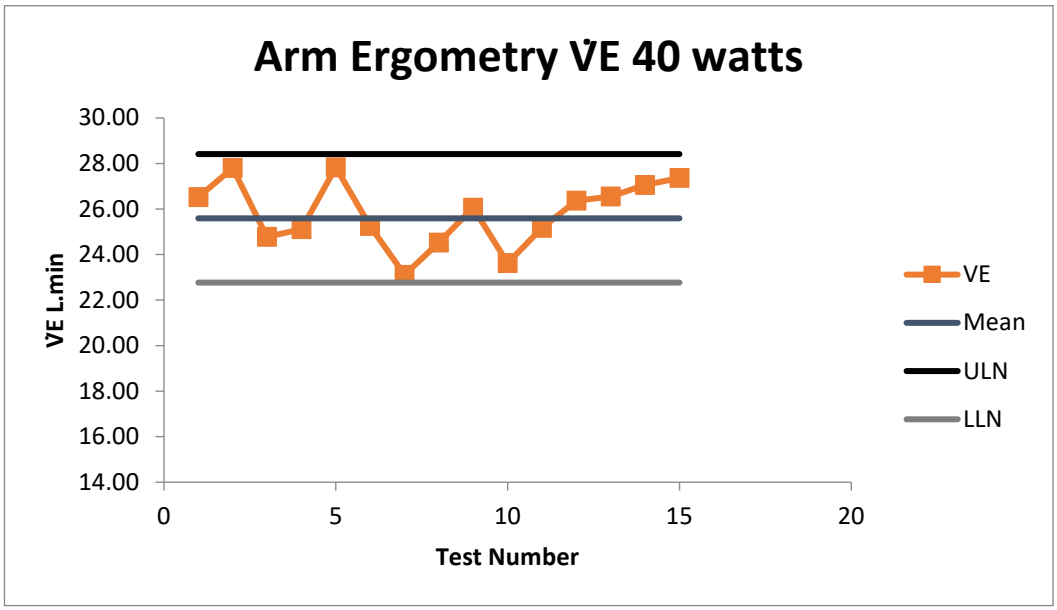


Figure 21 - Arm ergometry quality assurance VE

Quality assurance data for $\dot{V}E$ (L/min) during steady state arm ergometry exercise testing at 40 watts. Abbreviations: $\dot{V}E$ = ventilation; LLN = lower limit of normal; ULN = upper limit of normal.

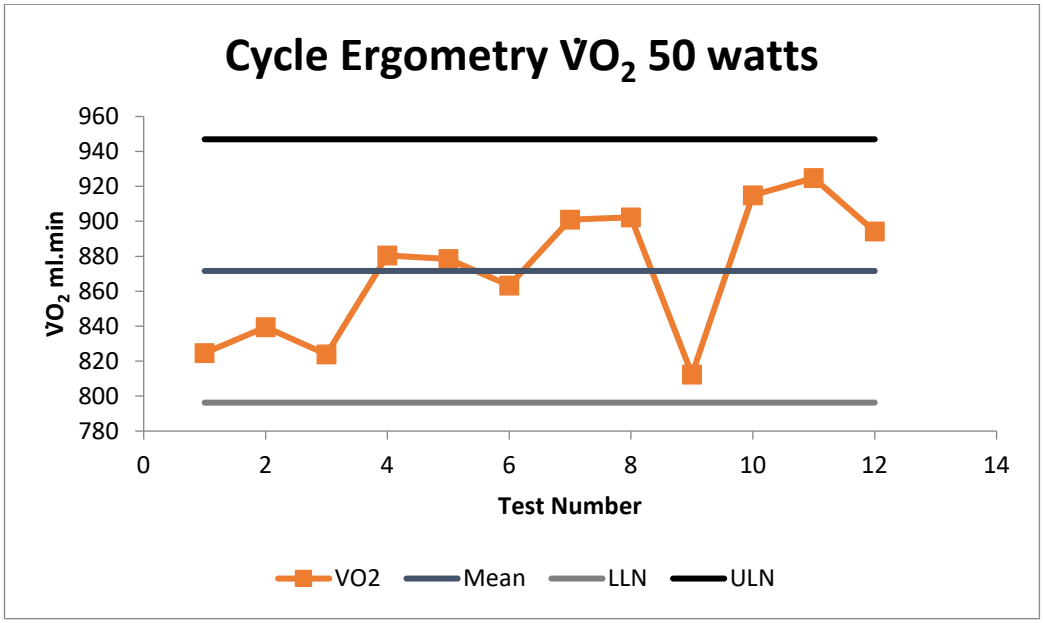


Figure 22 - Cycle ergometry quality assurance $\dot{V}O_2$

Quality assurance data for $\dot{V}O_2$ (mL/min) during steady state cycle ergometry exercise testing at 50 watts. Abbreviations: LLN = lower limit of normal; ULN = upper limit of normal.

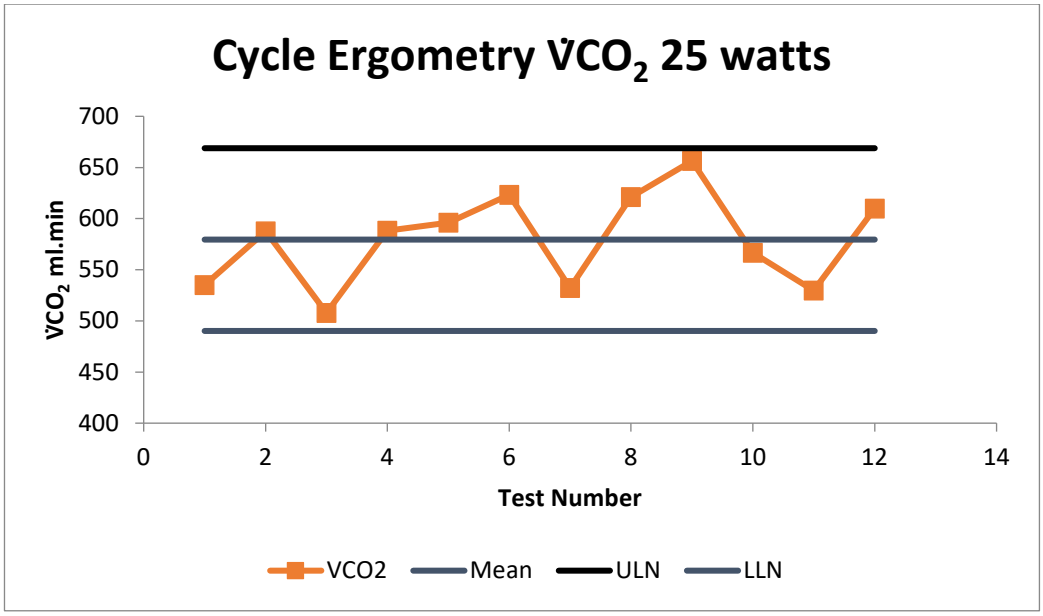


Figure 23 - Cycle ergometry quality assurance $\dot{V}CO_2$

Quality assurance data for $\dot{V}CO_2$ (mL/min) during steady state cycle ergometry exercise testing at 25 watts. Abbreviations: LLN = lower limit of normal; ULN = upper limit of normal.

3.10 Randomisation

Following successful pre-participation screening, individuals were randomised to either arm or leg ergometry for visit 1. Each subject was given a unique study ID commencing with the number 001. GraphPad random number generator was used using GraphPad Software 2021 (San Diego, California) to generate a table of random numbers using number 1 (arm ergometry) and number 2 (leg ergometry) as the identifier. A table of 10 columns and 10 rows was generated providing simple randomisation for 100 participants. Once the 101st subject was randomised the table of random numbers was started again from number 1.

3.11 Study Protocol

The study protocol required subjects to attend for testing on two separate occasions no less than 24 hours, to allow recovery from the first test, and no more than 2 weeks apart. A maximum of two weeks was selected to minimise the influence of any potential training effects on test comparisons.

3.11.1 Preparation for testing

At visit 1 subjects confirmed their consent to undertake the research trial and the nature of the investigations to be undertaken were explained. Anthropometric measurements of height and weight were made without shoes and wearing indoor clothing. Personal information such as date of birth, prescribed medication and smoking history was documented. Smoking history was calculated in pack years using the following equation:

$$\textbf{Pack years} = \frac{\text{Number of cigarettes smoked per day x Number of years smoked}}{20}$$

Baseline measurements of spirometry, to include FEV_1 and FVC, were performed in accordance with the ARTP Guidelines (Sylvester et al., 2020). Results were compared to the subjects calculated regression equations to ensure normality (Quanjer et al.,

2012). The subjects best measured FEV_1 was used to calculate their predicted maximal ventilation using the following equation:

Predicted Maximal Ventilation = FEV_1 * 0.35

Resting ECG was measured using the Mason-Likar (1966) configuration for electrode placement. Resting blood pressure was measured using an automated blood pressure cuff.

The subject was then fitted with a Hans Rudolph (Cranlea, Birmingham, UK) facemask as per Figure 24. The size of the mask and corresponding five-strap headgear was selected by the operator to ensure a tight fit without leak. The mask was assessed for leak by asking the subject to breathe in whilst wearing the mask. The operator covered the mask outlet with their hand and asked the subject to slowly exhale. If the mask was not fitted appropriately there would be a leak noted around the mask. If a leak was identified the mask would be refitted or an alternative size mask used.

Figure 24 - Hans Rudolph 7450 Series V2 face mask.

Once all the above was complete the subject was ready for testing. Following randomisation to either leg cycle or arm ergometry the appropriate modality specific protocol for the performance of a maximal exercise test was selected.

3.11.2 Cycle ergometry protocol selection

The cycle ergometry protocol utilises a ramp protocol where the work rate continuously increases in small increments throughout the test. This work rate was calculated for each subject individually using the equation of Cooper and Storer (Cooper and Storer, 2001).

$$\textbf{Watts/min} = \frac{\text{Predicted } \dot{V}O_2 \text{ max} - \dot{V}O_2 \text{ unloaded}}{103}$$

$\dot{V}O_2$ unloaded = 5.8 x body weight (kg) + 151

Predicted $\dot{V}O_2$ max was calculated using the Wasserman regression equations below (Wasserman et al., 1999):

$$\textbf{Male - Predicted } \dot{V}O_2 \textbf{ (L/min) = BW * [50.72-(0.372*age)]/1000}$$

$$\textbf{Female - Predicted } \dot{V}O_2 \textbf{ (L/min) = (BW+42.8) * (22.78-0.17*age)/1000}$$

where BW = body weight in kilograms

The predicted work rate should provide a workload that will allow a total test time of between 8 and 12 minutes (Roca et al., 1997). Where the subject's history suggested that they may be able to work at a higher/lower work rate, the operator used their experience to modify the calculated workload accordingly to prevent a test that was excessively short/long in duration.

Once the protocol was selected the subject was seated on the cycle and the seat height was adjusted according to the heel method whereby, when the pedal is at its lowest position, the knee is slightly bent (5-15° knee flexion). The feet were strapped tightly to the pedals using an adjustable Velcro strap. The protocol for the performance of a maximal cardiopulmonary exercise test was then followed.

3.11.3 Arm ergometry protocol selection

As with the cycle ergometer, the arm ergometry protocol utilises a ramp protocol with gradual increases in work rate throughout the test. The work rate for arm ergometry exercise was calculated according to the following equation by Cooper & Storer (2001).

Arm work rate max = [(Predicted $\dot{V}O_2$ max *0.70) + (BW*3.5)]/18.36

Predicted $\dot{V}O_2$ max using the arms is estimated to be 70% that of the legs, hence the multiplication by 0.70. BW is the subjects' body weight in kilograms. The predicted $\dot{V}O_2$ max utilised in this equation is the same as that defined in section 3.11.2. This equation predicts the subjects maximal work rate, the work rate per minute is then calculated by dividing the predicted peak value by 10, the estimated total test time.

Once the protocol was selected the subject was seated in front of the arm ergometer crank. Seat height was not adjustable on the arm ergometer and so the arm crank was adjusted to ensure that the arm was slightly bent at the elbow during furthest extension as per knee flexion for cycle ergometry (Pina et al., 1995).

Once the subject was sat ready to commence the exercise test, the preVent® device was fitted to the front of the mask with the sample line attached to the top of the headgear using the adjustable Velcro straps to keep it secure. When leg cycling a pulse oximeter probe was attached to the subject's finger and to the ear when arm cycling, using appropriate adaptors.

3.11.4 Resting phase

Resting measurements were obtained for a minimum of two minutes. This was to ensure correct calibration and functioning of the equipment and to allow the subject time to familiarise themselves with the equipment. It also allowed resting measurements of SpO_2, blood pressure, ECG, $\dot{V}E$ and gas exchange variables to be

made. Resting RER measurements were assessed to ensure that they were <1.0 and therefore the subject was not hyperventilating prior to exercise.

The breath-by-breath fluctuations in measured ventilatory and metabolic variables can be minimised by mathematical manipulation of the breath-by-breath data. There are several options recommended to present breath by breath data and these include calculating the average of 5 breaths out of 7 breaths completed which was the method adopted for this study (ATS/ACCP., 2003).

3.11.5 Unloaded phase

A three-minute warm up was performed with the ergometers set to a work load of 0 watts and the participants instructed to pedal at a cadence of 60 rpm. This 'unloaded phase' is important in assessing baseline $\dot{V}O_2$ and ventilation, allows the subject to familiarise themselves with the equipment and the expected cadence and to warm up effectively (Radtke et al., 2019).

The blood pressure equipment was programmed to automatically perform a blood pressure measurement at the end of the unloaded phase and every three minutes thereafter during exercise. When a subject was exercising using the arm ergometer this automatic blood pressure measurement was cancelled as it was not possible to determine blood pressure whilst exercising with the arms.

3.11.6 Incremental exercise phase

On completion of the unloaded exercise phase the calculated exercise protocol commenced immediately. During testing the blood pressure, SpO_2, heart rate, ECG, ventilation and gas exchange parameters were continuously monitored for signs of subject intolerance or inaccuracies due to equipment fault/error.

The subject was actively encouraged to exercise to their symptom limited end point e.g., leg fatigue or breathlessness. The test was stopped by the operator when the subject indicated that they could no longer continue, or they were unable to maintain

the required cadence (i.e., cadence fall of ≥5%) or one of the test termination criteria was identified, see Table 8.

3.11.7 Recovery phase

On completion of exercise the subject undertook a period of recovery. During recovery they were encouraged to decrease their cycling cadence to approximately 30 rpm. Breath by breath data was continued to be collected for the first two minutes of recovery. After two minutes the gas exchange measurements were terminated, and the headgear and mask were removed to make the subject more comfortable. They then continued a period of recovery with ECG monitoring until their heart rate had recovered to within 5% of their resting value.

Once resting heart rate values were achieved testing was complete. All monitoring equipment was removed from the subject and they were thanked for their participation and arrangements made for their second visit. Single patient items were immediately disposed of on completion of testing and all remaining equipment cleaned in accordance with the department cleaning and infection control standard operating procedures.

Subjects returned for a second exercise test between 24 hours and two weeks following their first attendance. The second test was conducted using the alternative exercise modality to the first visit. The test was performed as per the test protocol summarised above however baseline spirometry was not repeated and the results of the first test were used to predict maximal ventilation for the second test using the equation in section 3.11.1.

3.11.8 Premature termination of testing

Determination of $\dot{V}O_2$ requires a maximal test and therefore subjects were encouraged to exercise to a symptom limited end point, usually breathlessness or leg fatigue. The test was also be terminated by the operator if the subject was no longer able to maintain the required cadence (fall in cadence ≥5%). Other reasons to terminate a test included the development of clinically inappropriate symptoms, listed in Table 8.

Table 8. Indications for the premature termination of testing

- >2mm ST depression if symptomatic or 4mm if asymptomatic or >1mm ST elevation
- Significant arrhythmias causing symptoms or haemodynamic compromise
- Fall in systolic blood pressure >20mmHg from the highest value during the test
- Hypertension >250mmHg systolic; >120mmHg diastolic
- Severe desaturation: SpO_2 <80%
- Loss of coordination
- Mental confusion
- Dizziness or faintness

Adapted from (Radtke et al., 2019)

3.12 Analysis of Results

3.12.1 Identification of a maximal test

There is no gold standard way for defining maximal effort on cardiopulmonary exercise testing, with considerable variability in the significance level of objective markers used for the determination of a maximal test (ATS/ACCP., 2003; Levett et al., 2018; Chambers and Wisely, 2019; Radtke et al., 2019). Maximal subject effort was considered to have been achieved if one or more of the criteria listed in Table 9 were achieved. For cycle ergometry testing, any results of exercise tests that were submaximal i.e., did not fulfil the maximal test criteria, were excluded from further analysis.

Table 9. Criteria for identifying a maximal exercise test

1. A plateau in $\dot{V}O_2$
2. Peak exercise ventilation ($\dot{V}E$ peak) >85% predicted
3. Maximum RER during exercise exceeding 1.10
4. Heart rate at or above 85% predicted
5. Peak work rate >85% predicted

3.12.2 $\dot{V}O2$ max determination

A $\dot{V}O_2$ max is determined when the highest achieved $\dot{V}O_2$ fails to increase despite further increases in work rate. This plateau in $\dot{V}O_2$ is defined by an increase in $\dot{V}O_2$ <2.0 $ml.min^{-1}kg^{-1}$ despite an increase in work rate of 5-10% (Radtke et al., 2019). In the absence of the subject achieving a $\dot{V}O_2$ max, the highest achieved $\dot{V}O_2$ was quoted and termed 'peak' $\dot{V}O_2$.

3.12.3 Anaerobic threshold determination

In the 1920's Hill (1924) first identified that lactate increases in the blood during heavy exercise. Above a certain work rate, the anaerobic component of metabolism increases and causes lactate to increase significantly. At the same time there is an equal reduction in bicarbonate concentration causing CO_2 production to accelerate which is seen by an increase in CO_2 output. The gold standard way of detecting this metabolic transition is to measure arterial lactate levels at frequent intervals throughout the exercise test. In 1986, Beaver (1986) first described a non-invasive method for determining the lactate or anaerobic threshold, the V-slope. Due to the complexity of the V-slope method it has more recently been replaced by a simplified method known as the modified V-slope (Schneider et al., 1993).

3.12.4 Modified V-Slope

The anaerobic threshold was determined by visual inspection of the relationship of $\dot{V}CO_2$ versus $\dot{V}O_2$. The point at which $\dot{V}CO_2$ departed from a line with a slope equal to 1.00 was selected as the anaerobic threshold.

3.12.5 Dual criteria method

The modified V-slope method was supported by evaluating changes in the ventilatory equivalent and end-tidal partial pressures of O_2 and CO_2 to confirm hyperventilation with respect to O_2 but not CO_2 (Levett et al., 2018), Figure 25. Using the dual criteria method, the anaerobic threshold was defined by the events listed in Table 10 which all occur almost simultaneously.

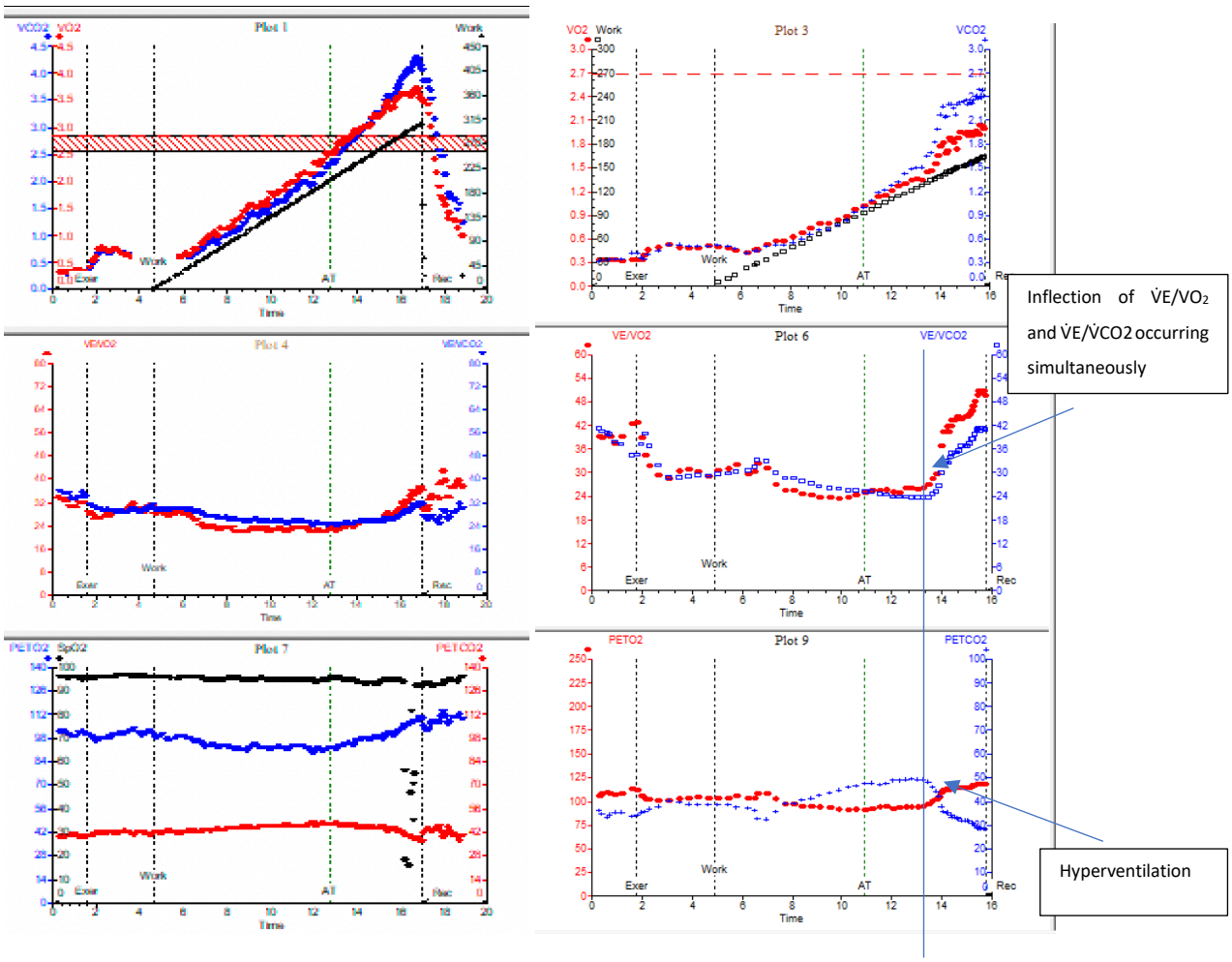


Figure 25 - Example of the dual criteria method

Figure 24 illustrates the role of the dual criteria method in the identification of acute hyperventilation relative to CO_2 as the cause of a V slope inflection. In this example the graphs on the left illustrate a normal response. At the point of AT there is an inflection in the $\dot{V}E/\dot{V}O_2$ slope with the inflection in the $\dot{V}E/\dot{V}CO_2$ occurring later. The graphs on the right illustrate a subject who was hypoventilating during exercise and then following AT there was acute hyperventilation resulting in simultaneous inflection of the $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slopes. Image by author.

Table 10. Criteria for identifying and confirming the anaerobic threshold

1. Identify excess $\dot{V}CO_2$ relative to $\dot{V}O_2$ above the anaerobic threshold using modified V-slope.
2. Identify hyperventilation relative to oxygen. - The $\dot{V}E/\dot{V}O_2$ relationship having been flat or decreasing begins to increase and does not return to baseline - The $P_{ET}O_2/\dot{V}O_2$ relationship having been declining or flat begins to increase and does not return to baseline
3. Exclude hyperventilation relative to CO_2 at the anaerobic threshold inflection point identified in 1 and 2. - The $\dot{V}E/\dot{V}CO_2$ relationship remains constant or continues to decrease at the points where $\dot{V}E/\dot{V}O_2$ starts to rise systematically - There is no reciprocal decrease in $P_{ET}CO_2$ at the point where $P_{ET}O_2$ starts to rise systematically

Experience and use of a systematic approach is essential for correctly identifying the anaerobic threshold (Dolezal et al., 2017). To prevent variability in anaerobic threshold identification, the author who had significant experience in the detection of anaerobic threshold, identified the AT for all investigations.

3.13 Data Collection

As per the recommendations of the National Institute for Health Research (NIHR) the author completed the Introduction to Good Clinical Practice (GCP) training with refresher training every two years (National Institute for Health and Care Excellence, n.d.). GCP are a set of internationally recognised ethical and scientific quality requirements for designing, conducting, recording, and reporting research that involves human participation. Participating in this training ensures that the author understands and conducts research in a manner that provides assurances that the rights, safety and wellbeing of research participants are protected, and that research data is reliable (Health Research Authority, 2021).

Each participant was provided with a unique study number. A log of participants and their study number was held by the lead investigator on a personal drive not accessible by any other individuals. This drive was backed up daily to the Trust's server.

Results of exercise tests were stored on the departments exercise testing system which was only accessible to named personnel within the department with each staff member having their own password allowing audit of activity. Exercise test data required for the purpose of the study was manually copied into a trial spreadsheet held on the departments shared drive. Participant data was entered and stored according to their unique identifier number only and was therefore anonymous. Results of screening investigations and questionnaires were stored in each participant's individual electronic folder.

3.14 Statistical Analysis

3.14.1 Sample size

Linear multiple regression was used to generate reference equations that predict arm ergometry CPET variables of $\dot{V}O_2$, AT, work rate and heart rate. As this was the primary outcome the study was powered for linear multiple regression. Independent values known to predict cycle ergometry CPET variables were used, and these included sex, age, and weight. A *priori* sample size was calculated using G* Power 3.1 (Faul et al., 2009). A sample of 99 subjects achieved 90% power to detect an effect size of 0.15 attributable to 3 independent variables (age, sex and weight) using an F-test with a significance level (alpha) of 0.05.

3.14.2 Statistics

3.14.2.1 Normal distribution

The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to assess the normality of distribution of investigated parameters. Not all parameters were normally distributed and therefore data were expressed as median and interquartile range (IQR).

3.14.2.2 Multiple regression

Multiple regression analysis describes the relationship between a dependent variable and several independent variables and can be used to predict a continuous dependent variable. In the current study the primary dependent variable was VO_2 (as measured by arm ergometry) and the independent variables were age, sex and weight. The multiple regression model 'Enter' method was used to generate a multiple correlation coefficient, R. The proportion of variance in the dependent variable explained by the independent variable was measured by the coefficient of determination, R^2. Statistical significance of the overall model was assessed by ANOVA with a p value <0.05 indicating statistical significance.

Prior to multiple regression analysis, data assumptions were assessed and met (Laerd Statistics, 2015). These included:

1. Independence of observations was assessed by a Durbin-Watson statistic with a value of approximately 2 indicating that there was no correlation between residuals and independence of errors (residuals).
2. Homoscedasticity and linearity of the relationship between the dependent and independent variables was assessed by visual inspection of a plot of studentised residuals versus unstandardised predicted values.
3. Multicollinearity occurs when two or more independent variables are highly correlated and leads to problems with understanding the contribution of each variable to the overall model. Multicollinearity was assessed using correlation coefficients with a value of >0.7 indicating a high correlation.

Additional assessment of tolerance >0.1 and VIF (1/Tolerance) <10 was used to confirm a lack of collinearity.

4. Outliers were identified by a standardized residual >±3SD.
5. A data point has high leverage if it has extreme predictor x values and is influential if it unduly influences any part of the regression analysis (Pennstate Eberly College of Science, 2018). High leverage was identified by a leverage value of >0.2. A Cook's distance of <1 identified a lack of influential cases.
6. Normal distribution of the residuals was assessed by visual inspection of histogram, normal Q-Q plots and box and whisker plots.

3.14.2.3 Comparison of arm and leg ergometry

Pearson correlation was used to analyse the association between all studied parameters obtained from arm and leg exercise. Due to the presence of outliers for all parameters, differences between CPET variables measured on arm and leg ergometry were assessed by Wilcoxon signed-rank test rather than paired t-test. Standardised test statistic (Z score) and the statistical significance were calculated with a $p<0.05$ considered statistically significant.

Statistical analysis was undertaken using IBM SPSS Statistics 27.0.1.0 statistical software (IBM Corporation).

Chapter 4: Results

A total of 120 subjects volunteered to participate in the study. One volunteer was not enrolled due to their age exceeding the upper limit of the age inclusion criteria (>70 years). A further volunteer was declined following initial screening due to moderate airflow obstruction on their baseline spirometry measurements relating to poorly controlled asthma. Consequently 118 subjects were recruited to the study.

Of the 118 subjects recruited, a further 2 (1.7%) had to be excluded from the study following their first exercise test. One participant demonstrated dysfunctional breathing on exercise which prohibited accurate interpretation of the results. The second participant demonstrated significant cardiac arrythmias during their first exercise test and was referred for a formal Cardiological assessment. Therefore, a total of 116 subjects completed all requirements of the study and are available to be included in the final analysis.

All subjects were randomised to perform either arm ergometry or leg ergometry first with an average time between tests of 4.69 (± 3.52), range 1- 14 days.

4.1 Subject Characteristics

A Shapiro-Wilk and Kolmogorov-Smirnov test ($p>0.05$) was used to assess the subjects' demographic data for normality. For both tests results for age, height and BMI suggested that these parameters were not representative of a normal population whereas weight was. Analysis for skewness and kurtosis suggested distribution of the sample was normal for age, skewness 0.277 (SE=0.225) and a kurtosis of -0.766 (SE=0.446); height, skewness 0.234 (SE=0.225) and a kurtosis of -0.777 (SE=0.446); and for weight, skewness 0.680 (SE=0.225) and a kurtosis of 0.595 (SE=0.446). Skewness and kurtosis analysis of BMI suggests distribution were not normal with values of 1.896 (SE=0.225) and 6.959 (SE=0.446) respectively.

Visual inspection in SPSS of the graphical analysis of distribution using histogram, normal Q-Q plots and box and whisker plots demonstrated that the data for age,

height and BMI was not normally distributed. Consequently, demographic and baseline characteristics are presented as median, interquartile range (IQR), minimum and maximum. The demographics of the participants are summarised in Table 11.

Table 11. Subject characteristics

n=116	Median	IQR	Minimum	Maximum
Age *years*	38	19	19	69
Height *m*	1.72	0.16	1.55	2.00
Weight *kg*	74.90	19.75	49.60	131.20
BMI kg/m^2	24.64	4.40	18.51	44.87
Smoking History *pack years*	0	0	0	24

4.1.1 Race

The majority of the subjects volunteering for the study were White (89.6%). Other groups represented included Asian (8.6%) and Black (1.7%).

4.1.2 Age

Subjects met the age range criterion of 18 to 69 years but there were no subjects aged 18 years, only one volunteer aged 19 years and only one male and one female subject between the ages of 60-69 years. The age distribution of the study sample according to sex is summarised in Figure 26.

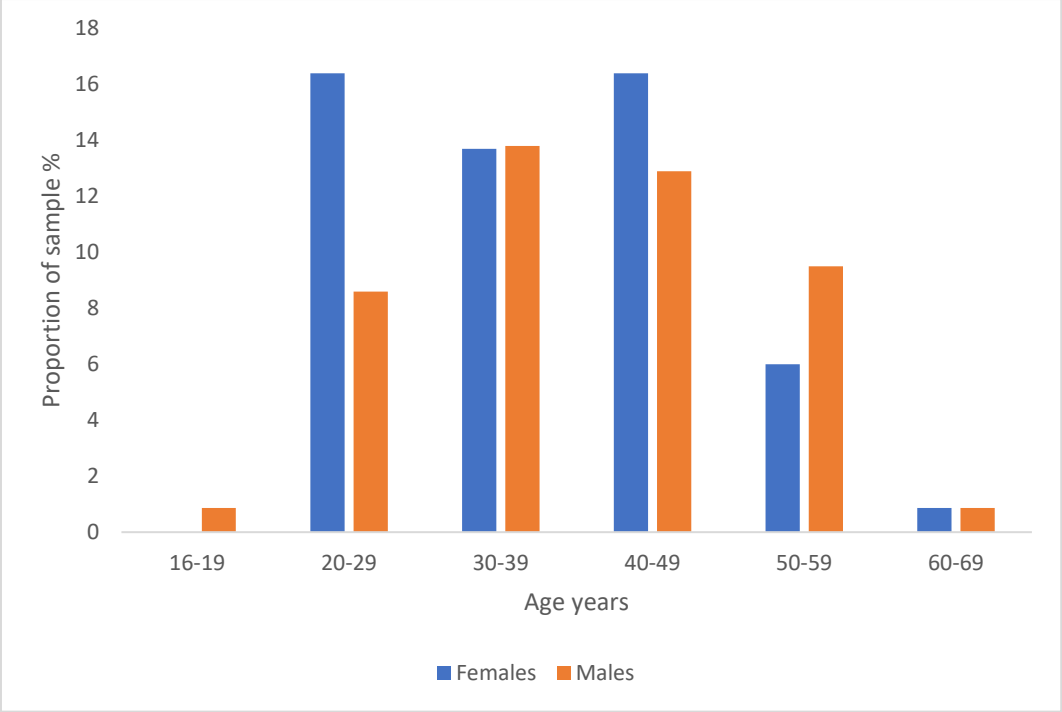


Figure 26 - Distribution of the study sample subdivided by decile.

4.1.3 Body Mass Index

The median BMI was normal. In total 52 subjects (44.8%) had a BMI of ≥25kg/m^2 with 42/116 (36%) classified as overweight but not obese. Ten subjects (8.6%) were classified as obese with a BMI ≥ 30kg/m^2. Of those classified as obese, 8/10 (80%) were obesity Class I (BMI 30-34.9 kg/m^2) and 2/10 (20%) obesity Class III (BMI ≥40 kg/m^2).

4.1.4 Smoking History

All subjects recruited had no history of respiratory or cardiac disease. None of the subjects were active smokers, however 14/116 (12%) had a history of cigarette / tobacco smoking with 2/14 (14%) reporting exposure of >15 pack years. Both of these individuals had normal spirometry and therefore no spirometric evidence of smoking-related lung disease (National Institute for Health and Care Excellence, 2019). Two other past smokers (pack year history <15) did have evidence of airflow obstruction on their baseline spirometry demonstrated by a FEV_1/FVC ratio of <-1.65 SR's.

4.2 Baseline Characteristics

All subjects performed resting measurements of spirometry, blood pressure, heart rate and oxygen saturation at screening. Data from these assessments are summarised in Table 12.

Table 12. Baseline characteristics

	n	Median	IQR	Minimum	Maximum
FEV_1 *L*	116	3.69	1.34	1.95	6.34
FEV_1 *SR*	116	0.07	1.19	-2.21	1.62
FVC *L*	116	4.52	1.85	2.65	7.48
FVC *SR*	116	0.40	1.00	-1.71	2.29
FEV_1/FVC *%*	116	80.80	9.03	62.89	95.87
FEV_1/FVC *SR*	116	-0.23	1.31	-2.69	2.09
SBP *mmHg*	115	126	17.25	86	190
DBP *mmHg*	115	78	13.50	51	104
Heart rate *bpm*	116	72	16.25	48	99
SpO_2 *%*	114	99	3.00	94	100

Abbreviations: FEV_1 = forced expiratory volume in one second; L = litres; SR = standardised residuals; FVC = forced vital capacity; % = percent; SBP = systolic blood pressure; mmHg = millimetre of mercury; DBP = diastolic blood pressure; SpO_2 = oxygen saturation

4.2.1 Spirometry

FEV_1, FVC and FEV_1/FVC ratio data was obtained from spirometry performed prior to exercise testing. Spirometry predicted values were generated using the Global Lung Initiative (GLI 2012) reference equations (Quanjer et al., 2012). Normal values are defined by a SR value of between -1.65 and +1.65. As a group spirometry was within normal limits with mean SR scores for all parameters within the expected normal range.

Figure 27 is a histogram of the distribution of FEV_1 SR score for the group illustrating that the data is a good fit to the GLI 2012 spirometry reference equations.

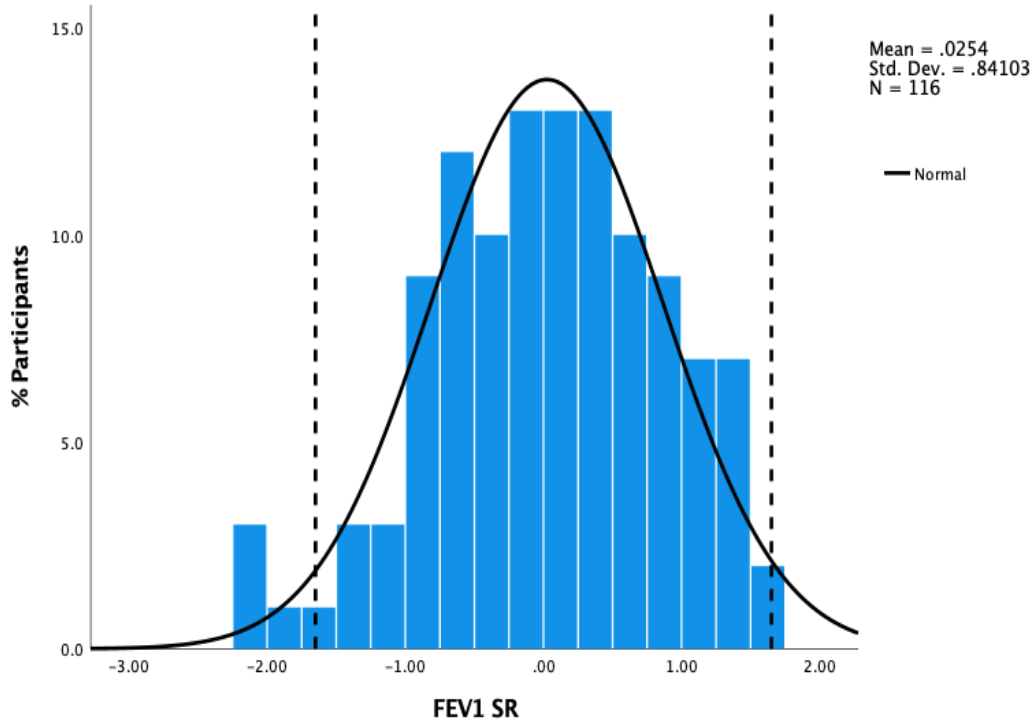


Figure 27 - Histogram of FEV_1 values obtained from the study group, expressed as a standardised residual.

SR – solid line represents normal curve; dashed lines represent the upper and lower normal ranges of +1.65 to -1.65

4.2.2 Blood pressure

Blood pressure measurements were within the normal range. One participant did not have resting blood pressure measurements made.

4.2.3 Heart rate

Median (IQR) resting heart rate for the study group was 72 (16.25) bpm which is within the expected normal range of 50-100 (Spodick, 1992). One male subject had a resting heart rate of 47 bpm but was asymptomatic.

4.2.4 Oxygen saturation

Median (IQR) resting oxygen saturation was normal at 99% (3.00). The normal range for oxygen saturation being 95-99% (Sylvester et al., 2020).

4.3 Cycle Ergometry Exercise Results

To enable comparison between exercise performed on a cycle ergometer and that performed on an arm ergometer, all subjects performed a maximal cardiopulmonary exercise test on each modality in a randomised order. All results from cycle ergometry are from tests that achieved at least one of the maximal exercise test criteria. Results of the cycle ergometry exercise tests are summarised in Table 13.

Table 13. Results of cycle ergometer exercise testing

	Median	IQR	Minimum	Maximum
HR *bpm*	171	22	127	197
WR *watts*	204	123	87	419
$\dot{V}E$ $L.min^{-1}$	92.00	48.15	49.50	198.70
AT $ml.kg^{-1}min^{-1}$	19.25	9.12	8.50	42.00
AT $ml.min^{-1}$	1414.50	779.00	688.00	3525.00
$\dot{V}O_2$ $ml.kg^{-1}.min^{-1}$	34.80	12.90	15.10	57.40
$\dot{V}O_2$ $ml.min^{-1}$	2481.00	1373.75	1240.00	4866.00
$\dot{V}CO_2$ $ml.min^{-1}$	2931.00	1741.00	1519.00	5681.00
RER	1.17	0.10	0.83	1.41
$\dot{V}O_2$/HR $ml.beat^{-1}$	15	9	7	30

Peak $\dot{V}O_2$ achieved during cycle ergometry was 107.01% (30.77) predicted. Anaerobic threshold occurred at 60.14% (24.37) predicted $\dot{V}O_2$ and 55.67% (11.52) of achieved peak $\dot{V}O_2$. Median peak heart rate was 86.94% (8.74) predicted with a peak ventilation of 74.86% (22.33) predicted. The peak work rate achieved was 117.99% (38.25) predicted.

4.4 Arm Ergometry Exercise Results

Results of cardiopulmonary exercise testing using arm ergometry for the group are summarised in Table 14. All values are at peak exercise with the exception of anaerobic threshold. The median protocol was 7.50 watts.min^{-1} and exercise duration 14.27 minutes.

Table 14. Results of arm ergometry exercise testing

	Median	IQR	Minimum	Maximum
HR *bpm*	157	31	99	192
WR *watts*	86	58	41	178
$\dot{V}E$ *L.min^{-1}*	69.70	40.80	27.10	162.00
AT *ml.kg^{-1}.min^{-1}*	11.30	3.80	5.90	29.10
AT *ml.min^{-1}*	814.00	395.00	407.00	2728.00
$\dot{V}O_2$ *ml.kg^{-1}.min^{-1}*	23.30	10.60	9.40	40.70
$\dot{V}O_2$ *ml.min^{-1}*	1744.00	914.50	808.00	3756.00
$\dot{V}CO_2$ *ml.min^{-1}*	1932.00	1137.50	779.00	4009.00
RER	1.14	0.10	0.89	1.45
$\dot{V}O_2$/HR *ml.beat^{-1}*	11.00	6.00	5.00	24.00

Abbreviations: HR = heart rate; WR = work rate; $\dot{V}E$ = ventilation; AT = anaerobic threshold; $\dot{V}O_2$ = maximal oxygen uptake; $\dot{V}CO_2$ = maximal carbon dioxide output; RER = respiratory exchange ratio; $\dot{V}O_2$/HR = oxygen pulse

Median (IQR) peak $\dot{V}O_2$ was 76.70% (25.73) of the predicted $\dot{V}O_2$ for cycle ergometry. Anaerobic threshold occurred at 35.28% (12.95) of the predicted $\dot{V}O_2$ and 49.18% (15.77) of the achieved peak arm ergometry $\dot{V}O_2$. Peak heart rate was 79.84% (13.01) of the Tanaka peak predicted heart rate.

Peak work rate for arm ergometry exercise was 53.34% (14.12) of that predicted for cycle ergometry and peak ventilation reached 60.46% (24.18) predicted.

4.5 Predicting Arm Ergometry Variables

4.5.1 Peak Oxygen Uptake ($\dot{V}O_2$ max)

Multiple regression was used to predict arm ergometry $\dot{V}O_2$ max ($AE\dot{V}O_2$) from sex, age, and weight. Prior to undertaking multiple regression analysis data was first assessed for the following six assumptions:

1. There was independence of errors (residuals)
2. There was a linear relationship between the predictor variables (age, sex, weight) and the dependent variable ($AEVO_2$ max)
3. There was homoscedasticity of residuals (equal error variances)
4. There was no multicollinearity
5. There were no significant outliers, high leverage points or highly influential points
6. The residuals were approximately normally distributed

The outcomes of the assessment of these assumptions for $\dot{V}O_2$ max are summarised below.

4.5.1.1 Independence of observations

There was independence of residuals as assessed by a Durbin-Watson statistic of 1.914.

4.5.1.2 Linearity

Partial regression plots of peak $\dot{V}O_2$ against age (Figure 28) and weight (Figure 29) were visually inspected and demonstrated that the assumption of linearity was met.

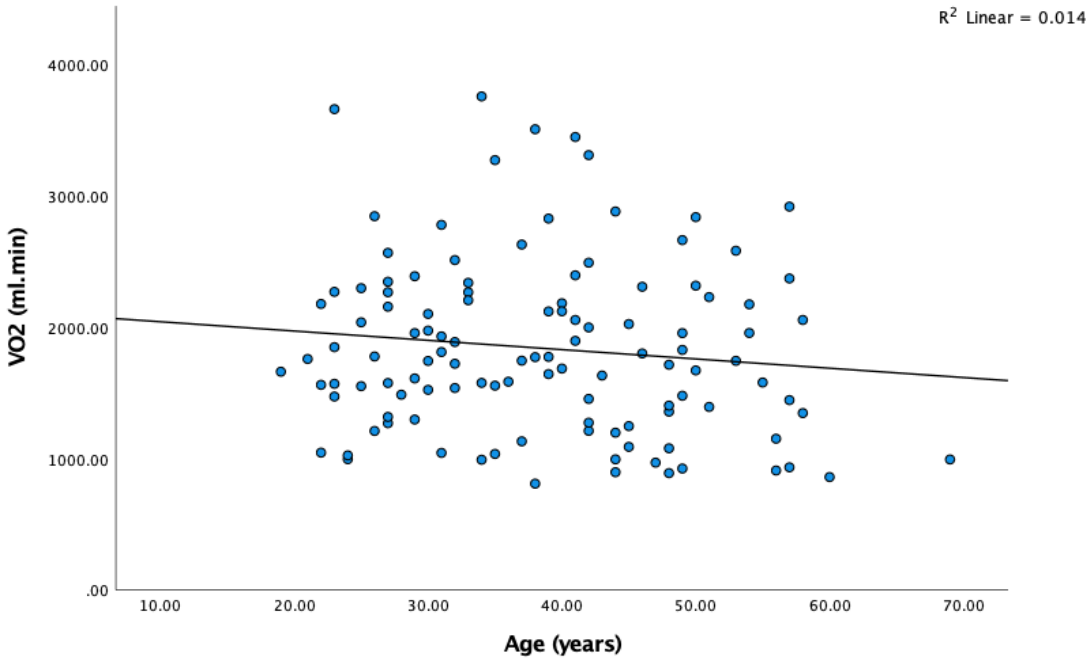


Figure 28 - Scatter plot of AE$\dot{V}O_2$ and age

The scatter plot of AE$\dot{V}O_2$ and age does not demonstrate a linear relationship as the relationship is almost flat however it does not fail the assumption of linearity.

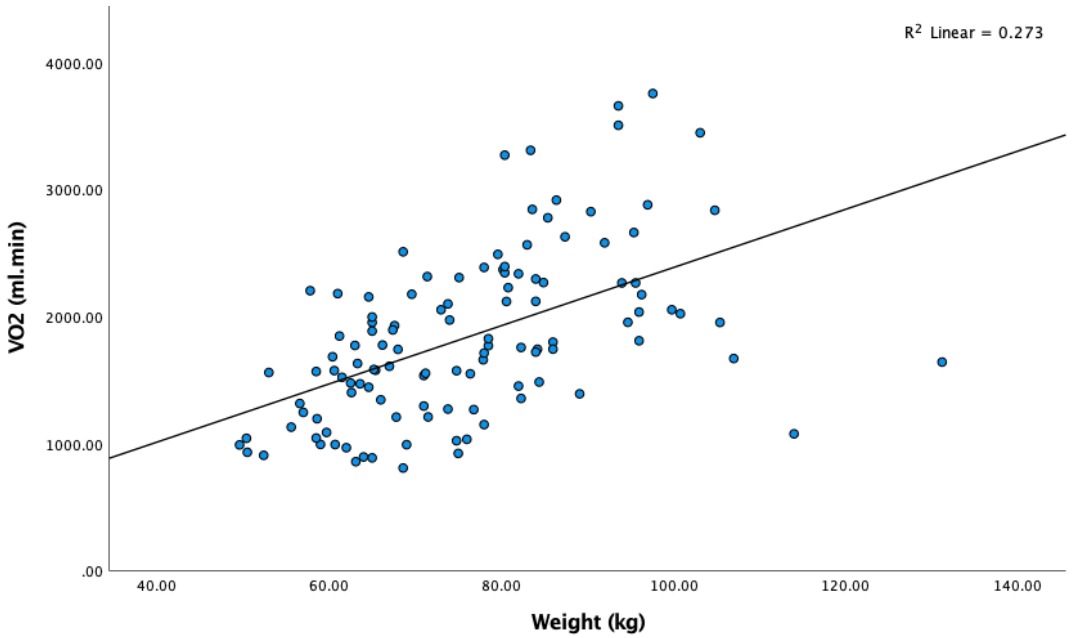


Figure 29 - Scatter plot of AE$\dot{V}O_2$ and weight

The scatter plot of AE$\dot{V}O_2$ and weight illustrates a linear relationship.

4.5.1.3 Homoscedasticity

There was homoscedasticity as assessed by visual inspection of a plot of studentised residuals versus unstandardised predicted values (Figure 30). This illustrates that the variance is equal for all values of the predicted dependent variable ($\dot{V}O_2$).

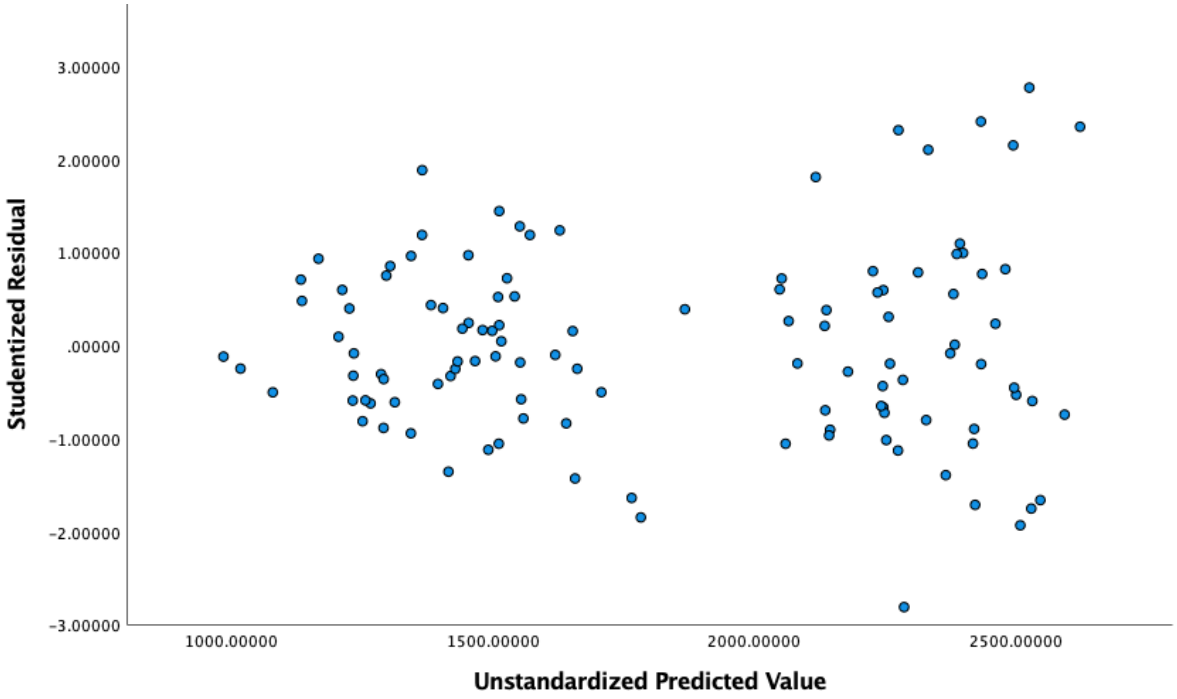


Figure 30 - Scatter plot confirming homoscedasticity of the data

4.5.1.4 Multicollinearity

Inspection of the correlation coefficients for $AE\dot{V}O_2$ and sex, age and weight demonstrate that none of the independent variables were strongly correlated with each other as demonstrated by a Pearson correlation coefficient of <0.7 for all variables, see Table 15. In addition, tolerance was >0.1 for all variables confirming a lack of multicollinearity.

Table 15. Pearson correlation coefficients for the dependent and independent variables

	$\dot{V}O_2$ *ml.min*$^{-1}$	Age *years*	Sex	Weight *kg*
$\dot{V}O_2$ *ml.min*$^{-1}$		-0.119^{NS}	-0.681**	0.522**
Age *years*	-0.119^{NS}		-0.109^{NS}	0.129^{NS}
Sex	-0.681**	-0.109^{NS}		-0.539**
Weight *kg*	0.522**	0.129^{NS}	-0.539**	

^{NS} not significant; *p<0.01; **p<0.001

4.5.1.5 Outliers

No case wise diagnostics were observed for AE$\dot{V}O_2$ and the studentised deleted residuals were all within ±3SD's therefore there was no evidence of outliers. Consequently, leverage points were <0.2 and there were no influential points.

4.5.1.6 Normality

Visual inspection of the histogram (Figure 31) demonstrates that the residuals are approximately normally distributed. Confirmation of these findings was made by visual inspection of the normal P-P plot (Figure 32) which illustrates that the data points were close enough to normal for the regression analysis to proceed.

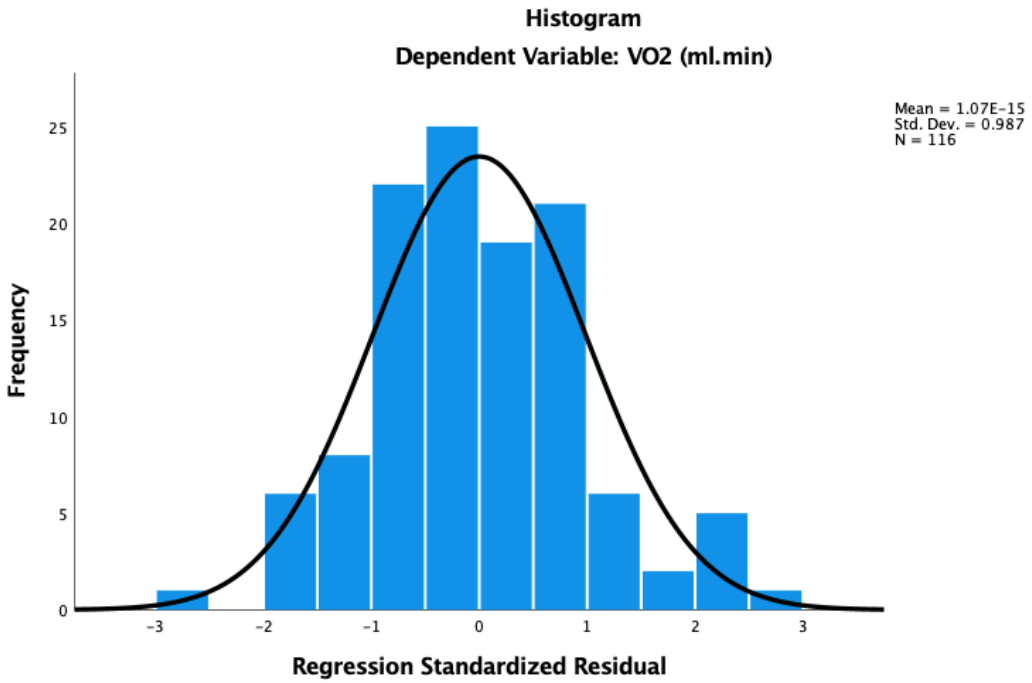


Figure 31 - Histogram of the distribution of the errors in the prediction (the residuals) illustrating a normal distribution.

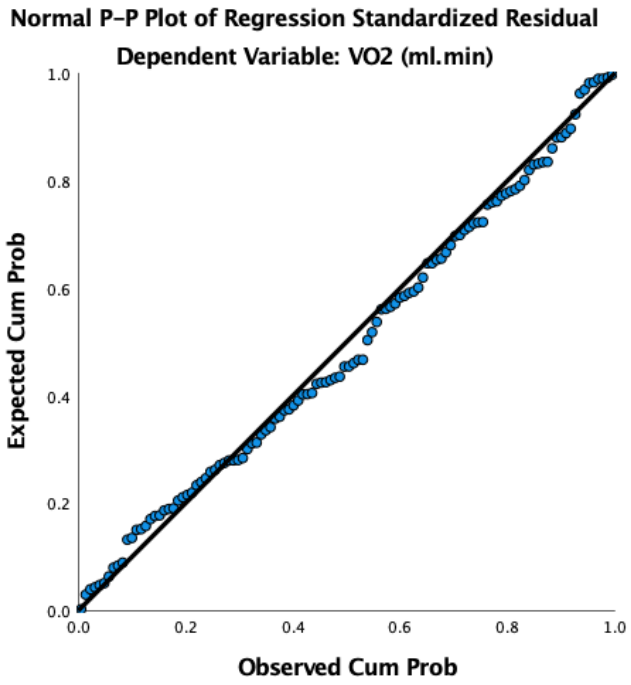


Figure 32 - Normal P-P plot of the errors in the prediction (the residuals)

4.5.1.7 Multiple Regression Model

As the assumptions for multiple regression analysis were all met a multiple regression model for determining AE$\dot{V}O_2$ using age, sex and weight was undertaken. The model can be found in Table 16.

Table 16. Multiple regression model for AE$\dot{V}O_2$

$\dot{V}O_2$ max	B	95% CI for B		SEB	β	R^2	ΔR^2
Model		LL	UL				
Constant	1930.803	1304.155	2557.452	316.270**		0.542	0.530
Age	-12.651	-20.270	-5.024	3.849*	-0.212*		
Sex	-756.095	-953.859	-558.330	99.812**	-0.575**		
Weight	10.507	3.890	17.123	3.339*	0.240*		

Model = "Enter" method in SPSS statistics. B = unstandardised regression coefficient; CI = confidence interval; LL = lower limit; UL = upper limit; SEB = standardised error of the coefficient; β = standardised coefficient; R^2 = coefficient of determination; ΔR^2 = adjusted R^2

*p<0.01; **p<0.001

The multiple correlation coefficient (R) value was 0.737 indicating a strong level of association. The coefficient of determination R^2 is a measure of the proportion of variance in the dependent variable (AE$\dot{V}O_2$) that is explained by the independent variables. The R^2 of 0.542 indicates that the addition of all of the independent variables into the regression model explains 54.2% of the variability in AEVO_2. The R^2 for the overall model was 54.2% with an adjusted R^2 of 53.0%, a large size effect according to Cohen (Cohen, 1988).

4.5.1.8 Summary

The multiple regression model statistically significantly predicted AE$\dot{V}O_2$ max, F(3, 112) = 44.266, p<0.001.

4.5.2 Arm Ergometry Anaerobic Threshold (AT)

Multiple regression was used to predict arm ergometry anaerobic threshold (AT) from sex, age, and weight. As with AE$\dot{V}O_2$, the six assumptions for accurate multiple regression analysis data were first assessed. With the exception of outliers, all assumptions were met.

4.5.2.1 Outliers

Three subjects were identified as outliers using case-wise diagnostics. These outliers demonstrated observations that did not follow the usual pattern and had measured anaerobic threshold levels higher than that predicted by the model: see Table 17.

Table 17. Outliers identified by case-wise diagnostic

ID	Std Residual	Act AT	Pred AT	Residual
4	3.261	1713.00	779.44	933.56
34	5.400	2728.00	1181.86	1546.14
95	4.365	2337.00	1087.26	1249.74

Review of the data for these individuals suggests that they were much fitter than the rest of the population (peak $\dot{V}O_2$ and anaerobic threshold on cycle ergometry significantly better than predicted) and this was the cause of the outliers. Leverage points were <0.2 for all individuals with the exception of subject 14 whose leverage point was 0.22. Review of their data identified that their BMI of 44.87 kg/m^2 was the cause of the leverage. Despite three outliers and one subject with leverage, Cooks' distance was <1 for all subjects and therefore there were no influential points.

To assess the impact of the outliers and leverage points the multiple correlation coefficient (R) was re-run firstly with the outliers suppressed and then again with the high leverage value suppressed. The correlation coefficient for the whole group was R = 0.570. With outliers suppressed it was R = 0.573 and with leverage suppressed R = 0.573. The lack of influence for these outliers and high leverage points resulted in

no significant impact on the overall model and therefore all data remained in the model.

4.5.2.2 Multiple Regression Model

As the assumptions for multiple regression analysis were all met a multiple regression model for determining anaerobic threshold using age, sex and weight was undertaken. The model can be found in Table 18.

Table 18. Multiple regression model for anaerobic threshold

AT	B	95% CI for B		SEB	β	R^2	ΔR^2
Model		LL	UL				
Constant	888.898	492.971	1284.825	199.825***		0.325	0.307
Age	-6.235	-11.054	-1.416	2.432*	-0.201*		
Sex	-276.662	-401.613	-151.711	63.063*	-0.405**		
Weight	5.178	0.998	9.359	2.110***	0.227*		

Model = "Enter" method in SPSS statistics. B = unstandardised regression coefficient; CI = confidence interval; LL = lower limit; UL = upper limit; SEB = standardised error of the coefficient; β = standardised coefficient; R^2 = coefficient of determination; ΔR^2 = adjusted R^2

*p<0.05; **p<0.01; ***p<0.001

R^2 for the overall model was 32.5% with an adjusted R^2 of 30.7%, a medium effect according to Cohen (Cohen, 1988).

4.5.2.3 Summary

The multiple regression model predicted anaerobic threshold with a high statistical significance, $F(3, 112) = 17.996$, $p<0.001$.

4.5.3 Arm Ergometry Work rate

Multiple regression was used to predict arm ergometry peak work rate from sex, age, and weight. As with AE$\dot{V}O_2$ and AT, the six assumptions for accurate multiple regression analysis data were assessed and met. The independent variable of sex was highly correlated with work rate (r = -0.788) however the tolerance value of 0.708 confirmed a lack of multicollinearity despite the high correlation.

4.5.3.1 Multiple Regression Model

As the assumptions for multiple regression analysis were all met a multiple regression model for determining work rate using age, sex and weight was undertaken. The model can be found in
Table 19.

Table 19. Multiple regression model for work rate

Work rate *watts*	**B**	**95% CI for B**		**SEB**	**β**	**R^2**	**ΔR^2**
Model		**LL**	**UL**				
Constant	96.003	70.078	121.928	13.084***		0.686	0.677***
Age	-0.511	-0.827	-0.196	0.159*	-0.172*		
Sex	-44.267	-52.449	-36.085	4.129***	-0.675**		
Weight	0.533	0.260	0.807	0.138**	0.244*		

Model = "Enter" method in SPSS statistics. B = unstandardised regression coefficient; CI = confidence interval; LL = lower limit; UL = upper limit; SEB = standardised error of the coefficient; β = standardised coefficient; R^2 = coefficient of determination; ΔR^2 = adjusted R^2

*p<0.05; **p<0.01; ***p<0.001

The multiple correlation coefficient (R) value was 0.828 indicating a strong level of association. The R^2 of 0.686 means that the addition of all of the independent variables into the regression model explains 68.6% of the variability in work rate. The

R^2 for the overall model was 68.6% with an adjusted R^2 of 67.7%, a large size effect according to Cohen (Cohen, 1988).

4.5.3.2 Summary

The multiple regression model statistically significantly predicted peak work rate, F(3, 112) = 81.451, p<0.001.

4.5.4 Heart Rate

Simple linear regression was used to assess the linear relationship between peak heart rate and age. As with multiple regression, prior to undertaking linear regression assumptions were clarified to ensure that the data was suitable for linear regression.

4.5.4.1 Outlier

One subject was identified as an outlier using case wise diagnostics. This outlier demonstrated a peak heart rate significantly lower than that predicted by the model, see Table 20.

Table 20. Outliers identified by case wise diagnostic

ID	Std Residual	Act HR	Pred HR	Residual
116	-3.392	99.00	156.60	-57.53

The individual in question only achieved a peak heart rate of 99bpm when exercising using their arms, rising from a resting heart rate of 65bpm. This peak heart rate equates to 54% of predicted heart rate (220-age) compared to the 87% predicted they achieved when exercising with their legs. These results suggest that the individual terminated the arm exercise early and that the test was not maximal. The study methodology states that only data from maximal exercise tests will be analysed. However, currently there are no recommendations for identifying a maximal exercise test when performed using arm ergometry. As this individual's heart rate did not rise significantly with arm exercise and was significantly different to that achieved when exercising with the legs, it is appropriate to conclude that this is a submaximal response from a submaximal test and the data point can be removed from further analysis. Following removal of the data point the assumptions for linearity were reassessed and met.

4.5.4.2 Linear Regression Model

As the assumptions for linear regression analysis were all met a linear regression model for determining heart rate using age was undertaken. The model can be found in Table 21.

Table 21. Linear regression model for heart rate

Heart rate *bpm*	**B**	**95% CI for B**		**SEB**	**β**	**R^2**	**ΔR^2**
Model		**LL**	**UL**				
Constant	191.833	180.999	202.667	5.468***		0.285	0.279***
Age	-0.916	-1.186	-0.646	0.136***	-0.534***		

Model = "Enter" method in SPSS statistics. B = unstandardised regression coefficient; CI = confidence interval; LL = lower limit; UL = upper limit; SEB = standardised error of the coefficient; β = standardised coefficient; R^2 = coefficient of determination; ΔR^2 = adjusted R^2

*p<0.05; **p<0.01; ***p<0.001

The correlation coefficient (R) value was 0.534 indicating a moderate level of association. The R^2 of 0.285 means that the addition of the independent variable into the regression model explains 28.5% of the variability in heart rate. The R^2 for the overall model was 28.5% with an adjusted R^2 of 27.9%, a medium size effect according to Cohen (Cohen, 1988).

4.5.4.3 Summary

The predicted equation was peak heart rate = 191.833 – 0.916*age. Age statistically significantly predicted peak heart rate, F(1,113) 45.094, p<0.001.

4.6 Arm Ergometry Regression Equations

Analysis of the arm ergometry data and the use of linear and multiple regression analysis has allowed the development of regression equations for the prediction of a normal cardiopulmonary exercise response to arm ergometry. Table 22 summarises the equations for reference values for peak oxygen uptake ($\dot{V}O_2$), oxygen uptake at the anaerobic threshold (AT), work rate (WR) and heart rate (HR) for arm ergometry exercise testing, based on the study sample (n=116).

Table 22. Equations for reference values for arm ergometry exercise

Parameter	Value	Constant	Age	Sex	Weight
$\dot{V}O_2$ *ml.min^{-1}*	Mean	1930.803	-12.651	-756.095	10.507
	ULN	2557.452	-5.024	-558.330	17.123
	LLN	1304.155	-20.270	-953.859	3.890
AT *ml.min^{-1}*	Mean	888.898	-6.235	-276.662	5.178
	ULN	1284.825	-1.416	-151.711	9.359
	LLN	49.971	-11.054	-401.613	0.998
WR *watts*	Mean	96.003	-0.440	-44.267	0.533
	ULN	121.928	-0.196	-36.085	0.807
	LLN	70.078	-0.827	-52.449	0.260
HR *bpm*	Mean	191.833	-0.916		
	ULN	202.667	-0.646		
	LLN	180.999	-1.186		

Data are multiple regression coefficients for VO_2, AT and WR. Data are linear regression coefficients for HR. For entering subject's characteristics, sex was coded as 0 for males and 1 for females.

4.7 Comparison of Cycle and Arm Ergometry Exercise Results

4.7.1 Relationship

Pearson correlation identified a significant linear relationship between parameters obtained from cycle ergometry and those obtained from arm ergometry, Table 23.

Table 23. Pearson correlation between exercise test parameters

	r	P
$\dot{V}O_2$ *ml.min*$^{-1}$	0.886	<0.001
AT *ml.min*$^{-1}$	0.657	<0.001
WR *watts*	0.917	<0.001
HR *bpm*	0.797	<0.001
$\dot{V}E$ *L.min*$^{-1}$	0.800	<0.001
RER	0.444	<0.001
$\dot{V}CO_2$ *ml.min*$^{-1}$	0.885	<0.001

Figure 33 illustrates the relationship between peak $\dot{V}O_2$ on arm ergometry with that obtained from cycle ergometry.

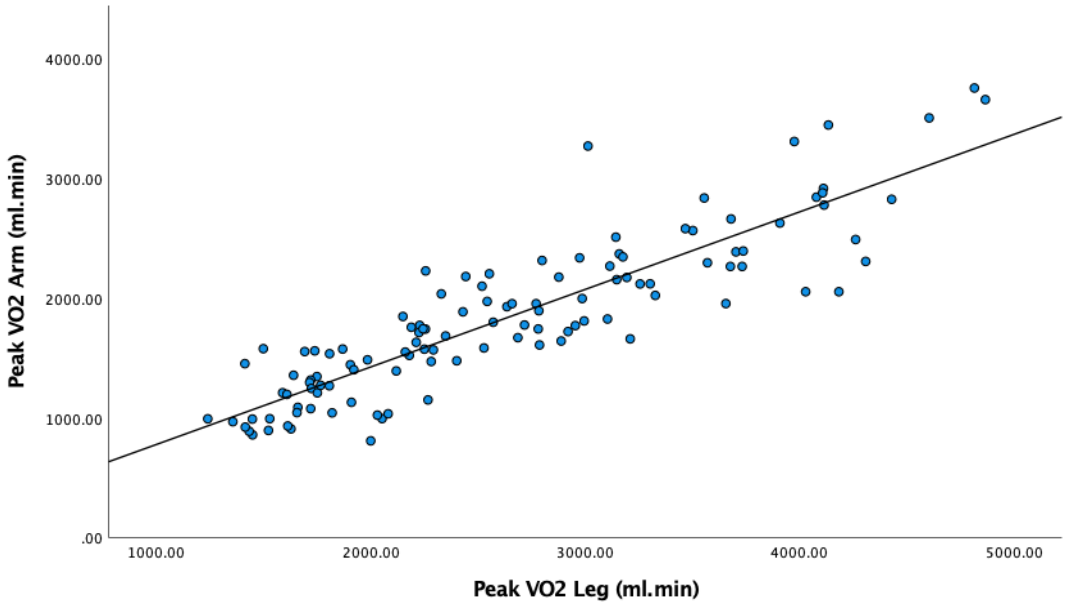


Figure 33 - Scatter plot of the relationship between peak $\dot{V}O_2$ on arm ergometry and cycle ergometry.

The mean differences between peak cycle and arm ergometry variables were assessed. All parameters, with the exception of AT, demonstrated normal distribution however inspection of box plots identified outliers for all parameters. Figure 34 illustrates the box plot for the mean difference between $\dot{V}O_2$, identifying case number 109 as an outlier.

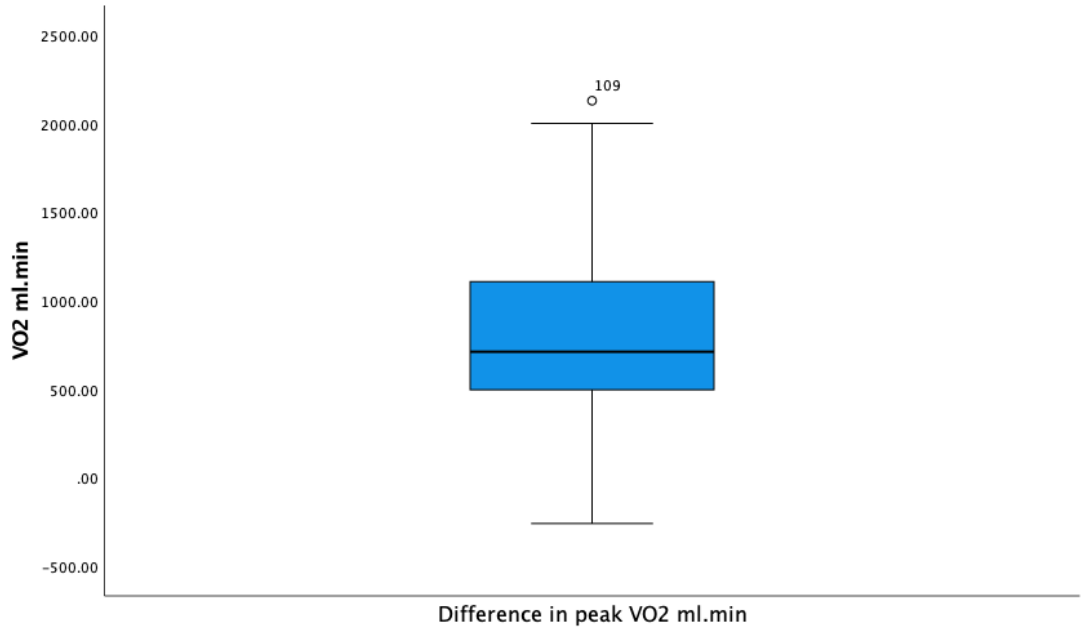


Figure 34 - Box plot of the mean difference between leg and arm ergometry peak $\dot{V}O_2$.

Due to the presence of outliers, a Wilcoxon signed-rank test was used to determine whether there was a significant median difference between the paired observations. Firstly, all parameters were assessed to ensure that the distribution of the median differences was symmetrical, and this was confirmed using histograms with superimposed normal curves. All variables demonstrated a normal distribution of the differences and the histograms for peak $\dot{V}O_2$, and heart rate can be seen in Figure 35 and Figure 36; respectively.

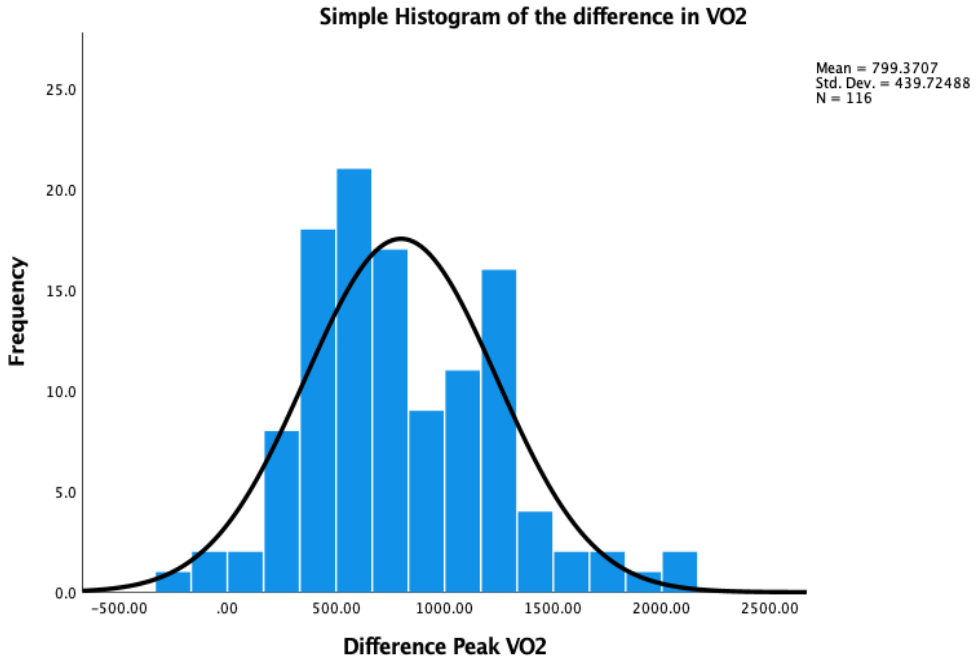


Figure 35 - Histogram illustrating the distribution of the median differences in peak $\dot{V}O_2$.

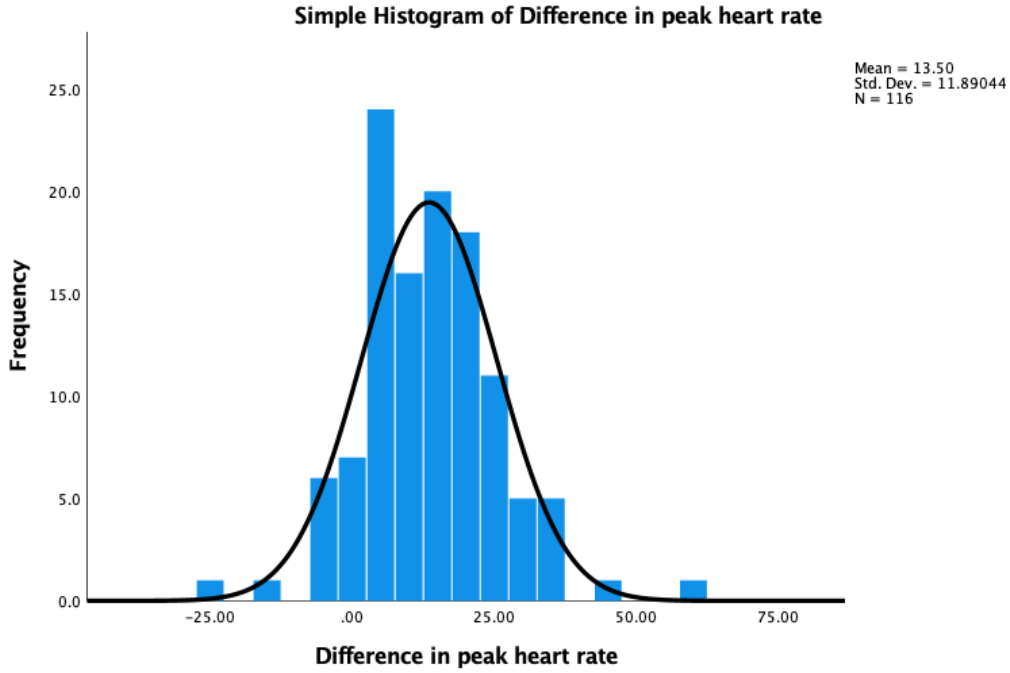


Figure 36 - Histogram illustrating the distribution of the median differences in heart rate.

The results of the Wilcoxon signed-rank test are summarised in Table 24 which includes the standardised test statistic (Z score) and the statistical significance.

Table 24. Comparison of cycle and arm ergometry peak exercise variables

	Cycle ergometry	Arm ergometry	Difference	Z score
$\dot{V}O_2$ *mlmin*$^{-1}$	2481.00	1744.00	799.37***	-9.314
$\dot{V}CO_2$ *ml.min*$^{-1}$	2931.00	1932.00	831.00***	-9.343
WR *watts*	203.50	86.00	117.5***	-9.348
HR *bpm*	170.50	157.00	14.00***	-8.521
$\dot{V}E$ *L.min*$^{-1}$	92.00	69.70	22.55**	-8.192
RER	1.17	1.14	0.20*	-2.114
AT *ml.min*$^{-1}$	1414.50	814.00	513.00***	-9.204
AT *%*$\dot{V}O_2$*pred*	60.14	35.28$^{\$}$	23.43***	-9.254
AT *%peak*$\dot{V}O_2$	55.67	49.18	6.74**	-5.025

Data expressed as mean values. *p<0.05; **p<0.01; ***p<0.0005; Z score = standardised test statistic; $ = predicted $\dot{V}O_2$ value is for cycle ergometry

Table 24 illustrates that peak exercise testing parameters obtained via cycle ergometry were all significantly higher than those achieved from arm ergometry.

4.7.2 Exploratory Analysis

The relationship between the $\dot{V}E/\dot{V}CO2$ slope and $\dot{V}O2/WR$ slope measured using cycle ergometry and arm ergometry was also assessed. Results of the Wilcoxon signed-rank test for these parameters are summarised in Table 25.

Table 25. Comparison of cycle and arm ergometry slope variables

	Cycle ergometry	Arm ergometry	Difference	Z score
$\dot{V}E/\dot{V}CO_2$ slope *ml.min^{-1}*	28.56	32.64	-4.08*	-7.646
$\dot{V}O_2$/WR slope *ml.min^{-1}.W^{-1}*	10.96	16.06	-5.10*	-9.279

Data expressed as mean values. *p<0.01; Z score = standardised test statistic

Table 25 illustrates that the $\dot{V}E/\dot{V}CO_2$ and $\dot{V}O_2$/WR slopes are both significantly higher on arm ergometry than cycle ergometry. The agreement between the slope variables was also assessed using Bland Altman plots with the cycle ergometry results classified as the reference method (Krouwer, 2008). One sample t test of the difference between $\dot{V}E/\dot{V}CO2$ on arm and leg and the difference between $\dot{V}O2$/WR on arm and leg demonstrated a statistically significant difference (p<0.001).

4.7.2.1 Slope of the ventilatory response ($\dot{V}E/\dot{V}CO_2$)

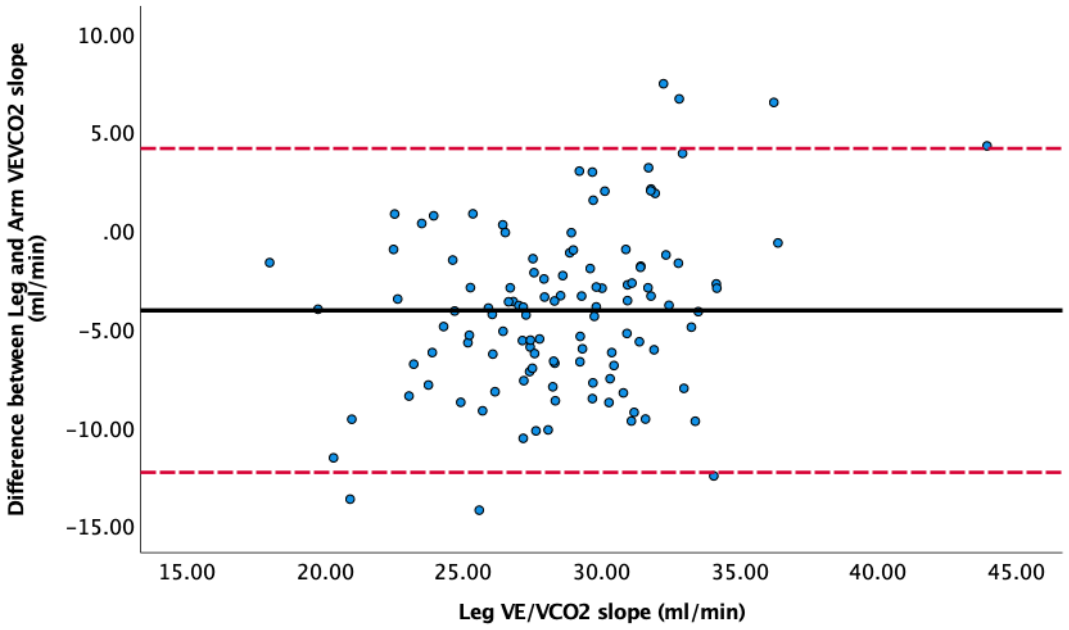


Figure 37 – Bland Altman plot of the difference between VE/VCO2 obtained from cycle and arm ergometry against the reference method (cycle ergometry)

Bold black line represents the mean value and hashed red lines represent the upper and lower 95% limit of agreement (SD*1.96).

Figure 37 demonstrates a proportional bias ($p<0.001$) with the difference in $\dot{V}E/\dot{V}CO_2$ between the two methods narrowing and then increasing as the value measured on cycle ergometry increases.

4.7.2.2 Work efficiency ($\dot{V}O_2$/WR slope)

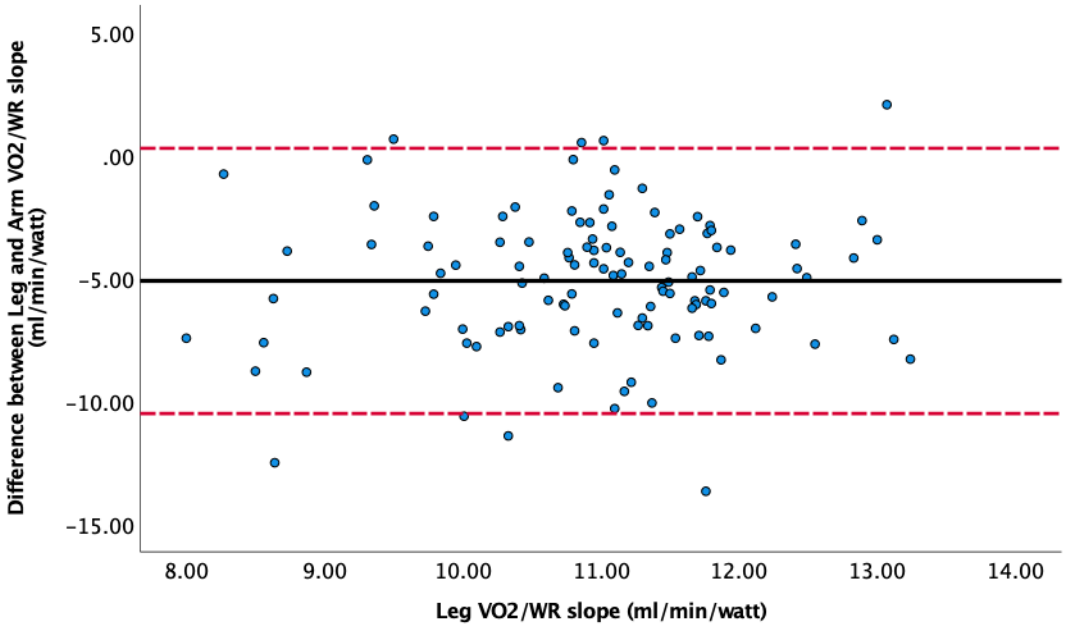


Figure 38 – Bland Altman plot of the difference between $\dot{V}O_2$/WR obtained from cycle and arm ergometry against the reference method (cycle ergometry)

Bold black line represents the mean value and hashed red lines represent the upper and lower 95% limit of agreement (SD*1.96).

The mean $\dot{V}O_2$/WR slope obtained during cycle ergometry testing was within the normal expected range of 8.3 to 12.3ml.min^{-1}.W^{-1} (Cooper and Storer, 2001). The $\dot{V}O_2$/WR slope obtained during arm ergometry demonstrated a linear response in keeping with that reported for cycle ergometry (Cooper and Storer, 2001), however it was higher in all but four individuals. There was no evidence of proportional bias between the difference in cycle and arm ergometry $\dot{V}O_2$/WR slope.

Chapter 5: Discussion

The present study represents the first study to provide data for the development of regression equations for $\dot{V}O_2$, anaerobic threshold, work rate and heart rate obtained by incremental cardiopulmonary exercise testing using arm ergometry exercise. Data was obtained from 116 normal healthy volunteers, which represents the largest sample size to date for arm ergometry reference values and includes a greater percentage of female participants (53.45%) than any previous study. It is also the first study of arm ergometry reference equations to use subject demographics and multiple regression analysis to develop equations according to age, sex, and weight similar to those published for cycle ergometry. The availability of arm ergometry predicted values will now enable the assessment of exercise capacity in clinical populations unable to perform cycle ergometry or treadmill testing ensuring equity of assessment and clinical decision making.

5.1 Subject Population

5.1.1 Smoking history and spirometry

Due to the decrease in peak $\dot{V}O_2$ associated with smoking, active smoking was an exclusion criteria for this study (Suminski et al., 2009). Therefore, none of the subjects included in the study were active smokers however 14/116 (12%) had a history of smoking. Previous studies of cycle ergometry reference values have also excluded current smokers with the large study by Koch (2008) finding no significant difference in measured $\dot{V}O_2$ between non-smokers and former smokers (Mylius et al., 2019).

The risk of lung disease increases significantly when an individual's pack year history is ≥10. In the current study two subjects exceeded this threshold however spirometry data for both these subjects were within normal limits (Guaraldi et al., 2015). There were two further subjects with a history of smoking who demonstrated moderate (FEV_1 50-80% predicted) airflow obstruction on spirometry (National Institute for Health and Care Excellence, 2019). Both subjects were asymptomatic with no history

of respiratory symptoms and therefore would not fulfil the criteria for a COPD diagnosis, however monitoring may be beneficial.

When compared to GLI regression equations, abnormal spirometry was identified in 7/116 (6%) of participants, despite being asymptomatic with no history of lung disease. As Figure 27 illustrates data was normally distributed with all data points lying within 2SD of the mean and therefore representative of a normal distribution and demonstrating that the study population was consistent with the normal population studied by GLI.

5.1.2 Hypertension

In the current study, resting hypertension was seen in 26/115 (22.6%) of subjects. Arterial hypertension has not been demonstrated to have a significant influence on peak $\dot{V}O_2$ or anaerobic threshold and therefore these subjects were included in the data analysis (Koch et al., 2008). Diagnosis of hypertension should not be made on a single visit with repeated home measurements having been proven to be more reliable. Much of this variability is related to 'white-coat syndrome' with between 10-30% of raised blood pressure measurements in a hospital setting being caused by pre-assessment anxiety (Unger et al., 2020). Isolated systolic hypertension (ISH) is common in young people and in this study 4/13 (31%) subjects with ISH were 27 years of age or younger (Lurbe and Redon, 2016).

5.1.3 Obesity

Fifty-two (44.8%) participants in the current study were overweight or obese as determined by BMI. Despite almost half of the study population being overweight, when assessing the impact of weight on peak $\dot{V}O_2$ and anaerobic threshold, only one individual with a BMI of 44.87 kg/m^2 demonstrated high leverage and this was for the prediction of anaerobic threshold only. Despite this high leverage the data point did not offer high influence and removal of the data point did not impact on the overall prediction model.

In Koch's (2008) study, subjects with a BMI >30kg/m^2 (13% of subjects) were excluded from analysis due to a significant influence on peak $\dot{V}O_2$ and anaerobic threshold. Other studies have shown that $\dot{V}O_2$ in obese subjects is similar to that obtained in non-obese subjects however maximal workload is lower, consistent with a decreased exercise efficiency in obese subjects (Brunani et al., 2017).

A recent UK Parliament document (2021) reports that the population prevalence of overweight but not obese (BMI 25-29.9 kg/m^2) is 36.2% which is consistent with our finding of 36%. The document also reports the prevalence of obesity (BMI ≥30) as 28%, significantly higher than our prevalence in a population of healthcare workers (8.6%). Obesity prevalence in healthcare workers has been found to vary according to profession with nurses having a significantly higher obesity rate of 25.12% compared with other registered healthcare professionals at 14.39% (Kyle et al., 2017). This lower prevalence for registered healthcare professionals compared with the general population is more consistent with our findings.

The prevalence of obesity in the current studies population is reflective of the population as a whole and consequently no subjects were excluded based on their BMI.

5.1.4 Race

The current study had no racial exclusions; however, participants were designated a race category (White, Black, Asian). In the 2011 census, 15% of people in England identified themselves as belonging to an ethnic minority group with 7.8% Asian and 3.5% Black. Our subject population of 89.6% White, 8.6% Asian and 1.7% Black is reflective of the national picture.

Provision of healthcare should not be influenced by ethnicity, skin colour or ancestry. To avoid discrimination, healthcare practices and procedures should be examined for possible influence by racism (Graham et al., 2022). Racial discrimination in medicine has been acknowledged in a range of procedures which includes lung function testing (Baugh et al., 2022), x-rays (Bavli and Jones, 2022), pulse oximetry (Bickler et al.,

2005; Feiner et al., 2007) and most recently temporal thermometers (Bhavani et al., 2022) and can result in delays in appropriate patient care (Bhavani et al., 2022).

Including race in clinical decision making causes problems for transparency and can restrict access to care whilst only offering modest benefits to precision (Eneanya et al., 2019). There is concern about the use of race in clinical algorithms (Flanagin et al., 2021) with its use generating discourse and potentially promoting systemic discrimination in healthcare (Powe, 2020) with many suggesting that race correction in healthcare should be abolished (Roberts, 2021).

The ATS/ACCP recommendations for high quality reference equations state that the removal of different racial groups ensures a higher reference value quality score. This requirement relates to the suggestion that exercise capacity in Asian and Black groups significantly differs from that measured in White populations and that this may relate to ethnic differences in physical activity (Nightingale et al., 2016) and/or to muscle oxidative capacity and oxygen pulse (Roy et al., 2006). However there is criticism of these findings with such studies often failing to take into account socioeconomic status and body composition and their effects on exercise capacity (Eyre and Duncan, 2013). It is also suggested that racial differences found in large data sets may reflect effects of racism i.e. the experience of being a particular race rather than the race itself (Vyas et al., 2020).

It would therefore be more appropriate to ensure that the subject population studied is representative of the patient population that it is to be applied to rather than artificially adjusting the population by removing different racial groups. This in itself would be a step nearer to ending race-based medicine (Roberts, 2021). Current reference values available for the interpretation of cardiopulmonary exercise testing are based on limited ethnic diversity which is promoted by the ATS/ACCP (2003) quality standards. Consequently, interpretation of results relies on comparison with studies based on populations of individuals representing limited racial categories such as the Koch (2008) study (entire sample is White) and should therefore be interpreted with caution when applying the findings to a more diverse population.

The universal application of including all racial groups into reference equations has the potential to widen confidence intervals. Consequently, accurate prediction may be more difficult (Graham et al., 2022) and abnormalities may be confirmed later in the course of a disease. However, as we develop a more multicultural society and by the inclusion of more racial diversity within study populations, accuracy will improve as reference values will be a better fit for the population they represent. In the current study, subjects' data was not excluded from analysis based on race (as for BMI) and consequently the findings better represent the local patient population.

5.2 Arm Ergometry Regression Equations

The selection of normal reference values for the evaluation of cardiopulmonary exercise test results is essential to ensure accurate interpretation by providing an assessment of normality which subsequently aids in clinical decision making. As recommended by the ATS/ACCP (2003), departments must select appropriate reference values that best reflect their local population. It is also essential to have reference values that correspond to the mode of exercise and type of ergometer used (Mylius et al., 2019).

Despite being the most widely utilised exercise modality (Porszasz et al., 2018), studies to develop reference equations for cycle ergometry are still limited by a lack of power analysis, quality assurance of equipment and validation of equations (Takken et al., 2019). Consequently, there is no single set of ideal reference values recommended and centres are encouraged to identify which best suits their local population by comparing reference equations to small samples of the local population (ATS/ACCP., 2003).

Of the four arm ergometry equations available to date, Balady (Balady et al., 1990) utilised a cycle ergometer adapted for arm ergometry and therefore the equipment is not reflective of current practice. Manfre (Manfre et al., 1990) is limited by its population of 12 normal healthy individuals and 19 with coronary artery disease and

the ACSM guidelines (Kenney et al., 1995) limited by both population (healthy young males) and protocol (fixed 25 watt increments).

The lack of widely available reference equations for arm ergometry led to the suggestion that 50-70% of cycle ergometry reference values be used as an estimate of arm ergometry predicted values (ATS/ACCP., 2003). This arbitrary value has been developed based on studies of single gender and limited age study groups and therefore may not be representative of the wider population (Franklin et al., 1983; Sawka et al., 1983; Martin et al., 1991). This relatively wide predicted range is also not specific enough when utilising exercise test results to make clinical decisions for example whether an individual is fit for surgery. Consequently, prior to the current study, interpretation of arm ergometry exercise test results was difficult which may be an important reason as to why this exercise modality has not been more widely adopted into routine clinical practice, despite its advantages in a growing cohort of subjects.

In addition to the methodological and equipment disadvantages of the previous four studies of reference values, three of the developed regression equations used peak wattage to determine predicted $\dot{V}O_2$ which is a significant contrast to published equations for cycle ergometry. Systematic reviews of cycle ergometry and treadmill references values illustrate that maximal oxygen uptake is dependent on age, sex and anthropometric properties and therefore it is these metrics that should be utilised in the development of reference values (Paap and Takken, 2014; Takken et al., 2019). The current study is the first study to develop arm ergometry regression equations using age, sex, and body weight to predict peak $\dot{V}O_2$, anaerobic threshold, peak work rate and peak heart rate.

The potential for sex based discrimination in sports and exercise medicine research has been highlighted with only 39% of over 6 million exercise research participants being female (Costello et al., 2014; Hagstrom et al., 2021). Suggested reasons for this include sex discrimination or investigator bias and volunteer bias (Hagstrom et al., 2021). Volunteer bias is suggested to relate to sex differences in the willingness to

participate in exercise research due to personality and interest traits and also to sex differences in exercise participation (Nuzzo, 2021). The current study includes the largest data set of female participants in arm ergometry exercise testing to date. Data from a total of 62 females were included in the study and they represented 53.45% of the subject population. The high prevalence of female participation in the present study may relate to participation bias with all subjects recruited from a UK NHS hospital where the prevalence of female health workers is known to be 77% (Regenold and Vindrola-Padros, 2021).

Previous studies of cycle ergometry reference values have also been criticised for only presenting the mean and/or median predicted value for the population. Normality is then often confirmed if the subject achieves a value of >80% of this value. The use of percentage predicted in the evaluation of normality has been widely criticised and subsequently abandoned in many areas of respiratory physiology and replaced with a lower and upper limit of normal of −1.96 SD and +1.96 SD, respectively (Quanjer et al., 2012; Blanchard et al., 2018; Sylvester et al., 2020). The present study provides both a mean reference value and upper and lower limit of normal using 95% confidence intervals of the mean with a 95% CI being equivalent to a z value of 1.96 allowing more accurate assessment of normality.

5.3 Quality of Regression Equations

In order to improve the quality of reference values, reference value studies are evaluated according to the ATS/ACCP quality standards with a score of ≥10 considered a high-quality score. Despite the publication of these quality standards, many studies still fail to achieve a high-quality score with only 4/29 (14%) of cycle ergometry reference value studies published between March 2014 and February 2019 achieving this standard. As previously described, the most frequent limitation of these studies is the omission of power analysis, quality assurance of equipment and validation of equations.

Table 26 illustrates the ATS/ACCP standards for high quality reference values and how the present study compares to these standards. The study achieved a total score of 10/14 which is consistent with a high-quality score. Standards that were not achieved include reporting of the level of physical activity, exclusion of different racial groups, sample size and validation of reference equations.

Table 26. Achievement of the standards for high quality reference value studies

1	Subjects' community based.	☑
2	Level of physical activity is reported.	☒
3	Exclusion of different racial groups.	☒
4	Exclusion of smokers in the sample studied.	☑
5	No lack of definition of the confidence limits for individual or specified characteristics.	☑
6	The number of subjects tested is sufficiently equal or larger than the appropriately powered sample size, with a uniform distribution of subjects for sex and groups.	☒
7	Randomisation was applied.	☑
8	A prospective study design.	☑
9	Quality control was applied.	☑
10	Exercise testing protocol and procedures are described.	☑
11	Results are obtained by either breath-by-breath analysis or mixing chamber.	☑
12	CPET result in interval averaged preferably every 30-60 seconds and the peak value reported represents the mean of the last completed stage or of all the data collected during the final stage, but preferably for no less than 30 seconds.	☑
13	Reference equations are validated in population other than those used to generate the existing data.	☒
14	The function that most accurately describes the distribution of the data are used.	☑

5.3.1 Physical Activity

The ATS/ACCP quality standards recommend that subjects report their level of physical activity to ensure that the subjects results are consistent with the population that they will be applied to. This is an attempt to limit participant bias as volunteers for exercise based research studies tend to be younger, more educated and undertake a higher volume of physical activity than non-volunteers (Barreto et al., 2013). The study methodology included the completion of the Recent Physical Activity Questionnaire (RPAQ) to quantify the level of activity regularly undertaken by participants. Unfortunately, participants found the questionnaire difficult to accurately answer and demonstrated a tendency to over report their recreational sporting activities. This is consistent with previous studies that have utilised questionnaires to enable subjects to self-report their level of physical activity in an effort to limit participation bias. Evidence suggests that these questionnaires have limited reliability and validity due to over reporting of exercise rates and exercise frequency, with those reporting the highest levels of physical activity having the greatest discrepancy with actual activity levels (Klesges et al., 1990; Durante and Ainsworth, 1996; Shephard, 2003). Consequently, data from the RPAQ questionnaire was excluded from further analysis.

Despite subjects recruited to this study not undertaking an assessment of their physical activity levels, It was confirmed that none of the participants undertook physical activity at a competitive level, consistent with other studies (Agostoni et al., 2017). Many subjects recruited were recreational athletes with cycling and running the most common pastimes reported.

5.3.2 Race

As previously discussed, racial groups were not removed from the current study sample as it was felt that this ensured a greater representation of our local

population. Eradication of the requirement to remove different racial groups would lead to a total quality score of 13 and a score for the present study of 10/13.

5.3.3 Sample size

The sample size of 116 in the current study was significantly larger than those employed in the currently available arm ergometry equations and exceeded the predicted sample size providing assurance of the positive predictive value of the findings. However, it should be recognised that in comparison to established equations for cycle ergometry, this sample size is significantly smaller and is limited to a local population.

5.3.4 External Validation

The current study's findings are limited by a lack of validation of the developed reference equations. Time constraints relating to the COVID-19 pandemic including the cessation of research studies and staff redeployment meant that validation of the equations could not be completed in time however this will be undertaken prior to publication of the new reference equations.

Newly developed reference values must be validated in populations other than those used to generate the existing data (ATS/ACCP., 2003). This external validation allows the assessment of equivalence and level of agreement and should be undertaken in at least 20 (10 males and 10 females) control subjects (Paap and Takken, 2014; Lewthwaite et al., 2020). Completion of external validation of the current study's findings would result in an ATS/ACCM quality score of 11/14 (11/13 with removal of race) which would represent one of the highest quality scores for exercise reference values in the last eight years and the only set of high-quality reference values for arm ergometry.

5.4 Comparison of Arm and Leg Ergometry

Muscles used for the performance of arm ergometry are significantly smaller, and in a normal population will generally be less well conditioned, than those of the legs. In addition, the muscle fibre type (Ørtenblad et al., 2018) and oxygen delivery ability

result in increased anaerobic metabolism and earlier cessation of exercise for any given workload (Wan et al., 2017; Muangkram et al., 2020). The current study has demonstrated that for all measured parameters, exercising with the legs elicited statistically significantly higher values than exercising with the arms. This is consistent with previous studies who all reported that peak $\dot{V}O_2$ was significantly lower when determined using arm ergometry however these studies were predominantly undertaken in young male subjects limiting the interpretation of these findings in a general population (Reybrouck et al., 1975; Davis et al., 1976; Nikolić and Todorović, 1984; Eston and Brodie, 1986). The current data confirms that this relationship persists in a more diverse study population.

Studies have been more conflicting with regards to anaerobic threshold. The earlier studies by Reybrouck (Reybrouck et al., 1975) and Davis (Davis et al., 1976) found AT as a percentage of peak $\dot{V}O_2$ to be significantly lower on arm ergometry and also generally less than 50%. In contrast, Sawka (Sawka et al., 1983) and Dekerle (Dekerle et al., 2002) reported no significant difference in AT across the two exercise modalities. All these studies were undertaken in male only populations, aged mid-twenties with sample sizes varying from 1 to 30. The current study, in a significantly larger study sample, has demonstrated that AT was statistically significantly lower when determined using the arms when expressed as both a percentage of predicted $\dot{V}O_2$ (60.14% versus 35.28%; $p<0.0005$) and as a percentage of peak $\dot{V}O_2$ (55.67% versus 49.18%; $p<0.01$). AT expressed as a percentage of predicted is limited by the predicted value being for cycle ergometry and hence the much lower value. When expressed as a percentage of peak $\dot{V}O_2$, arm ergometry elicits a median value of 49.18% which is within the range of 45 to 65% expected in healthy untrained individuals undertaking cycle ergometry (Balady et al., 2010). However, 43/116 (37%) subjects in our study had an AT of <45% peak $\dot{V}O_2$ when performing arm ergometry suggesting that the expected range of 45-65% is not appropriate for arm ergometry interpretation. Smaller muscles need to develop a greater percentage of their maximal tension during exercise which leads to lactate production and accumulation in the blood earlier than would occur in a larger muscle. The current study data

suggests that an AT%peak $\dot{V}O_2$ value as low as 24% could be considered normal when performing arm ergometry exercise.

A systematic review of arm versus leg ergometry in 2016 found that the mean difference in peak $\dot{V}O_2$ (leg-arm) in pooled data from 415 participants was 0.89 $L.min^{-1}$ or 890 $ml.min^{-1}$ (Larsen et al., 2016). The current study found a slightly smaller mean difference of 799 $ml.min^{-1}$ which may relate to the greater percentage of female participants in the study (53% compared to 34%) with the mean difference in $\dot{V}O_2$ greater in men than women (1014.83 $ml.min^{-1}$ and 611.71 $ml.min^{-1}$ respectively). Larsen (Larsen et al., 2016) also reported that the mean difference in peak $\dot{V}O_2$ decreased with increasing age (mean coefficient -2.1 (95%CI -0.3 to -0.1); p=<0.001) and increased with better aerobic capacity (mean coefficient 4.1 (95%CI 1.5 to 6.6); p=0.003). They concluded that this was to be expected as aerobic capacity decreases with increasing age. In contrast the current study found no relationship between the mean difference in peak $\dot{V}O_2$ and age (r^2 = -0.008; p=0.932) but the increase in mean difference with increasing aerobic capacity remained (r^2 = 0.681; p<0.001). This difference could be explained by the lack of age diversity in the studies included in the systematic review where the median age was 28.4 years (IQR 25.0 to 32.3) compared to our much wider age range of 38.5 years (IQR 29.0 to 48.0). Larsen (Larsen et al., 2016) reported that non-athletic healthy individuals would be expected to have a larger aerobic capacity when exercising using the legs due to everyday use and the larger lower limb muscle mass. It could also therefore be suggested that non-athletic healthy adults that undertake exercise for general fitness purposes (generally running and/or cycling) would see a widening of the mean difference in peak $\dot{V}O_2$ due to generalised improved fitness that is related to exercise that predominantly utilises the legs with minimal arm involvement. It is therefore this conditioning of the legs that causes the increased mean difference with increasing aerobic capacity and not increasing age. It could be hypothesised that this relationship may not persist in individuals that train their upper body to the same extent as their lower body.

Exploratory analysis of the $\dot{V}E/VCO_2$ and $\dot{V}O_2/WR$ slopes demonstrated statistically significantly higher values were achieved when exercising with the arms compared

with the legs. The increased $\dot{V}E/\dot{V}CO_2$ slope suggests a decreased ventilatory efficiency when exercising with the arms with a greater volume of air required to exhale 1 litre of CO_2 and a higher percentage of peak $\dot{V}O_2$ being required for a given work intensity.

As described previously, arm muscle contains a greater proportion of Type II muscle fibres which have a higher oxygen cost than slow twitch fibres resulting in an increased reliance on anaerobic metabolism. An increased in anaerobic metabolism would reduce the slope of the $\dot{V}O_2$/WR relationship in contrast to the findings in the present study. The increased slope may therefore relate to the lower oxygen conductance seen in arm muscle resulting in an increased oxygen delivery requirement for a given oxygen demand. An increased slope is also seen when a greater muscle bulk is recruited. In arm exercise where the muscle bulk is significantly smaller than the legs, this may suggest that there is a greater recruitment of additional muscles such as those of the shoulders, back and core which contribute to the increased oxygen delivery requirement.

5.5 Limitations

Limitations associated with this study include the lack of reference equations for other commonly utilised CPET parameters. Authors of CPET reference values are encouraged to publish values for multiple CPET parameters as the use of different reference value sources adds additional noise to test interpretation (Takken et al., 2019). Parameters commonly used in the clinical assessment of patients that are not included in this study include the $\dot{V}E/\dot{V}CO2$ slope, $\dot{V}E/\dot{V}CO_2$ at AT and the $\dot{V}O_2$/WR slope. The performance of CPET includes the measurement of all these variables and consequently the data is available for further analysis.

In March 2020 the World Health Organisation (WHO) declared the COVID-19 outbreak a global pandemic leading to the implementation of social distancing measures such as ‘lockdowns’ to reduce the rate of COVID-19 transmission. National lockdowns in England occurred between 23rd March 2020 and 1st June 2020, the 5th November and 2nd December 2020 and 6th January 2021 and 8th March 2021. Data

collection for the study occurred between November 2017 and May 2021 and therefore all three lockdowns occurred during the data collection period. Periods of lockdown have been demonstrated to lead to a decrease in physical activity levels and an increase in sedentary behaviours (Stockwell et al., 2021). Deconditioning leads to a reduction in peak $\dot{V}O_2$ and anaerobic threshold and therefore subjects tested after 23rd March 2021 may have produced lower values for these parameters than they would have if tested prior to lockdown (Fritzen et al., 2020).

In addition to the decrease in physical activity and increase in sedentary behaviours, COVID-19 infection itself has been demonstrated to lead to a decrease in peak $\dot{V}O_2$ in between 30-40% of hospitalised individuals (Clavario et al., 2020; Dorelli et al., 2021; Skjørten et al., 2021). All subjects attending for testing following the declaration of the COVID-19 pandemic undertook COVID-19 screening prior to undertaking any investigations. Screening included the recording of subject body temperature and questioning with regards to the presence of any SARS-Cov-2 related symptoms such as loss of taste and smell and cough. None of the subjects reported any symptoms suggestive of SARS-Cov-2 or previous known infection with COVID-19.

The performance of a CPET relies on the concomitant measurements of ECG and blood pressure. Both provide important clinical information on the cardiovascular response to exercise, but they also allow the identification of test termination criteria relating to patient safety. The most common site for blood pressure measurement is the upper arm however arm ergometry exercise limits accurate measurement due to continual movement of the arm during testing. The calf is the most commonly chosen site for blood pressure measurements when the arm is not possible however the large muscle bulk of the calf leads to significantly increased discomfort during measurements (Moore et al., 2008). It has been suggested that utilisation of the posterior tibial artery in the ankle may be preferable to the calf due to ease of access and similar circumference to the arm in addition the lack of muscle bulk in the ankle makes it less uncomfortable than calf measurements (Block and Schulte, 1996).

Unfortunately, the blood pressure device utilised in our study repeatably failed to obtain measurements when positioned on the ankle. Oscillometric blood pressure measurements have previously been demonstrated to be a reliable alternative to conventional blood pressure measurements made at the ankle (Beckman et al., 2006; Chongthawonsatid and Dutsadeevettakul, 2017). The poor reliability of the readings in the current study may therefore relate to the blood pressure device itself which is not listed on the British and Irish Hypertension Societies (British and Irish Hypertension Society, 2021) list of recommended oscillometric devices for specialist use. As a result, accurate measurement of blood pressure was not possible during arm ergometry testing. Due to the low risk of exercise induced hypertension in the study population this was not considered to pose a safety risk. However, prior to any further work in patient populations it will be essential to identify equipment that will accurately measure ankle blood pressure so that test termination criteria can be identified and acted upon accordingly. In addition, systolic blood pressure measurements have been shown to be on average 17.8 mmHg and as much as 33 mmHg higher on the ankle than the arm. A systolic blood pressure of 250mmHg (220mmHg in aortic aneurysm patients) during CPET is an indication to terminate exercise testing on safety grounds. The higher values obtained from the ankle may therefore lead to earlier termination of exercise when performing exercise tests using arm ergometry in patient populations and the potential impact of this needs to be evaluated.

Accurate ECG signals during exercise testing rely on the reduction of motion artefact which can be achieved by good skin preparation prior to electrode placement. This is important as the presence of motion artefact in ECG signals can cause misleading interpretation of cardiovascular status. Wandering baseline artifact relates to patient movement during ECG measurement which can be precipitated by exercise. During cycle ergometry testing subjects predominantly use the muscles of the legs. During arm ergometry muscles of the chest as well as the arms are used and the requirement to grip the arm crank handles results in an increased static exercise component. The current study found an increase in the tendency for ECG sway during arm ergometry exercise due to motion artefact. The likelihood to this finding was

increased in female subjects due to movement of breast tissue when moving the arms. Arm ergometry exercise demonstrates a lower sensitivity for detecting significant coronary artery disease than treadmill exercise testing and this may be influenced by motion artefact. This needs to be taken into consideration if arm ergometry exercise testing is to be utilised for the assessment of cardiac disease.

The reference values developed are from a study population aged 19 to 69 years of age, however it should be recognised that only two subjects over 60 years were recruited. The applicability of the reference values to an older population is therefore not known. Ethical approval for this study was for Trust staff and therefore limited to working age. Obtaining normative data in the older age group is more difficult due to the increased likelihood of co-morbidities. The Global Lung Initiative predicted values for spirometry for the 3–95-year age range have been widely adopted internationally (Quanjer et al., 2012). However only 0.8% of the 97,759 subjects included were aged 80 years and above. Due to this the authors recommend that results from individuals aged above approximately 75-80 years should be interpreted with caution. The use of these predicted values and reference ranges is however still recommended as the alternative equations have additional significant limitations.

5.6 Further Work

Given the growth of CPET for preoperative assessments and the potential increase in individuals unable to perform cycle ergometry and the recognised limitations of the present study, continual update of the predicted equations will be required. Other centres in the UK are purchasing arm ergometers to expand their exercise capabilities in addition to university research facilities and therefore pooling of data may be possible to further develop the normal value dataset.

Accurate interpretation of a cardiopulmonary exercise test relies on the subject performing a maximal test as submaximal effort will result in submaximal results. Identification of a maximal exercise test when performing cycle ergometry is assessed by the achievement of at least one of the following:

1. A plateau in $\dot{V}O_2$

2. Peak exercise ventilation (V̇E peak) >85% predicted
3. Maximum RER during exercise exceeding 1.10
4. Heart rate at or above 85% predicted
5. Peak work rate >85% predicted

Results of the present study have identified that all of these parameters are statistically significantly lower when obtained by arm ergometry exercise. Consequently, validation of these criteria using the newly developed reference equations will be required.

The application of arm ergometry in the clinical assessment of patients' needs to be evaluated. Since Older's (Older et al., 1993) seminal paper surgeons have relied on the achievement of an anaerobic threshold of 11 $ml.min^{-1}.kg^{-1}$ as an indication of fitness for surgery. The current study has demonstrated that anaerobic threshold obtained using arm ergometry is significantly lower than when obtained using the legs and 46.6% of subjects failed to achieve an AT of $11ml.min^{-1}kg^{-1}$. Therefore, a new threshold level for assessing safety of surgical intervention when exercising with the arms will need to be established.

Chapter 6: Conclusions

The current study of 116 healthy male and female volunteers aged 19-69 years has provided data for the development of predicted values and reference ranges for $\dot{V}O_2$, anaerobic threshold, work rate and heart rate obtained using arm ergometry exercise. This is the largest data set for arm ergometry reference values to date and represents the widest age range for healthy individuals.

The implementation of the predicted values and reference ranges developed in the current study for routine CPET parameters will potentially improve the interpretation of arm ergometry exercise tests and standardise interpretation across sites in the UK. The data will enable the assessment of clinical populations against a normal range with the view to developing interpretation strategies for a range of clinical applications.

Chapter 7: References

2019 exceptional surveillance of lung cancer: diagnosis and management (NICE guideline NG122) (2019). London: National Institute for Health and Care Excellence (UK).

Agostoni, P., Vignati, C., Gentile, P., Boiti, C., Farina, S., Salvioni, E., Mapelli, M., Magrì, D., Paolillo, S., Corrieri, N., Sinagra, G. and Cattadori, G. (2017) 'Reference Values for Peak Exercise Cardiac Output in Healthy Individuals.' *Chest*, 151(6) pp. 1329–1337.

Akkurt, H., Karapolat, H. U., Kirazli, Y. and Kose, T. (2017) 'The effects of upper extremity aerobic exercise in patients with spinal cord injury: a randomized controlled study.' *European Journal of Physical and Rehabilitation Medicine*, 53(2) pp. 219–227.

Albouaini, K., Egred, M., Alahmar, A. and Wright, D. J. (2007) 'Cardiopulmonary exercise testing and its application.' *Heart (British Cardiac Society)*, 93(10) pp. 1285–1292.

American College of Sports Medicine (2013) *ACSM's guidelines for exercise testing and prescription*. Lippincott williams & wilkins.

Arena, R., Myers, J., Abella, J., Peberdy, M. A., Bensimhon, D., Chase, P. and Guazzi, M. (2007) 'Development of a Ventilatory Classification System in Patients With Heart Failure.' *Circulation*, 115(18) pp. 2410–2417.

Arena, R., Myers, J. and Guazzi, M. (2008) 'The clinical and research applications of aerobic capacity and ventilatory efficiency in heart failure: an evidence-based review.' *Heart Failure Reviews*, 13(2) pp. 245–269.

'ATS/ACCP Statement on Cardiopulmonary Exercise Testing' (2003a) *American Journal of Respiratory and Critical Care Medicine*, 167(2) pp. 211–277.

'ATS/ACCP Statement on Cardiopulmonary Exercise Testing' (2003b) *American Journal of Respiratory and Critical Care Medicine*, 167(2) pp. 211–277.

Babbs, C. F. (2012) 'Oscillometric measurement of systolic and diastolic blood pressures validated in a physiologic mathematical model.' *Biomedical Engineering Online*, 11, August, p. 56.

Bailey, J., Berson, A. and Garson, A. (1990) 'Recommendations for standardization and specification in automated electrocardiography: Bandwidth and digital signal processing.' *Circulation: Special Report*, 81(2) pp. 730–739.

Balady, G. J., Arena, R., Sietsema, K., Myers, J., Coke, L., Fletcher, G. F., Forman, D., Franklin, B., Guazzi, M., Gulati, M., Keteyian, S. J., Lavie, C. J., Macko, R., Mancini, D., Milani, R. V., Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research (2010) 'Clinician's Guide to Cardiopulmonary Exercise Testing in Adults: A Scientific Statement From the American Heart Association.' *Circulation*, 122(2) pp. 191–225.

Balady, G. J., Weiner, D. A., Rose, L., Ryan, T. J. and Erario, M. (1990) 'Physiologic responses to arm ergometry exercise relative to age and gender.' *Journal of the American College of Cardiology*, 16(1) pp. 130–135.

Barreto, P. de S., Ferrandez, A.-M. and Saliba-Serre, B. (2013) 'Are Older Adults Who Volunteer to Participate in an Exercise Study Fitter and Healthier Than Nonvolunteers? The Participation Bias of the Study Population.' *Journal of Physical Activity and Health*, 10(3) pp. 359–367.

Barron, A., Dhutia, N., Mayet, J., Hughes, A. D., Francis, D. P. and Wensel, R. (2014) 'Test–retest repeatability of cardiopulmonary exercise test variables in patients with cardiac or respiratory disease.' *European Journal of Preventive Cardiology*, 21(4) pp. 445–453.

Bartsokas, T. W., Earnest, C. P. and Heiselman, D. E. (1989) 'MAXIMUM CARDIORESPIRATORY RESPONSES OF MEN AND WOMEN DURING ARM CRANK

ERGOMETRY: EFFECT OF CRANKING SPEED: 519.' *Medicine and Science in Sports and Exercise*, 21(Supplement) p. S87.

Baugh, A. D., Shiboski, S., Hansel, N. N., Ortega, V., Barjaktarevic, I., Barr, R. G., Bowler, R., Comellas, A. P., Cooper, C. B., Couper, D., Criner, G., Curtis, J. L., Dransfield, M., Ejike, C., Han, M. K., Hoffman, E., Krishnan, J., Krishnan, J. A., Mannino, D., Paine, R., Parekh, T., Peters, S., Putcha, N., Rennard, S., Thakur, N. and Woodruff, P. G. (2022) 'Reconsidering the Utility of Race-Specific Lung Function Prediction Equations.' *American Journal of Respiratory and Critical Care Medicine*, 205(7) pp. 819–829.

Bavli, I. and Jones, D. S. (2022) 'Race Correction and the X-Ray Machine — The Controversy over Increased Radiation Doses for Black Americans in 1968.' Malina, D. (ed.) *New England Journal of Medicine*, 387(10) pp. 947–952.

Beaver, W. L., Lamarra, N. and Wasserman, K. (1981) 'Breath-by-breath measurement of true alveolar gas exchange.' *Journal of Applied Physiology*, 51(6) pp. 1662–1675.

Beaver, W. L., Wasserman, K. and Whipp, B. J. (1986) 'A new method for detecting anaerobic threshold by gas exchange.' *Journal of Applied Physiology*, 60(6) pp. 2020–2027.

Beckman, J. A., Higgins, C. O. and Gerhard-Herman, M. (2006) 'Automated Oscillometric Determination of the Ankle–Brachial Index Provides Accuracy Necessary for Office Practice.' *Hypertension*, 47(1) pp. 35–38.

Bensimhon, D. R., Leifer, E. S., Ellis, S. J., Fleg, J. L., Keteyian, S. J., Piña, I. L., Kitzman, D. W., McKelvie, R. S., Kraus, W. E., Forman, D. E., Kao, A. J., Whellan, D. J., O'Connor, C. M., Russell, S. D., and HF-ACTION Trial Investigators (2008) 'Reproducibility of peak oxygen uptake and other cardiopulmonary exercise testing parameters in patients with heart failure (from the Heart Failure and A Controlled Trial Investigating Outcomes of exercise traiNing).' *The American Journal of Cardiology*, 102(6) pp. 712–717.

Bernal, W., Martin-Mateos, R., Lipcsey, M., Tallis, C., Woodsford, K., Mcphail, M. J., Willars, C., Auzinger, G., Sizer, E., Heneghan, M., Cottam, S., Heaton, N. and Wendon, J. (2014) 'Aerobic capacity during cardiopulmonary exercise testing and survival with and without liver transplantation for patients with chronic liver disease.' *Liver Transplantation*, 20(1) pp. 54–62.

Besson, H., Brage, S., Jakes, R. W., Ekelund, U. and Wareham, N. J. (2010) 'Estimating physical activity energy expenditure, sedentary time, and physical activity intensity by self-report in adults.' *The American Journal of Clinical Nutrition*, 91(1) pp. 106–114.

Best, C. and Shepherd, E. (2020) 'Accurate measurement of height and weight 2: height and BMI calculation.' *Nursing Times [online]*, 116(5) pp. 42–44.

Bhavani, S. V., Wiley, Z., Verhoef, P. A., Coopersmith, C. M. and Ofotokun, I. (2022) 'Racial Differences in Detection of Fever Using Temporal vs Oral Temperature Measurements in Hospitalized Patients.' *JAMA*, 328(9) p. 885.

Bickler, P. E., Feiner, J. R. and Severinghaus, J. W. (2005) 'Effects of Skin Pigmentation on Pulse Oximeter Accuracy at Low Saturation.' *Anesthesiology*, 102(4) pp. 715–719.

Bingisser, R., Kaplan, V., Scherer, T., Russi, E. W. and Bloch, K. E. (1997) 'Effect of training on repeatability of cardiopulmonary exercise performance in normal men and women:' *Medicine &amp Science in Sports &amp Exercise*, 29(11) pp. 1499–1504.

Blanchard, J., Blais, S., Chetaille, P., Bisson, M., Counil, F. P., Huard-Girard, T., Berbari, J., Boulay, P. and Dallaire, F. (2018) 'New Reference Values for Cardiopulmonary Exercise Testing in Children:' *Medicine & Science in Sports & Exercise*, 50(6) pp. 1125–1133.

Block, F. E. and Schulte, G. T. (1996) 'Ankle blood pressure measurement, an acceptable alternative to arm measurements.' *International Journal of Clinical Monitoring and Computing*, 13(3) pp. 167–171.

Bolliger, C. T., Jordan, P., Solèr, M., Stulz, P., Grädel, E., Skarvan, K., Elsasser, S., Gonon, M., Wyser, C. and Tamm, M. (1995) 'Exercise capacity as a predictor of postoperative complications in lung resection candidates.' *American Journal of Respiratory and Critical Care Medicine*, 151(5) pp. 1472–1480.

Bongers, B. C., Hulzebos, E. H., Helbing, W. A., Ten Harkel, A. D., van Brussel, M. and Takken, T. (2016) 'Response profiles of oxygen uptake efficiency during exercise in healthy children.' *European Journal of Preventive Cardiology*, 23(8) pp. 865–873.

Bonini, M. and Fiorenzano, G. (2017) 'Exertional dyspnoea in interstitial lung diseases: the clinical utility of cardiopulmonary exercise testing.' *European Respiratory Review*, 26(143) p. 160099.

Bonora, M., Patergnani, S., Rimessi, A., De Marchi, E., Suski, J. M., Bononi, A., Giorgi, C., Marchi, S., Missiroli, S., Poletti, F., Wieckowski, M. R. and Pinton, P. (2012) 'ATP synthesis and storage.' *Purinergic Signalling*, 8(3) pp. 343–357.

Bougenot, M.-P., Tordi, N., Betik, A. C., Martin, X., Le Foll, D., Parratte, B., Lonsdorfer, J. and Rouillon, J. D. (2003) 'Effects of a wheelchair ergometer training programme on spinal cord-injured persons.' *Spinal Cord*, 41(8) pp. 451–456.

British and Irish Hypertension Society (2021) 'Blood Pressure Monitors.' [Online] [Accessed on 29th September 2021] https://bihsoc.org/bp-monitors/.

Brunani, A., Lanzi, S., Codecasa, F., Cornacchia, M., Maestrini, S., Soranna, D., Zambon, A., Cattaldo, S., Fanari, P., Malatesta, D. and Salvadori, A. (2017) 'Vascular Dynamics and Peripheral Oxygen Uptake in Obese Individuals during Progressive Physical Exercise.' *Respiration*, 94(6) pp. 493–500.

Brunelli, A., Kim, A. W., Berger, K. I. and Addrizzo-Harris, D. J. (2013) 'Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines.' *Chest*, 143(5 Suppl) pp. e166S-e190S.

Bulthuis, Y., Drossaers-Bakker, W., Oosterveld, F., van der Palen, J. and van de Laar, M. (2010) 'Arm Crank Ergometer is Reliable and Valid for Measuring Aerobic Capacity During Submaximal Exercise:' *Journal of Strength and Conditioning Research*, 24(10) pp. 2809–2815.

Buys, R., Coeckelberghs, E., Vanhees, L. and Cornelissen, V. A. (2015) 'The oxygen uptake efficiency slope in 1411 Caucasian healthy men and women aged 20-60 years: reference values.' *European Journal of Preventive Cardiology*, 22(3) pp. 356–363.

Calbet, J. A. L., Holmberg, H.-C., Rosdahl, H., van Hall, G., Jensen-Urstad, M. and Saltin, B. (2005) 'Why do arms extract less oxygen than legs during exercise?' *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 289(5) pp. R1448–R1458.

Casaburi, R., Whipp, B. J., Wasserman, K. and Koyal, S. N. (1978) 'Ventilatory and gas exchange responses to cycling with sinusoidally varying pedal rate.' *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology*, 44(1) pp. 97–103.

Chambers, D. J. and Wisely, N. A. (2019) 'Cardiopulmonary exercise testing—a beginner's guide to the nine-panel plot.' *BJA Education*, 19(5) pp. 158–164.

Chan, E. D., Chan, Michael M. and Chan, Mallory M. (2013) 'Pulse oximetry: Understanding its basic principles facilitates appreciation of its limitations.' *Respiratory Medicine*, 107(6) pp. 789–799.

Chicharro, J. L. (2000) 'Effects of endurance training on the isocapnic buffering and hypocapnic hyperventilation phases in professional cyclists.' *British Journal of Sports Medicine*, 34(6) pp. 450–455.

Chongthawonsatid, S. and Dutsadeevettakul, S. (2017) 'Validity and reliability of the ankle-brachial index by oscillometric blood pressure and automated ankle-brachial index.' *Journal of Research in Medical Sciences*, 22(1) p. 44.

Cintrão Samouco, G. A., Natal, R., Costa, J., Carriço, A. F., Fernandes, A. F. and Vaz Rodrigues, L. (2018) 'Value of cardiopulmonary exercise testing in interstitial lung diseases.' *In Clinical respiratory physiology, exercise and functional imaging*. European Respiratory Society, p. PA2480.

Clavario, P., De Marzo, V., Lotti, R., Barbara, C., Porcile, A., Russo, C., Beccaria, F., Bonavia, M., Bottaro, L. C., Caltabellotta, M., Chioni, F., Santangelo, M., Hautala, A. J., Ameri, P., Canepa, M. and Porto, I. (2020) *Assessment of functional capacity with cardiopulmonary exercise testing in non-severe COVID-19 patients at three months follow-up*. Cardiovascular Medicine.

CO2Meter.com (n.d.) 'How does an NDIR CO2 sensor work.'

Cohen, J. (1988) *Statistical power analysis for the behavioral sciences*. 2nd ed, Hillsdale, N.J: L. Erlbaum Associates.

Cooper, C. B. and Storer, T. W. (2001) *Exercise testing and interpretation: a practical approach*. Cambridge, U.K. ; New York, NY, USA: Cambridge University Press.

Cooper, D. M. and Weiler-Ravell, D. (1984) 'Gas Exchange Response to Exercise in Children [1, 2].' *American Review of Respiratory Disease*, 129(2P2) pp. S47–S48.

Corrà, U., Mezzani, A., Bosimini, E., Scapellato, F., Imparato, A. and Giannuzzi, P. (2002) 'Ventilatory response to exercise improves risk stratification in patients with chronic heart failure and intermediate functional capacity.' *American Heart Journal*, 143(3) pp. 418–426.

Coso, J. D., Hamouti, N., Aguado-Jimenez, R. and Mora-Rodriguez, R. (2009) 'Respiratory compensation and blood pH regulation during variable intensity exercise in trained versus untrained subjects.' *European Journal of Applied Physiology*, 107(1) pp. 83–93.

Costello, J. T., Bieuzen, F. and Bleakley, C. M. (2014) 'Where are all the female participants in Sports and Exercise Medicine research?' *European Journal of Sport Science*, 14(8) pp. 847–851.

Crawford, M. H. (2007) 'Screening athletes for heart disease.' *Heart (British Cardiac Society)*, 93(7) pp. 875–879.

Davis, J. A., Storer, T. W. and Caiozzo, V. J. (1997) 'Prediction of normal values for lactate threshold estimated by gas exchange in men and women.' *European Journal of Applied Physiology*, 76(2) pp. 157–164.

Davis, J. A., Vodak, P., Wilmore, J. H., Vodak, J. and Kurtz, P. (1976) 'Anaerobic threshold and maximal aerobic power for three modes of exercise.' *Journal of Applied Physiology*, 41(4) pp. 544–550.

De Bacquer, D. (2000) 'Prevalences of ECG findings in large population based samples of men and women.' *Heart*, 84(6) pp. 625–633.

Decato, T. W., Bradley, S. M., Wilson, E. L. and Hegewald, M. J. (2018) 'Repeatability and Meaningful Change of CPET Parameters in Healthy Subjects.' *Medicine & Science in Sports & Exercise*, 50(3) pp. 589–595.

Dekerle, J., Caby, I., Marais, G., Lavoie, J. M., Dupont, L., Vanvelcenaher, J. and Pelayo, P. (2002) 'Ventilatory Thresholds in Arm and Leg Exercises with Spontaneously Chosen Crank and Pedal Rates.' *Perceptual and Motor Skills*, 95(3_suppl) pp. 1035–1046.

Dhakal, B. P., Malhotra, R., Murphy, R. M., Pappagianopoulos, P. P., Baggish, A. L., Weiner, R. B., Houstis, N. E., Eisman, A. S., Hough, S. S. and Lewis, G. D. (2015) 'Mechanisms of Exercise Intolerance in Heart Failure With Preserved Ejection Fraction: The Role of Abnormal Peripheral Oxygen Extraction.' *Circulation: Heart Failure*, 8(2) pp. 286–294.

DiCarlo, S. E., Supp, M. D. and Taylor, H. C. (1983) 'Effect of Arm Ergometry Training on Physical Work Capacity of Individuals with Spinal Cord Injuries.' *Physical Therapy*, 63(7) pp. 1104–1107.

Dolezal, B. A., Storer, T. W., Neufeld, E. V., Smooke, S., Tseng, C.-H. and Cooper, C. B. (2017) 'A Systematic Method to Detect the Metabolic Threshold from Gas Exchange

during Incremental Exercise.' *Journal of Sports Science & Medicine*, 16(3) pp. 396–406.

Dorelli, G., Braggio, M., Gabbiani, D., Busti, F., Caminati, M., Senna, G., Girelli, D., Laveneziana, P., Ferrari, M., Sartori, G., Dalle Carbonare, L., Crisafulli, E., and on behalf of the RESPICOVID Study Investigators (2021) 'Importance of Cardiopulmonary Exercise Testing amongst Subjects Recovering from COVID-19.' *Diagnostics*, 11(3) p. 507.

Drory, Y., Ohry, A., Brooks, M. E., Dolphin, D. and Kellermann, J. J. (1990) 'Arm crank ergometry in chronic spinal cord injured patients.' *Archives of Physical Medicine and Rehabilitation*, 71(6) pp. 389–392.

Durante, R. and Ainsworth, B. E. (1996) 'The recall of physical activity: using a cognitive model of the question-answering process:' *Medicine &amp Science in Sports &amp Exercise*, 28(10) pp. 1282–1291.

Durrand, J. W., Wagstaff, K., Kasim, A., Cawthorn, L., Danjoux, G. R. and Kothmann, E. (2018) 'Reliability of repeated arm-crank cardiopulmonary exercise tests in patients with small abdominal aortic aneurysm.' *Anaesthesia*, 73(8) pp. 967–971.

van der Ende, M. Y., Siland, J. E., Snieder, H., van der Harst, P. and Rienstra, M. (2017) 'Population-based values and abnormalities of the electrocardiogram in the general Dutch population: The LifeLines Cohort Study: Electrocardiographic abnormal and average values in Lifelines.' *Clinical Cardiology*, 40(10) pp. 865–872.

Endorsed by: the European Stroke Organisation (ESO), Authors/Task Force Members, Tendera, M., Aboyans, V., Bartelink, M.-L., Baumgartner, I., Clement, D., Collet, J.-P., Cremonesi, A., De Carlo, M., Erbel, R., Fowkes, F. G. R., Heras, M., Kownator, S., Minar, E., Ostergren, J., Poldermans, D., Riambau, V., Roffi, M., Rother, J., Sievert, H., van Sambeek, M., Zeller, T., ESC Committee for Practice Guidelines (CPG), Bax, J., Auricchio, A., Baumgartner, H., Ceconi, C., Dean, V., Deaton, C., Fagard, R., Funck-Brentano, C., Hasdai, D., Hoes, A., Knuuti, J., Kolh, P., McDonagh, T., Moulin, C., Poldermans, D., Popescu, B., Reiner, Z., Sechtem, U., Sirnes, P. A., Torbicki, A.,

Vahanian, A., Windecker, S., Document Reviewers, Kolh, P., Torbicki, A., Agewall, S., Blinc, A., Bulvas, M., Cosentino, F., De Backer, T., Gottsater, A., Gulba, D., Guzik, T. J., Jonsson, B., Kesmarky, G., Kitsiou, A., Kuczmik, W., Larsen, M. L., Madaric, J., Mas, J.-L., McMurray, J. J. V., Micari, A., Mosseri, M., Muller, C., Naylor, R., Norrving, B., Oto, O., Pasierski, T., Plouin, P.-F., Ribichini, F., Ricco, J.-B., Ruilope, L., Schmid, J.-P., Schwehr, U., Sol, B. G. M., Sprynger, M., Tiefenbacher, C., Tsioufis, C. and Van Damme, H. (2011) 'ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries * The Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC).' *European Heart Journal*, 32(22) pp. 2851–2906.

Eneanya, N. D., Yang, W. and Reese, P. P. (2019) 'Reconsidering the Consequences of Using Race to Estimate Kidney Function.' *JAMA*, 322(2) p. 113.

Eston, R. G. and Brodie, D. A. (1986) 'Responses to arm and leg ergometry.' *British Journal of Sports Medicine*, 20(1) pp. 4–6.

Eyre, E. L. J. and Duncan, M. J. (2013) 'The Impact of Ethnicity on Objectively Measured Physical Activity in Children.' *ISRN Obesity*, 2013, January, pp. 1–15.

Faul, F., Erdfelder, E., Buchner, A. and Lang, A.-G. (2009) 'Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses.' *Behavior Research Methods*, 41(4) pp. 1149–1160.

Feiner, J. R., Severinghaus, J. W. and Bickler, P. E. (2007) 'Dark Skin Decreases the Accuracy of Pulse Oximeters at Low Oxygen Saturation: The Effects of Oximeter Probe Type and Gender.' *Anesthesia & Analgesia*, 105(6) pp. S18–S23.

Ferrazza, A. M., Martolini, D., Valli, G. and Palange, P. (2009) 'Cardiopulmonary Exercise Testing in the Functional and Prognostic Evaluation of Patients with Pulmonary Diseases.' *Respiration*, 77(1) pp. 3–17.

Flanagin, A., Frey, T., Christiansen, S. L. and Bauchner, H. (2021) 'The Reporting of Race and Ethnicity in Medical and Science Journals: Comments Invited.' *JAMA*, 325(11) p. 1049.

Fleisher, L. A., Beckman, J. A., Brown, K. A., Calkins, H., Chaikof, E. L., Fleischmann, K. E., Freeman, W. K., Froehlich, J. B., Kasper, E. K., Kersten, J. R., Riegel, B. and Robb, J. F. (2007) 'ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery).' *Circulation*, 116(17).

Fletcher, G. F., Balady, G., Froelicher, V. F., Hartley, L. H., Haskell, W. L. and Pollock, M. L. (1995) 'Exercise Standards: A Statement for Healthcare Professionals From the American Heart Association.' *Circulation*, 91(2) pp. 580–615.

Fluck, R. R., Schroeder, C., Frani, G., Kropf, B. and Engbretson, B. (2003) 'Does ambient light affect the accuracy of pulse oximetry?' *Respiratory Care*, 48(7) pp. 677–680.

Fox, S. M., Naughton, J. P. and Haskell, W. L. (1971) 'Physical activity and the prevention of coronary heart disease.' *Annals of Clinical Research*, 3(6) pp. 404–432.

Franklin, B. A., Vander, L., Wrisley, D. and Rubenfire, M. (1983) 'Aerobic Requirements of Arm Ergometry: Implications for Exercise Testing and Training.' *The Physician and Sportsmedicine*, 11(10) pp. 81–90.

Fritzen, A. M., Andersen, S. P., Qadri, K. A. N., Thøgersen, F. D., Krag, T., Ørngreen, M. C., Vissing, J. and Jeppesen, T. D. (2020) 'Effect of Aerobic Exercise Training and Deconditioning on Oxidative Capacity and Muscle Mitochondrial Enzyme Machinery in Young and Elderly Individuals.' *Journal of Clinical Medicine*, 9(10) p. 3113.

GASTEC Corporation (n.d.) 'Galvanic Cell Sensor.'

Gastin, P. B. (2001) 'Energy System Interaction and Relative Contribution During Maximal Exercise:' *Sports Medicine*, 31(10) pp. 725–741.

Genberg, M., Andrén, B., Lind, L., Hedenström, H. and Malinovschi, A. (2018) 'Commonly used reference values underestimate oxygen uptake in healthy, 50-year-old Swedish women.' *Clinical Physiology and Functional Imaging*, 38(1) pp. 25–33.

Gläser, S., Ittermann, T., Schäper, C., Obst, A., Dörr, M., Spielhagen, T., Felix, S. B., Völzke, H., Bollmann, T., Opitz, C. F., Warnke, C., Koch, B. and Ewert, R. (2013) '[The Study of Health in Pomerania (SHIP) reference values for cardiopulmonary exercise testing].' *Pneumologie (Stuttgart, Germany)*, 67(1) pp. 58–63.

Goodyear, S. J., Yow, H., Saedon, M., Shakespeare, J., Hill, C. E., Watson, D., Marshall, C., Mahmood, A., Higman, D. and Imray, C. H. (2013) 'Risk stratification by pre-operative cardiopulmonary exercise testing improves outcomes following elective abdominal aortic aneurysm surgery: a cohort study.' *Perioperative Medicine*, 2(1) p. 10.

Gorman, P. H., Geigle, P. R., Chen, K., York, H. and Scott, W. (2014) 'Reliability and relatedness of peak VO2 assessments during body weight supported treadmill training and arm cycle ergometry in individuals with chronic motor incomplete spinal cord injury.' *Spinal Cord*, 52(4) pp. 287–291.

Graham, B. L., Miller, M. R. and Thompson, B. R. (2022) 'Addressing the effect of ancestry on lung volume.' *European Respiratory Journal*, 59(6) p. 2200882.

Grant, S. W., Hickey, G. L., Wisely, N. A., Carlson, E. D., Hartley, R. A., Pichel, A. C., Atkinson, D. and McCollum, C. N. (2015) 'Cardiopulmonary exercise testing and survival after elective abdominal aortic aneurysm repair †.' *British Journal of Anaesthesia*, 114(3) pp. 430–436.

Grasbeck, R. and Saris, N. (1969) 'Establishment and use of normal values.' *Scand J Clin Lab Invest*, 26(Suppl 110) pp. 62–62.

Guaraldi, G., Raggi, P., Gomes, A., Zona, S., Marchi, E., Santoro, A., Besutti, G., Scaglioni, R., Ligabue, G., Leipsic, J., Man, P. and Sin, D. (2015) 'Lung and Heart Diseases Are Better Predicted by Pack-Years than by Smoking Status or Duration of Smoking Cessation in HIV Patients.' Kumar, A. (ed.) *PLOS ONE*, 10(12) p. e0143700.

Hagan, R. D., Gettman, L. R., Upton, S. J., Duncan, J. J. and Cummings, J. M. (1983) 'Cardiorespiratory responses to arm, leg, and combined arm and leg work on an air-braked ergometer.' *Journal of Cardiac Rehabilitation*, 3(10) pp. 689–703.

Häggström, M. (2014) 'Establishment and clinical use of reference ranges.' *WikiJournal of Medicine*, 1(1).

Hagstrom, A. D., Yuwono, N., Warton, K. and Ford, C. E. (2021) 'Sex Bias in Cohorts Included in Sports Medicine Research.' *Sports Medicine*, 51(8) pp. 1799–1804.

Hansen, J. E., Sue, D. Y. and Wasserman, K. (1984) 'Predicted Values for Clinical Exercise Testing [1–3].' *American Review of Respiratory Disease*, 129(2P2) pp. S49–S55.

Hanson, P., Pease, M., Berkoff, H., Turnipseed, W. and Detmer, D. (1988) 'Arm exercise testing for coronary artery disease in patients with peripheral vascular disease.' *Clinical Cardiology*, 11(2) pp. 70–74.

Hartley, R. A., Pichel, A. C., Grant, S. W., Hickey, G. L., Lancaster, P. S., Wisely, N. A., McCollum, C. N. and Atkinson, D. (2012) 'Preoperative cardiopulmonary exercise testing and risk of early mortality following abdominal aortic aneurysm repair.' *British Journal of Surgery*, 99(11) pp. 1539–1546.

Haykowsky, M. J., Brubaker, P. H., John, J. M., Stewart, K. P., Morgan, T. M. and Kitzman, D. W. (2011) 'Determinants of Exercise Intolerance in Elderly Heart Failure Patients With Preserved Ejection Fraction.' *Journal of the American College of Cardiology*, 58(3) pp. 265–274.

Health Research Authority (2021) 'Good Clinical Practice.' HRA.

Hendrickse, P. and Degens, H. (2019) 'The role of the microcirculation in muscle function and plasticity.' *Journal of Muscle Research and Cell Motility*, 40(2) pp. 127–140.

Hietanen, E. (1984) 'Cardiovascular responses to static exercise.' *Scandinavian Journal of Work, Environment & Health*, 10(6 Spec No) pp. 397–402.

Higgins, J. and Green, S. (2011) *Cochrane Handbook for Systemtic Reviews of Interventions*. Version 5.1.0, The Cochrane Collaboration.

Hill, A. V., Long, C. N. H. and Lupton, H. (1924) 'Muscular exercise, lactic acid, and the supply and utilization of oxygen. VI The oxygen debt at the end of exercise.' *B. Biol. Sci*, 97 pp. 127–137.

Hill, M., Talbot, C. and Price, M. (2016) 'Predicted maximal heart rate for upper body exercise testing.' *Clinical Physiology and Functional Imaging*, 36(2) pp. 155–158.

Hopker, J. G., Jobson, S. A. and Pandit, J. J. (2011) 'Controversies in the physiological basis of the "anaerobic threshold" and their implications for clinical cardiopulmonary exercise testing: Controversies in the "anaerobic threshold."' *Anaesthesia*, 66(2) pp. 111–123.

Hughes, E. F., Turner, S. C. and Brooks, G. A. (1982) 'Effects of glycogen depletion and pedaling speed on "anaerobic threshold."' *Journal of Applied Physiology*, 52(6) pp. 1598–1607.

Ilias, N. A., Xian, H., Inman, C. and Martin, W. H. (2009) 'Arm exercise testing predicts clinical outcome.' *American Heart Journal*, 157(1) pp. 69–76.

Jamnick, N. A., Pettitt, R. W., Granata, C., Pyne, D. B. and Bishop, D. J. (2020) 'An Examination and Critique of Current Methods to Determine Exercise Intensity.' *Sports Medicine*, 50(10) pp. 1729–1756.

Jaussaud, J., Aimable, L. and Douard, H. (2011) 'The time for a new strong functional parameter in heart failure: The VE/VCO2 slope.' *International Journal of Cardiology*, 147(2) pp. 189–190.

Jetté, M., Sidney, K. and Blümchen, G. (1990) 'Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity.' *Clinical Cardiology*, 13(8) pp. 555–565.

Jubran, A. (2015) 'Pulse oximetry.' *Critical Care*, 19(1) p. 272.

Junejo, M. A., Mason, J. M., Sheen, A. J., Bryan, A., Moore, J., Foster, P., Atkinson, D., Parker, M. J. and Siriwardena, A. K. (2014) 'Cardiopulmonary Exercise Testing for Preoperative Risk Assessment before Pancreaticoduodenectomy for Cancer.' *Annals of Surgical Oncology*, 21(6) pp. 1929–1936.

Junejo, M. A., Mason, J. M., Sheen, A. J., Moore, J., Foster, P., Atkinson, D., Parker, M. J. and Siriwardena, A. K. (2012) 'Cardiopulmonary exercise testing for preoperative risk assessment before hepatic resection.' *British Journal of Surgery*, 99(8) pp. 1097–1104.

Kaafarani, M., Schroer, C. and Takken, T. (2017) 'Reference values for blood pressure response to cycle ergometry in the first two decades of life: comparison with patients with a repaired coarctation of the aorta.' *Expert Review of Cardiovascular Therapy*, 15(12) pp. 945–951.

Kalra, A., Lowe, A. and Al-Jumaily, A. (2018) 'Critical review of electrocardiographymeasurement systems and technology.' *Measurement Science and Technology*, November.

Kaminsky, L. A., Imboden, M. T., Arena, R. and Myers, J. (2017) 'Reference Standards for Cardiorespiratory Fitness Measured With Cardiopulmonary Exercise Testing Using Cycle Ergometry: Data From the Fitness Registry and the Importance of Exercise National Database (FRIEND) Registry.' *Mayo Clinic Proceedings*, 92(2) pp. 228–233.

Kang, J., Robertson, R. J., Goss, F. L., Dasilva, S. G., Suminski, R. R., Utter, A. C., Zoeller, R. F. and Metz, K. F. (1997) 'Metabolic efficiency during arm and leg exercise at the same relative intensities.' *Medicine and Science in Sports and Exercise*, 29(3) pp. 377–382.

Kenney, W. L., Humphrey, R. H., Bryant, C. X. and Mahler, D. A. (eds) (1995) *ACSM's guidelines for exercise testing and prescription*. 5th ed, Baltimore, Md: Williams & Wilkins.

Klesges, R. C., Eck, L. H., Mellon, M. W., Fulliton, W., Somes, G. W. and Hanson, C. L. (1990) 'The accuracy of self-reports of physical activity:' *Medicine & Science in Sports & Exercise*, 22(5) pp. 690–697.

Koch, B., Schaper, C., Ittermann, T., Spielhagen, T., Dorr, M., Volzke, H., Opitz, C. F., Ewert, R. and Glaser, S. (2008) 'Reference values for cardiopulmonary exercise testing in healthy volunteers: the SHIP study.' *European Respiratory Journal*, 33(2) pp. 389–397.

Kokkinos, P., Kaminsky, L. A., Arena, R., Zhang, J. and Myers, J. (2018) 'A new generalized cycle ergometry equation for predicting maximal oxygen uptake: The Fitness Registry and the Importance of Exercise National Database (FRIEND).' *European Journal of Preventive Cardiology*, 25(10) pp. 1077–1082.

Korpelainen, R., Lämsä, J., Kaikkonen, K. M., Korpelainen, J., Laukkanen, J., Palatsi, I., Takala, T. E., Ikäheimo, T. M. and Hautala, A. J. (2016) 'Exercise capacity and mortality – a follow-up study of 3033 subjects referred to clinical exercise testing.' *Annals of Medicine*, 48(5) pp. 359–366.

Krouwer, J. S. (2008) 'Why Bland–Altman plots should useX, not (Y+X)/2 whenX is a reference method.' *Statistics in Medicine*, 27(5) pp. 778–780.

Kyle, R. G., Wills, J., Mahoney, C., Hoyle, L., Kelly, M. and Atherton, I. M. (2017) 'Obesity prevalence among healthcare professionals in England: a cross-sectional study using the Health Survey for England.' *BMJ Open*, 7(12) p. e018498.

Laerd Statistics (2015) 'Multiple regression using SPSS statistics. Statistical tutorials and software guides.'

Lai, C. W., Minto, G., Challand, C. P., Hosie, K. B., Sneyd, J. R., Creanor, S. and Struthers, R. A. (2013) 'Patients' inability to perform a preoperative cardiopulmonary

exercise test or demonstrate an anaerobic threshold is associated with inferior outcomes after major colorectal surgery.' *British Journal of Anaesthesia*, 111(4) pp. 607–611.

Lama, V. N., Flaherty, K. R., Toews, G. B., Colby, T. V., Travis, W. D., Long, Q., Murray, S., Kazerooni, E. A., Gross, B. H., Lynch, J. P. and Martinez, F. J. (2003) 'Prognostic Value of Desaturation during a 6-Minute Walk Test in Idiopathic Interstitial Pneumonia.' *American Journal of Respiratory and Critical Care Medicine*, 168(9) pp. 1084–1090.

Lanooy, C. and Bonjer, F. H. (1956) '*A Hyperbolic Ergometer for Cycling and Cranking*.' *Journal of Applied Physiology*, 9(3) pp. 499–500.

Larsen, R. T., Christensen, J., Tang, L. H., Keller, C., Doherty, P., Zwisler, A.-D., Taylor, R. S. and Langberg, H. (2016) 'A SYSTEMATIC REVIEW AND META-ANALYSIS COMPARING CARDIOPULMONARY EXERCISE TEST VALUES OBTAINED FROM THE ARM CYCLE AND THE LEG CYCLE RESPECTIVELY IN HEALTHY ADULTS.' *International Journal of Sports Physical Therapy*, 11(7) pp. 1006–1039.

Laukkanen, J. A., Mäkikallio, T. H., Rauramaa, R. and Kurl, S. (2009) 'Asymptomatic ST-segment depression during exercise testing and the risk of sudden cardiac death in middle-aged men: a population-based follow-up study.' *European Heart Journal*, 30(5) pp. 558–565.

Leeper, N. J., Myers, J., Zhou, M., Nead, K. T., Syed, A., Kojima, Y., Caceres, R. D. and Cooke, J. P. (2013) 'Exercise capacity is the strongest predictor of mortality in patients with peripheral arterial disease.' *Journal of Vascular Surgery*, 57(3) pp. 728–733.

Lehmann, G. and Kölling, K. (1996) 'Reproducibility of cardiopulmonary exercise parameters in patients with valvular heart disease.' *Chest*, 110(3) pp. 685–692.

Leicht, A. S., Sealey, R. M. and Sinclair, W. H. (2009) 'The Reliability of VO_{2peak} Determination in Healthy Females during an Incremental Arm Ergometry Test.' *International Journal of Sports Medicine*, 30(07) pp. 509–515.

Levett, D. Z. H., Jack, S., Swart, M., Carlisle, J., Wilson, J., Snowden, C., Riley, M., Danjoux, G., Ward, S. A., Older, P. and Grocott, M. P. W. (2018) 'Perioperative cardiopulmonary exercise testing (CPET): consensus clinical guidelines on indications, organization, conduct, and physiological interpretation.' *British Journal of Anaesthesia*, 120(3) pp. 484–500.

Lewthwaite, H., Benedetti, A., Stickland, M. K., Bourbeau, J., Guenette, J. A., Maltais, F., Marciniuk, D. D., O'Donnell, D. E., Smith, B. M., Tan, W. C., Jensen, D., AaronK, S. E., Chapman, R., Hernandez, P., Sin, D. D. and Walker, B. (2020) 'Normative Peak Cardiopulmonary Exercise Test Responses in Canadian Adults Aged ≥40 Years.' *Chest*, 158(6) pp. 2532–2545.

Lintu, N., Viitasalo, A., Tompuri, T., Veijalainen, A., Hakulinen, M., Laitinen, T., Savonen, K. and Lakka, T. A. (2015) 'Cardiorespiratory fitness, respiratory function and hemodynamic responses to maximal cycle ergometer exercise test in girls and boys aged 9-11 years: the PANIC Study.' *European Journal of Applied Physiology*, 115(2) pp. 235–243.

Lurbe, E. and Redon, J. (2016) 'Isolated Systolic Hypertension in Young People Is Not Spurious and Should Be Treated: Con Side of the Argument.' *Hypertension*, 68(2) pp. 276–280.

Malhotra, R., Bakken, K., D'Elia, E. and Lewis, G. D. (2016) 'Cardiopulmonary Exercise Testing in Heart Failure.' *JACC: Heart Failure*, 4(8) pp. 607–616.

Mancini, D. M., Eisen, H., Kussmaul, W., Mull, R., Edmunds, L. H. and Wilson, J. R. (1991) 'Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure.' *Circulation*, 83(3) pp. 778–786.

Manfre, M. J., Mallis, G. I., Varma, A., Yen, O. and Plon, M. (1990) 'Oxygen uptake, electrocardiographic, and symptomatic response during two arm cranking and treadmill testing in healthy older adult men and patients with coronary artery disease.' *Journal of Cardiopulmonary Rehabilitation*, 10(1) pp. 12–20.

Marburger, C., Brubaker, P., Pollock, W., Morgan, T. and Kitzman, D. (1998) 'Reproducibility of cardiopulmonary exercise testing in elderly patients with congestive heart failure.' *The American Journal of Cardiology*, 82(7) pp. 905–909.

Maréchal, G. (2020) *Phosphocreatine and Adenosine Triphosphate in Muscle Contraction Biochemical, Thermal and Mechanical Energetic Balances*. 1. Auflage, Saarbrücken: Scholars' Press.

Martin, T. W., Zeballos, R. J. and Weisman, I. M. (1991) 'Gas exchange during maximal upper extremity exercise.' *Chest*. 420, p. 420+.

Martin, W. H., Xian, H., Chandiramani, P., Bainter, E. and Klein, A. J. P. (2015) 'Cardiovascular mortality prediction in veterans with arm exercise vs pharmacologic myocardial perfusion imaging.' *American Heart Journal*, 170(2) pp. 362-370.e2.

Mason, K. A. and Johnson, G. B. (2014) *Biology*. Tenth edition, New York, NY: McGraw-Hill.

Mason, R. E. and Likar, I. (1966) 'A new system of multiple-lead exercise electrocardiography.' *American Heart Journal*, 71(2) pp. 196–205.

McCallum, S. (2017) 'Muscle fatigue, muscle recovery and how this knowledge applies to rock climbers.' *The Duluth Journal of Undergraduate Biology*. (Review), 4(Spring) pp. 12–18.

Mesleh, A., Skopin, D., Baglikov, S. and Quteishat, A. (2012) 'Heart Rate Extraction from Vowel Speech Signals.' *Journal of Computer Science and Technology*, 27(6) pp. 1243–1251.

Meyer, K., Westbrook, S., Schwaibold, M., Hajric, R., Peters, K. and Roskamm, H. (1997) 'Short-term reproducibility of cardiopulmonary measurements during exercise testing in patients with severe chronic heart failure.' *American Heart Journal*, 134(1) pp. 20–26.

Milani, J., Fernhall, B. and Manfredi, T. (1996) 'Estimating Oxygen Consumption During Treadmill and Arm Ergometry Activity in Males With Coronary Artery Disease:' *Journal of Cardiopulmonary Rehabilitation*, 16(6) pp. 394–401.

Mitropoulos, A., Gumber, A., Crank, H. and Klonizakis, M. (2017) 'Validation of an Arm Crank Ergometer Test for Use in Sedentary Adults.' *Journal of Sports Science & Medicine*, 16(4) pp. 558–564.

Molgat-Seon, Y., Schaeffer, M. R., Ryerson, C. J. and Guenette, J. A. (2020) 'Cardiopulmonary Exercise Testing in Patients With Interstitial Lung Disease.' *Frontiers in Physiology*, 11, July, p. 832.

Moore, C., Dobson, A., Kinagi, M. and Dillon, B. (2008) 'Comparison of blood pressure measured at the arm, ankle and calf.' *Anaesthesia*, 63(12) pp. 1327–1331.

Moran, J., Wilson, F., Guinan, E., McCormick, P., Hussey, J. and Moriarty, J. (2016) 'Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review.' *British Journal of Anaesthesia*, 116(2) pp. 177–191.

MRC Epidemiology Unit (2006) 'RPAQ Recent Physical Activity Questionnaire.' Cambridge University Press.

Muangkram, Y., Honda, M., Amano, A., Himeno, Y. and Noma, A. (2020) 'Exploring the role of fatigue-related metabolite activity during high-intensity exercise using a simplified whole-body mathematical model.' *Informatics in Medicine Unlocked*, 19 p. 100355.

Muraki, S., Tsunawake, N. and Yamasaki, M. (2004) 'Limitation of muscle deoxygenation in the triceps during incremental arm cranking in women.' *European Journal of Applied Physiology*, 91(2–3) pp. 246–252.

Myers, J., Prakash, M., Froelicher, V., Do, D., Partington, S. and Atwood, J. E. (2002) 'Exercise Capacity and Mortality among Men Referred for Exercise Testing.' *New England Journal of Medicine*, 346(11) pp. 793–801.

Mylius, C. F., Krijnen, W. P., van der Schans, C. P. and Takken, T. (2019) 'Peak oxygen uptake reference values for cycle ergometry for the healthy Dutch population: data from the LowLands Fitness Registry.' *ERJ Open Research*, 5(2) pp. 00056–02018.

National Institute for Health and Care Excellence (2019) 'Chronic obstructive pulmonary disease in over 16s: diagnosis and management.' *NICE*, NG115, July, pp. 1–69.

National Institute for Health and Care Excellence (n.d.) 'Good Clinical Practice (GCP).' Department of Health and Social Care.

Nightingale, C. M., Donin, A. S., Kerry, S. R., Owen, C. G., Rudnicka, A. R., Brage, S., Westgate, K. L., Ekelund, U., Cook, D. G. and Whincup, P. H. (2016) 'Cross-sectional study of ethnic differences in physical fitness among children of South Asian, black African–Caribbean and white European origin: the Child Heart and Health Study in England (CHASE).' *BMJ Open*, 6(6) p. e011131.

Nikolić, Z. and Todorović, B. (1984) 'Anaerobic Threshold During Arm and Leg Exercises and Cardiorespiratory Fitness Tests in a Group of Male and Female Students.' *International Journal of Sports Medicine*, 05(06) pp. 330–335.

Nitzan, M., Romem, A. and Koppel, R. (2014) 'Pulse oximetry: fundamentals and technology update.' *Medical Devices: Evidence and Research*, July, p. 231.

Nuzzo, J. (2021) 'Volunteer Bias and Female Participation in Exercise and Sports Science Research.' *Quest*, 73(1) pp. 82–101.

O'Donnell, D. E., Elbehairy, A. F., Faisal, A., Webb, K. A., Neder, J. A. and Mahler, D. A. (2016) 'Exertional dyspnoea in COPD: the clinical utility of cardiopulmonary exercise testing.' *European Respiratory Review*, 25(141) pp. 333–347.

O'Donnell, D. E., Travers, J., Webb, K. A., He, Z., Lam, Y.-M., Hamilton, A., Kesten, S., Maltais, F. and Magnussen, H. (2009) 'Reliability of ventilatory parameters during cycle ergometry in multicentre trials in COPD.' *European Respiratory Journal*, 34(4) pp. 866–874.

Office for National Statistics (2019) ‘Population denominators by ethnic group, regions and countries. England and Wales, 2011 to 2018.’ *ONS Website*, September.

Older, P., Hall, A. and Hader, R. (1999) ‘Cardiopulmonary Exercise Testing as a Screening Test for Perioperative Management of Major Surgery in the Elderly.’ *Chest*, 116(2) pp. 355–362.

Older, P., Smith, R., Courtney, P. and Hone, R. (1993) ‘Preoperative evaluation of cardiac failure and ischemia in elderly patients by cardiopulmonary exercise test.’ *Chest*, (104) pp. 701–704.

on behalf of the British and Irish Hypertension Society’s Blood Pressure Measurement Working Party and Lewis, P. S. (2019) ‘Oscillometric measurement of blood pressure: a simplified explanation. A technical note on behalf of the British and Irish Hypertension Society.’ *Journal of Human Hypertension*, 33(5) pp. 349–351.

Orr, J. L., Williamson, P., Anderson, W., Ross, R., McCafferty, S. and Fettes, P. (2013) ‘Cardiopulmonary exercise testing: arm crank vs cycle ergometry.’ *Anaesthesia*, 68(5) pp. 497–501.

Ørtenblad, N., Nielsen, J., Boushel, R., Söderlund, K., Saltin, B. and Holmberg, H.-C. (2018) ‘The Muscle Fiber Profiles, Mitochondrial Content, and Enzyme Activities of the Exceptionally Well-Trained Arm and Leg Muscles of Elite Cross-Country Skiers.’ *Frontiers in Physiology*, 9 p. 1031.

Otto, J. M., Levett, D. Z. H. and Grocott, M. P. W. (2020) ‘Cardiopulmonary Exercise Testing for Preoperative Evaluation: What Does the Future Hold?’ *Current Anesthesiology Reports*, 10(1) pp. 1–11.

Ozemek, C., Whaley, M. H., Finch, W. H. and Kaminsky, L. A. (2017) ‘Maximal heart rate declines linearly with age independent of cardiorespiratory fitness levels.’ *European Journal of Sport Science*, 17(5) pp. 563–570.

Paap, D. and Takken, T. (2014) 'Reference values for cardiopulmonary exercise testing in healthy adults: a systematic review.' *Expert Review of Cardiovascular Therapy*, 12(12) pp. 1439–1453.

Palange, P., Laveneziana, P., Neder, J. A., Ward, S. A. and Bals, R. (2018) *Clinical exercise testing*.

Park, M. K., Menard, S. W. and Yuan, C. (2001) 'Comparison of Auscultatory and Oscillometric Blood Pressures.' *Archives of Pediatrics & Adolescent Medicine*, 155(1) p. 50.

Pennstate Eberly College of Science (2018) '9.1 Distinction between outliers and high leverage observations.' *STAT 462 Applied Regression Analysis*.

Pina, I. L., Balady, G. J., Hanson, P., Labovitz, A. J., Madonna, D. W. and Myers, J. (1995) 'Guidelines for Clinical Exercise Testing Laboratories: A Statement for Healthcare Professionals From the Committee on Exercise and Cardiac Rehabilitation, American Heart Association.' *Circulation*, 91(3) pp. 912–921.

Pistea, C., Lonsdorfer, E., Doutreleau, S., Oswald, M., Enache, I. and Charloux, A. (2016) 'Maximal aerobic capacity in ageing subjects: actual measurements versus predicted values.' *ERJ open research*, 2(1).

Pogliaghi, S., Terziotti, P., Cevese, A., Balestreri, F. and Schena, F. (2006) 'Adaptations to endurance training in the healthy elderly: arm cranking versus leg cycling.' *European Journal of Applied Physiology*, 97(6) pp. 723–731.

Ponikowski, P., Francis, D. P., Piepoli, M. F., Davies, L. C., Chua, T. P., Davos, C. H., Florea, V., Banasiak, W., Poole-Wilson, P. A., Coats, A. J. S. and Anker, S. D. (2001) 'Enhanced Ventilatory Response to Exercise in Patients With Chronic Heart Failure and Preserved Exercise Tolerance: Marker of Abnormal Cardiorespiratory Reflex Control and Predictor of Poor Prognosis.' *Circulation*, 103(7) pp. 967–972.

Porszasz, J., Stringer, W. and Casaburi, R. (2018) 'Equipment, measurements and quality control.' *In* Palange, P., Laveneziana, P., Neder, J. A., and Ward, S. A. (eds)

Clinical Exercise Testing. Sheffield, United Kingdom: European Respiratory Society, pp. 59–81.

Powe, N. R. (2020) 'Black Kidney Function Matters: Use or Misuse of Race?' *JAMA*, 324(8) p. 737.

Prentis, J. M., Manas, D. M. D., Trenell, M. I., Hudson, M., Jones, D. J. and Snowden, C. P. (2012) 'Submaximal cardiopulmonary exercise testing predicts 90-day survival after liver transplantation: CPET Predicts Mortality After Liver Transplantation.' *Liver Transplantation*, 18(2) pp. 152–159.

Prentis, J. M., Trenell, M. I., Jones, D. J., Lees, T., Clarke, M. and Snowden, C. P. (2012) 'Submaximal exercise testing predicts perioperative hospitalization after aortic aneurysm repair.' *Journal of Vascular Surgery*, 56(6) pp. 1564–1570.

Price, M. J., Collins, L., Smith, P. M. and Goss-Sampson, M. (2007) 'The effects of cadence and power output upon physiological and biomechanical responses to incremental arm-crank ergometry.' *Applied Physiology, Nutrition, and Metabolism*, 32(4) pp. 686–692.

Quanjer, P. H., Stanojevic, S., Cole, T. J., Baur, X., Hall, G. L., Culver, B. H., Enright, P. L., Hankinson, J. L., Ip, M. S. M., Zheng, J., Stocks, J., and the ERS Global Lung Function Initiative (2012) 'Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations.' *European Respiratory Journal*, 40(6) pp. 1324–1343.

Radtke, T., Crook, S., Kaltsakas, G., Louvaris, Z., Berton, D., Urquhart, D. S., Kampouras, A., Rabinovich, R. A., Verges, S., Kontopidis, D., Boyd, J., Tonia, T., Langer, D., De Brandt, J., Goërtz, Y. M. J., Burtin, C., Spruit, M. A., Braeken, D. C. W., Dacha, S., Franssen, F. M. E., Laveneziana, P., Eber, E., Troosters, T., Neder, J. A., Puhan, M. A., Casaburi, R., Vogiatzis, I. and Hebestreit, H. (2019) 'ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases.' *European Respiratory Review*, 28(154) p. 180101.

Rapp, D., Scharhag, J., Wagenpfeil, S. and Scholl, J. (2018) 'Reference values for peak oxygen uptake: cross-sectional analysis of cycle ergometry-based cardiopulmonary exercise tests of 10 090 adult German volunteers from the Prevention First Registry.' *BMJ Open*, 8(3) p. e018697.

Reece, J. B., Urry, L. A., Cain, M. L., Wasserman, S. A., Minorsky, P. V., Jackson, R. B. and Campbell, N. A. (2014) *Campbell biology*. Tenth edition, Boston: Pearson.

Regenold, N. and Vindrola-Padros, C. (2021) 'Gender Matters: A Gender Analysis of Healthcare Workers' Experiences during the First COVID-19 Pandemic Peak in England.' *Social Sciences*, 10(2) p. 43.

Revill, S. M. and Morgan, M. D. L. (2000) 'Biological quality control for exercise testing.' *Thorax*, 55(1) pp. 63–66.

Reybrouck, T., Heigenhauser, G. F. and Faulkner, J. A. (1975) 'Limitations to maximum oxygen uptake in arms, leg, and combined arm-leg ergometry.' *Journal of Applied Physiology*, 38(5) pp. 774–779.

Ritt, L. E., Myers, J., Stein, R., Arena, R., Guazzi, M., Chase, P., Bensimhon, D., Ashley, E., Cahalin, L. P. and Forman, D. E. (2015) 'Additive prognostic value of a cardiopulmonary exercise test score in patients with heart failure and intermediate risk.' *International Journal of Cardiology*, 178, January, pp. 262–264.

Roberts, D. E. (2021) 'Abolish race correction.' *The Lancet*, 397(10268) pp. 17–18.

Roca, J., Whipp, B. J., Agusti, A. G. N. and Anderson, S. D. (1997) 'Clinical exercise testing with reference to lung diseases: indications, standardization and interpretation strategies.' *European Respiratory Journal*, 10 pp. 2662–2689.

Roy, J. L. P., Hunter, G. R., Fernandez, J. R., McCarthy, J. P., Larson-Meyer, D. E., Blaudeau, T. E. and Newcomer, B. R. (2006) 'Cardiovascular factors explain genetic background differences in VO2max.' *American Journal of Human Biology*, 18(4) pp. 454–460.

Roy, P. M. (2018) 'Preoperative pulmonary evaluation for lung resection.' *Journal of Anaesthesiology, Clinical Pharmacology*, 34(3) pp. 296–300.

van de Sande, D. A. J. P., Breuer, M. A. W. and Kemps, H. M. C. (2016) 'Utility of Exercise Electrocardiography in Pre-participation Screening in Asymptomatic Athletes: A Systematic Review.' *Sports Medicine*, 46(8) pp. 1155–1164.

Sawka, M. N., Foley, M. E., Pimental, N. A., Toner, M. M. and Pandolf, K. B. (1983) 'Determination of maximal aerobic power during upper-body exercise.' *Journal of Applied Physiology*, 54(1) pp. 113–117.

Schneider, D. A., Phillips, S. E. and Stoffolano, S. (1993) 'The simplified V-slope method of detecting the gas exchange threshold.' *Medicine and Science in Sports and Exercise*, 25(10) pp. 1180–1184.

Seiler, S. (2011) 'A brief history of endurance testing in athletes.' *Sport Science*, 15 pp. 40–86.

Sharma, S., Mehta, P. K., Arsanjani, R., Sedlak, T., Hobel, Z., Shufelt, C., Jones, E., Kligfield, P., Mortara, D., Laks, M., Diniz, M. and Bairey Merz, C. N. (2018) 'False-positive stress testing: Does endothelial vascular dysfunction contribute to ST-segment depression in women? A pilot study.' *Clinical Cardiology*, 41(8) pp. 1044–1048.

Shephard, R. J. (2003) 'Limits to the measurement of habitual physical activity by questionnaires * Commentary.' *British Journal of Sports Medicine*, 37(>3) pp. 197–206.

Sherrill, D. L. and Swanson, G. D. (1989) 'Application of the general linear model for smoothing gas exchange data.' *Computers and Biomedical Research*, 22(3) pp. 270–281.

Skjørten, I., Ankerstjerne, O. A. W., Trebinjac, D., Brønstad, E., Rasch-Halvorsen, Ø., Einvik, G., Lerum, T. V., Stavem, K., Edvardsen, A. and Ingul, C. B. (2021)

'Cardiopulmonary exercise capacity and limitations 3 months after COVID-19 hospitalisation.' *European Respiratory Journal*, 58(2) p. 2100996.

Smith, P. M., Price, M. J. and Doherty, M. (2001) 'The influence of crank rate on peak oxygen consumption during arm crank ergometry.' *Journal of Sports Sciences*, 19(12) pp. 955–960.

Solberg, H. E. (2004) 'The IFCC recommendation on estimation of reference intervals. The RefVal Program.' *Clinical Chemistry and Laboratory Medicine (CCLM)*, 42(7).

Spodick, D. H. (1992) 'Normal sinus heart rate: Sinus tachycardia and sinus bradycardia redefined.' *American Heart Journal*, 124(4) pp. 1119–1121.

Stefanov, L. and Kolev, I. (2016) 'Cyclists saddle height importance on the results of bicylce ergometer test "Astand & Rhyming."' *Activities in Physical Education and Sport*, 6(1) pp. 45–47.

Stockwell, S., Trott, M., Tully, M., Shin, J., Barnett, Y., Butler, L., McDermott, D., Schuch, F. and Smith, L. (2021) 'Changes in physical activity and sedentary behaviours from before to during the COVID-19 pandemic lockdown: a systematic review.' *BMJ Open Sport & Exercise Medicine*, 7(1) p. e000960.

Sullivan, G. M. and Feinn, R. (2012) 'Using Effect Size—or Why the *P* Value Is Not Enough.' *Journal of Graduate Medical Education*, 4(3) pp. 279–282.

Suminski, R. R., Wier, L. T., Poston, W., Arenare, B., Randles, A. and Jackson, A. S. (2009) 'The Effect of Habitual Smoking on Measured and Predicted VO2max.' *Journal of Physical Activity and Health*, 6(5) pp. 667–673.

Sylvester, K. P., Clayton, N., Cliff, I., Hepple, M., Kendrick, A., Kirkby, J., Miller, M., Moore, A., Rafferty, G. F., O'Reilly, L., Shakespeare, J., Smith, L., Watts, T., Bucknall, M. and Butterfield, K. (2020) 'ARTP statement on pulmonary function testing 2020.' *BMJ Open Respiratory Research*, 7(1) p. e000575.

Takken, T., Mylius, C. F., Paap, D., Broeders, W., Hulzebos, H. J., Van Brussel, M. and Bongers, B. C. (2019) 'Reference values for cardiopulmonary exercise testing in

healthy subjects – an updated systematic review.' *Expert Review of Cardiovascular Therapy*, 17(6) pp. 413–426.

Tanaka, H., Monahan, K. D. and Seals, D. R. (2001) 'Age-predicted maximal heart rate revisited.' *Journal of the American College of Cardiology*, 37(1) pp. 153–156.

Thomas, S., Reading, J. and Shephard, R. J. (1992) 'Revision of the Physical Activity Readiness Questionnaire (PAR-Q).' *Canadian Journal of Sport Sciences = Journal Canadien Des Sciences Du Sport*, 17(4) pp. 338–345.

Tompuri, T., Lintu, N., Laitinen, T. and Lakka, T. A. (2018) 'Relation of oxygen uptake to work rate in prepubertal healthy children - reference for VO2 /W-slope and effect on cardiorespiratory fitness assessment.' *Clinical Physiology and Functional Imaging*, 38(4) pp. 645–651.

Triantafillidou, C., Manali, E., Lyberopoulos, P., Kolilekas, L., Kagouridis, K., Gyftopoulos, S., Vougas, K., Kotanidou, A., Alchanatis, M., Karakatsani, A. and Papiris, S. A. (2013) 'The Role of Cardiopulmonary Exercise Test in IPF Prognosis.' *Pulmonary Medicine*, 2013 pp. 1–9.

UK Parliament (2021) 'Obesity Statistics.' House of Commons Library.

Unger, T., Borghi, C., Charchar, F., Khan, N. A., Poulter, N. R., Prabhakaran, D., Ramirez, A., Schlaich, M., Stergiou, G. S., Tomaszewski, M., Wainford, R. D., Williams, B. and Schutte, A. E. (2020) '2020 International Society of Hypertension Global Hypertension Practice Guidelines.' *Hypertension*, 75(6) pp. 1334–1357.

Vainshelboim, B., Kramer, M., Izhakian, S., Lima, R. and Oliveira, J. (2016) 'Physical Activity and Exertional Desaturation Are Associated with Mortality in Idiopathic Pulmonary Fibrosis.' *Journal of Clinical Medicine*, 5(8) p. 73.

Van de Poppe, D. J., Hulzebos, E., Takken, T., and on behalf of the Low-Land Fitness Registry Study group (2019) 'Reference values for maximum work rate in apparently healthy Dutch/Flemish adults: data from the LowLands fitness registry.' *Acta Cardiologica*, 74(3) pp. 223–230.

Vyas, D. A., Eisenstein, L. G. and Jones, D. S. (2020) 'Hidden in Plain Sight — Reconsidering the Use of Race Correction in Clinical Algorithms.' Malina, D. (ed.) *New England Journal of Medicine*, 383(9) pp. 874–882.

Wallaert, B., Guetta, A., Wemeau-Stervinou, L., Tercé, G., Valette, M., Nevière, R. and Aguilaniu, B. (2011) '[Prognostic value of clinical exercise testing in idiopathic pulmonary fibrosis].' *Revue Des Maladies Respiratoires*, 28(3) pp. 290–296.

Wan, J., Qin, Z., Wang, P., Sun, Y. and Liu, X. (2017) 'Muscle fatigue: general understanding and treatment.' *Experimental & Molecular Medicine*, 49(10) pp. e384–e384.

Waschki, B., Kirsten, A., Holz, O., Müller, K.-C., Meyer, T., Watz, H. and Magnussen, H. (2011) 'Physical Activity Is the Strongest Predictor of All-Cause Mortality in Patients With COPD.' *Chest*, 140(2) pp. 331–342.

Wasserman, K. (1986) 'The anaerobic threshold: definition, physiological significance and identification.' *Advances in Cardiology*, 35 pp. 1–23.

Wasserman, K., Hansen, J. E., Sue, D. Y., Casaburi, R. and Whipp, B. J. (1999) *Principles of Exercise Testing and Interpretation*. 3rd ed., Philadelphia: Lippincott Williams & Wilkins.

Wasserman, K. and Mcilroy, M. B. (1964) 'DETECTING THE THRESHOLD OF ANAEROBIC METABOLISM IN CARDIAC PATIENTS DURING EXERCISE.' *The American Journal of Cardiology*, 14, December, pp. 844–852.

Waterfall, J. L., Burns, P., Shackell, D., Pepke-Zaba, J., Oates, K. E. and Sylvester, K. P. (2020) 'The risks of applying normative values in paediatric cardiopulmonary exercise testing: a case report.' *ERJ Open Research*, October, pp. 00333–02020.

Weber, K. T. and Janicki, J. S. (1985) 'Cardiopulmonary exercise testing for evaluation of chronic cardiac failure.' *The American Journal of Cardiology*, 55(2) pp. A22–A31.

Weber, K. T., Janicki, J. S. and Likoff, M. J. (1984) 'Exercise testing in the evaluation of cardiopulmonary disease. A cardiologist's point of view.' *Clinics in Chest Medicine*, 5(1) pp. 173–180.

Weissland, T., Pelayo, P., Vanvelcenaher, J., Marais, G., Lavoie, J.-M. and Robin, H. (1997) 'Physiological effects of variations in spontaneously chosen crank rate during incremental upper-body exercise.' *European Journal of Applied Physiology*, 76(5) pp. 428–433.

Wickerson, L., Brooks, D. and Mathur, S. (2016) 'Peripheral Muscle Dysfunction in Interstitial Lung Disease: A Scoping Study.' *Journal of Physiotherapy & Physical Rehabilitation*, 01(03).

Wijeysundera, D. N., Pearse, R. M., Shulman, M. A., Abbott, T. E. F., Torres, E., Ambosta, A., Croal, B. L., Granton, J. T., Thorpe, K. E., Grocott, M. P. W., Farrington, C., Myles, P. S., Cuthbertson, B. H., Wallace, S., Thompson, B., Ellis, M., Borg, B., Kerridge, R. K., Douglas, J., Brannan, J., Pretto, J., Godsall, G., Beauchamp, N., Allen, S., Kennedy, A., Wright, E., Malherbe, J., Ismail, H., Riedel, B., Melville, A., Sivakumar, H., Murmane, A., Kenchington, K., Kirabiyik, Y., Gurunathan, U., Stonell, C., Brunello, K., Steele, K., Tronstad, O., Masel, P., Dent, A., Smith, E., Bodger, A., Abolfathi, M., Sivalingam, P., Hall, A., Painter, T. W., Macklin, S., Elliott, A., Carrera, A. M., Terblanche, N. C., Pitt, S., Samuel, J., Wilde, C., Leslie, K., MacCormick, A., Bramley, D., Southcott, A. M., Grant, J., Taylor, H., Bates, S., Towns, M., Tippett, A., Marshall, F., Mazer, C. D., Kunasingam, J., Yagnik, A., Crescini, C., Yagnik, S., McCartney, C. J., Somascanthan, P., Choi, S., Flores, K., Au, S., Beattie, W. S., Karkouti, K., Clarke, H. A., Jerath, A., McCluskey, S. A., Wasowicz, M., Day, L., Pazmino-Canizares, J., Oh, P., Belliard, R., Lee, L., Dobson, K., Chan, V., Brull, R., Ami, N., Stanbrook, M., Hagen, K., Campbell, D., Short, T., Van Der Westhuizen, J., Higgie, K., Lindsay, H., Jang, R., Wong, C., McAllister, D., Ali, M., Kumar, J., Waymouth, E., Kim, C. J., Dimech, J., Lorimer, M., Tai, J., Miller, R., Sara, R., Collingwood, A., Olliff, S., Gabriel, S., Houston, H., Dalley, P., Hurford, S., Hunt, A., Andrews, L., Navarra, L., Jason-Smith, A., Thompson, H., McMillan, N., Back, G., Lum, M., Martin, D., James, S., Filipe, H., Pinto, M., Kynaston, S., Phull, M., Beilstein, C., Bodger, P., Everingham, K., Hu, Y., Niebrzegowska, E.,

Corriea, C., Creary, T., Januszewska, M., Ahmad, T., Whalley, J., Haslop, R., McNeil, J., Brown, A., MacDonald, N., Pakats, M. L., Greaves, K., Jhanji, S., Raobaikady, R., Black, E., Rooms, M., Lawrence, H., Koutra, M., Pirie, K., Gertsman, M., Jack, S., Celinski, M., Levett, D., Edwards, M., Salmon, K., Bolger, C., Loughney, L., Seaward, L., Collins, H., Tyrell, B., Tantony, N., Golder, K., Ackland, G. L., Stephens, R., Gallego-Paredes, L., Reyes, A., Gutierrez del Arroyo, A., Raj, A., Lifford, R., Melo, M., Mamdani, M., Hillis, G. and Wijeysundera, H. C. (2018) 'Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study.' *The Lancet*, 391(10140) pp. 2631–2640.

Williams, A. M. M., Chisholm, A. E., Lynn, A., Malik, R. N., Eginyan, G. and Lam, T. (2020) 'Arm crank ergometer "spin" training improves seated balance and aerobic capacity in people with spinal cord injury.' *Scandinavian Journal of Medicine & Science in Sports*, 30(2) pp. 361–369.

Wilson, M. G., Basavarajaiah, S., Whyte, G. P., Cox, S., Loosemore, M. and Sharma, S. (2008) 'Efficacy of personal symptom and family history questionnaires when screening for inherited cardiac pathologies: the role of electrocardiography.' *British Journal of Sports Medicine*, 42(3) p. 207.

Young, E. L., Karthikesalingam, A., Huddart, S., Pearse, R. M., Hinchliffe, R. J., Loftus, I. M., Thompson, M. M. and Holt, P. J. E. (2012) 'A Systematic Review of the Role of Cardiopulmonary Exercise Testing in Vascular Surgery.' *European Journal of Vascular and Endovascular Surgery*, 44(1) pp. 64–71.

Yu, C., McManus, A., Li, A., Sung, R. and Armstrong, N. (2010) 'Cardiopulmonary exercise testing in children.' *Hong Kong Journal of Paediatrics*, 15(1) pp. 35–47.

Appendix A – Participant Information Sheet

NHS
University Hospitals
Coventry and Warwickshire
NHS Trust

PARTICIPANT INFORMATION SHEET

Study Title: Normal values for arm ergometry

Chief Investigator: Joanna Shakespeare

Local Research team: Edward Parkes, Iuri Mata

Dear Participant,

You are invited to take part in a research study. Before you decide, it is important for you to understand why the study is being done and what it will involve for you. Please take time to read the following information carefully. Discuss it with friends, relatives or your GP if you wish. It is up to you to decide whether or not to take part in this study. If there is anything that is unclear, or you would like more information, please do not hesitate to ask.

What is the purpose of the study?

We are looking to recruit 250 healthy volunteers to perform an exercise test on both a cycle ergometer and arm ergometer to allow us to understand the relationship between the two and start to generate normal values for arm ergometry. This information will allow us to better assess our patients prior to surgery in the future. This research is being undertaken as part of a PhD qualification.

Why have I been invited?

You have expressed an interest in learning more about the study after hearing about the study from an advertisement.

Do I have to take part?

It is up to you to decide whether or not to take part. We will go through this information sheet with you, which we will then give you to keep. If you do agree to take part, you will be asked to sign a consent form. You are free to withdraw at any time without giving a reason.

What will happen to me if I take part?

Performing baseline diagnostic tests such as a breathing test, a heart trace and blood pressure measurements may identify an unknown abnormality. Where this occurs you will be provided with a copy of your results and requested to discuss them with your GP. Performing a maximal cycle ergometry test will provide information with regards to your current fitness status. We will be able to provide you with a summary of these findings which you may find useful if considering fitness/lifestyle changes.

What does the study involve?

Participants in the study will be required to visit the department of Respiratory Physiology and Sleep on three occasions. At the first visit an assessment of your suitability to perform a maximal exercise test will be undertaken. This will include a basic breathing test, an ECG (heart trace) and blood pressure measurements. You will also be asked to complete a short questionnaire.

If you fulfil the criteria to undertake a maximal exercise test and you consent to participate in the study, you will be given an appointment within four weeks to undertake your first exercise test. This visit will be approximately one hour in duration. At this visit you will again undertake a basic breathing test, an ECG and measurements of your blood pressure. You will then have a face mask attached which links your breathing to an exercise testing machine. You will be seated at either an arm ergometer or a cycle ergometer to commence an exercise test. The first stage of the exercise test will require you to turn the pedals slowly for 3 minutes, after this the pedals will begin to get harder and harder to turn and you will therefore need to exercise harder and harder until you are physically too tired to continue. This part of the exercise test will last between 8-12 minutes. At the end of testing you will be given time to rest and recover before leaving the department.

You will then need to re-attend the department no sooner than 24 hours later and within 72 hours to perform the second exercise test. This visit will be a repeat of your previous visit but using the exercise device i.e. arm or cycle ergometer that you did not use at your first visit.

If more than four weeks passes between your initial screening visit and the first exercise test, the screening visit will have to be repeated to confirm your ongoing suitability to undertake the tests.

What are the benefits of taking part?

Taking part in this study will allow us to generate normal values for arm ergometry. This will enable us to begin to use arm ergometry as a pre-operative assessment tool for patients who do not find it possible to use a standard cycle ergometer or a treadmill. This means that exercise testing as a pre-operative tool will become available to all patients regardless of the mobility/disability.

What are the risks of taking part?

Adverse events occurring as a result of undertaking a maximal exercise test are rare particularly when supervised by competent staff. The main risk is of a cardiac complication and this occurs in <1 per 10 000 tests. Continuous monitoring of heart function will be undertaken throughout the test and the test will be terminated if changes are noted.

Will I receive reimbursement for taking part (i.e. travel costs/parking)

As this study is looking to recruit staff we anticipate that appointments will be scheduled around working hours. This will prevent additional visits to the hospital and avoid extra burden for you. Therefore, there is no provision for travel expenses.

What if something goes wrong?

In the very unlikely event of you being harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it. If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanism is available to you. Please contact:

Complaints Manager
University Hospitals of Coventry & Warwickshire NHS Trust
Clifford Bridge Road

Telephone no: 02476 965 198

For independent advice on research, you can contact PALS (Patient Advice and Liaison Service) on freephone 0800 028 4203, Email: feedback@uhcw.nhs.uk

After participating in the study if you experience any problems specific to the study or if you wish to make a formal complaint you can do so by writing to:

Ceri Jones

Head of Research & Development

Research & Development Department

University Hospitals Coventry & Warwickshire
University Hospitals

Coventry CV2 2DX

Direct Tel: 02476966069

For independent advice on research, you can contact PALS (Patient Advice and Liaison Service) on freephone 0800 028 4203.

In the unlikely event of you losing your capacity to consent during the course of the study, you would be withdrawn from the study. Identifiable data already collected with consent would be retained and used in the study. No further data would be collected.

Will my taking part in this study be kept confidential?

If you consent to take part in the study, all information which is collected about you during the course of the research will be kept strictly confidential. Your name and address will be removed from all study data (anonymised) and a study identification number assigned.

What data will be collected?

University Hospitals Coventry and Warwickshire NHS Trust

What will happen to the results of the research study?

We hope to publish results of this study in national or international journals and present it at conferences. In addition the results will form the basis for further work looking at the use of arm ergometry in patients requiring surgery.

Who has reviewed this project?

This study has been reviewed and approved *by Wales REC 7 Ref 17/WA/0284* HRA Approval was granted on 20th September 2017.

Contact for further information:
If you require further information or have any questions, please contact:-

Chief Investigator/Local Research Team Details

Name: Joanna Shakespeare
Address: Department of Respiratory Physiology and Sleep, UHCW NHS Trust, Coventry, CV2 2DX
Telephone: 024 76966738
Email: Joanna.shakespeare@uhcw.nhs.uk

Thank you for considering taking part in this research study. Whilst we would obviously be delighted if you can help us, there is no obligation to do so.

Appendix B – Consent Form

University Hospitals Coventry and Warwickshire NHS Trust

Participant Identification Number for this trial:

CONSENT FORM

Title of Project: Normal values for arm ergometry

Name of Researcher: Joanna Shakespeare

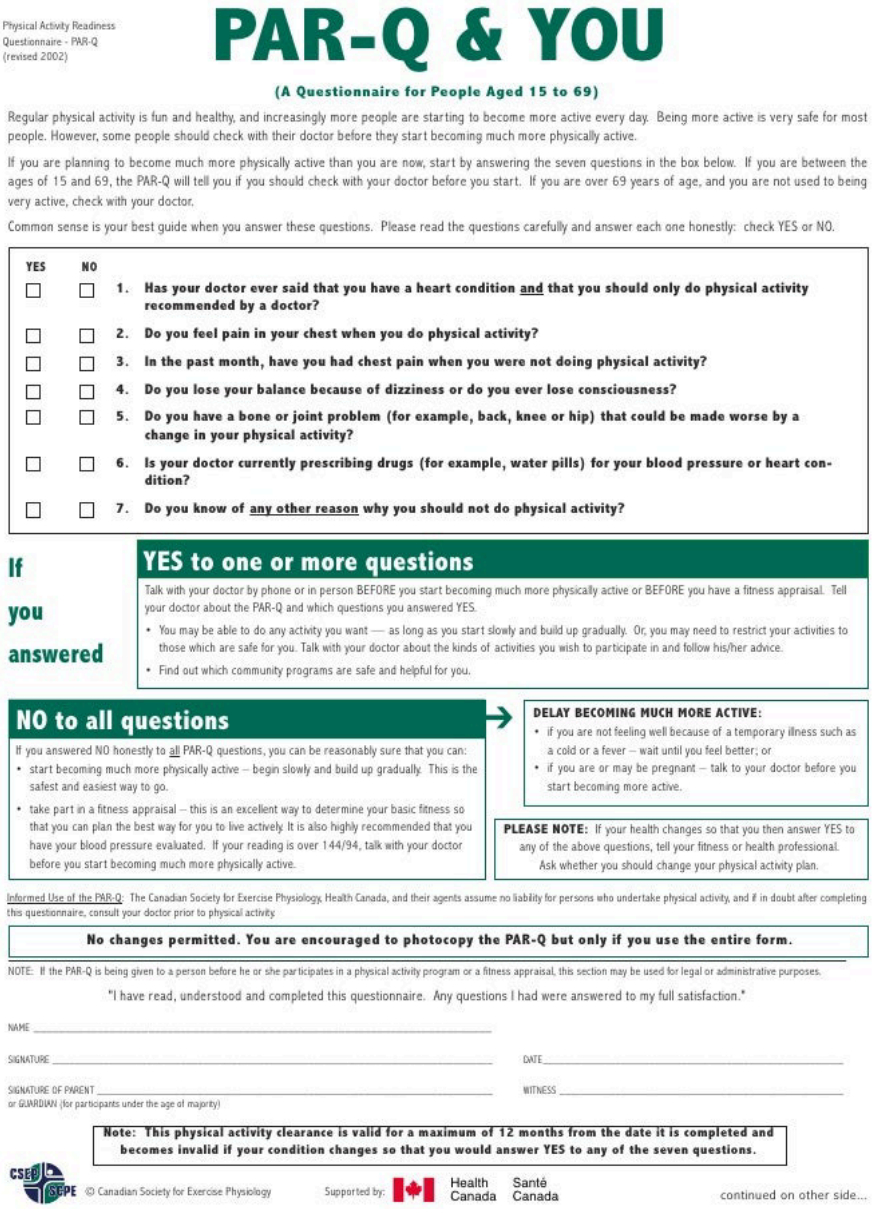
Please initial box

1. I confirm that I have read the information sheet dated 20th September 2017 Version 1.3 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason. ☐
3. I understand that relevant data collected during the study, may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers. ☐
5. I understand that if more than 4 weeks pass between my initial screening and 1st exercise test I will need to attend another screening visit to confirm suitability to complete the tests. ☐
6. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.
226248_Consent Form_V1.3_20.09.2017

Appendix C – PAR-Q & You



Physical Activity Readiness Questionnaire - PAR-Q (revised 2002)

PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO	
☐	☐	1. **Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?**
☐	☐	2. **Do you feel pain in your chest when you do physical activity?**
☐	☐	3. **In the past month, have you had chest pain when you were not doing physical activity?**
☐	☐	4. **Do you lose your balance because of dizziness or do you ever lose consciousness?**
☐	☐	5. **Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?**
☐	☐	6. **Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?**
☐	☐	7. **Do you know of any other reason why you should not do physical activity?**

If you answered

YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

DELAY BECOMING MUCH MORE ACTIVE:

- if you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
- if you are or may be pregnant – talk to your doctor before you start becoming more active.

PLEASE NOTE: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME _____

SIGNATURE _____ DATE _____

SIGNATURE OF PARENT or GUARDIAN (for participants under the age of majority) _____ WITNESS _____

Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.

Supported by: Health Canada Santé Canada

continued on other side...

Appendix D – RPAQ

-
-
-

Section A Home Activities

Getting about

Which form of transport have you used **most often** in the last 4 weeks apart from your journey to and from work? (Please tick (✓) one box only)

Usual mode of travel			
Car / motor vehicle	Walk	Public transport	Cycle

TV, DVD or Video Viewing (Please put a tick (✓) on every line)

Hours of TV, DVD or video watched per day	Average over the last 4 weeks					
	None	Less than 1 hour a day	1 to 2 hours a day	2 to 3 hours a day	3 to 4 hours a day	More than 4 hours a day
On a weekday before 6 pm						
On a weekday after 6 pm						
On a weekend day before 6 pm						
On a weekend day after 6 pm						

Computer use at home *but not at work* (e.g. internet, email, Playstation, Xbox, Gameboy etc) (Please put a tick (✓) on every line)

Hours of home computer use per day	Average over the last 4 weeks					
	None	Less than 1 hour a day	1 to 2 hours a day	2 to 3 hours a day	3 to 4 hours a day	More than 4 hours a day
On a weekday before 6 pm						
On a weekday after 6 pm						
On a weekend day before 6 pm						
On a weekend day after 6 pm						

Stair climbing at home (please put a tick (✓) on every line)

Number of times you climbed up a flight of stairs (approx 10 steps) each day at home	Average over the last 4 weeks					
	None	1 to 5 times a day	6 to 10 times a day	11 to 15 times a day	16 to 20 times a day	More than 20 times a day
On a weekday						
On a weekend day						

Section B Activity at work

Please answer this section to describe if you have been in paid employment at any time **during the last 4 weeks** or you have done regular, organised voluntary work.

Have you been in employment during the last 4 weeks? *Yes* ☐ *No* ☐

During the last 4 weeks how many hours work did you do per week?

	4 weeks ago	3 weeks ago	2 weeks ago	1 week ago
Work hours (excluding travel)				

Type of work

We would like to know the type and amount of physical activity involved in your work. **Please tick** (✓) the option that **best** corresponds with your occupation(s) in the last 4 weeks from the following four possibilities:

Please tick only one of the following

1. Sedentary occupation
You spend most of your time sitting (such as in an office) ☐

2. Standing occupation
You spend most of your time standing or walking. However, your work does not require intense physical effort (e.g. shop assistant, hairdresser, guard) ☐

3. Manual work
This involves some physical effort including handling of heavy objects and use of tools (e.g. plumber, electrician, carpenter) ☐

4. Heavy manual work
This implies very vigorous physical activity including handling of very heavy objects (e.g. dock worker, miner, bricklayer, construction worker) ☐

Section B Activity at work

Travel to and from work in the last 4 weeks

What is the approximate distance from your home to your work?

☐☐☐ Miles *or* ☐☐☐ Kilometers

How many times a week did you travel from home to your main work? ☐☐
Count outward journeys only

Please tick (✓) one box **only** per line

How did you normally travel to work?	Always	Usually	Occasionally	Never or rarely
By car/motor vehicle				
By works or public transport				
By bicycle				
Walking				

What is the postcode for your main place of work during the last 4 weeks?

Postcode ☐☐☐☐☐☐☐

If not known please give your work address
Work address - _____
_____
_____

What is the postcode for your home address?

Postcode ☐☐☐☐☐☐☐

Section C Recreation

The following questions ask about how you spent your leisure time.

Please indicate how often you did each activity on average over the last 4 weeks

Please indicate the average length of time that you spent doing the activity on each occasion.

Example

If you went walking for pleasure for 40 minutes once a week.
If you had done weeding or pruning every fortnight and took 1 hour and 10 minutes on each occasion.
You would complete the table below as follows:

Please give an answer for the NUMBER OF TIMES you did the following activities in the past 4 weeks and the AVERAGE TIME you spent on each activity.

Please complete EACH line

	Number of times you did the activity in the last 4 weeks							Average time per episode	
	None	Once in the last 4 weeks	2 to 3 times in the last 4 weeks	Once a week	2 to 3 times a week	4 to 5 times a week	Every day	Hours	Minutes
Weeding and pruning			✓					*1*	*10*
Walking for pleasure				✓					*40*

Now complete the table on pages 6 and 7

Please give an answer for the average time you spent on each activity and the number of times you did that activity in the past 4 weeks

Please complete each line

	Number of times you did the activity in the last 4 weeks							Average time per episode	
	None	Once in the last 4 weeks	2 to 3 times in the last 4 weeks	Once a week	2 to 3 times a week	4 to 5 times a week	Every day	Hours	Minutes
Swimming - competitive									
Swimming leisurely									
Backpacking or mountain climbing									
Walking for pleasure *(not as a means of transport)*									
Racing or rough terrain cycling									
Cycling for pleasure *(not as a means of transport)*									
Mowing the lawn									
Watering the lawn or garden									
Digging, shovelling or chopping wood									
Weeding or pruning									
DIY e.g. carpentry, home or car maintenance									
High impact aerobics or step aerobics									
Other types of aerobics									
Exercise with weights									
Conditioning exercises e.g. using a bike or rowing machine									

Please complete each line

	Number of times you did the activity in the last 4 weeks							Average time per episode	
	None	Once in the last 4 weeks	2 to 3 times in the last 4 weeks	Once a week	2 to 3 times a week	4 to 5 times a week	Every day	Hours	Minutes
Floor exercises e.g. stretching, bending, keep fit or yoga									
Dancing e.g. ballroom or disco									
Competitive running									
Jogging									
Bowling- indoor, lawn or 10 pin									
Tennis or badminton									
Squash									
Table tennis									
Golf									
Football, rugby or hockey									
Cricket									
Rowing									
Netball, volleyball or basketball									
Fishing									
Horse-riding									
Snooker, billiards or darts									
Musical instrument playing or singing									
Ice skating									
Sailing, wind-surfing or boating									
Martial arts, boxing or wrestling									

Appendix E – HSST Modules

Module	Description	Credit Value	Grade
A1	Professionalism and professional development in the healthcare environment	30	P
A2	Theoretical foundations of leadership	20	P
A3	Personal and professional development to enhance performance	30	P
A4	Leadership and quality improvement in the clinical and science environment	20	P
A5	Research and innovation in health and social care	20	P
B1	Advanced history taking and communication skills	15	P
B2	Clinical presentation and management of respiratory and sleep disorders - 1	20	P
B3	Therapeutics	10	P
B4	Diagnostics and monitoring in respiratory and sleep physiology	15	P
B5	Contemporary issues in healthcare science	20	P
B6	Clinical presentation and management of respiratory and sleep disorders - 2	15	P
B7	Teaching, learning and assessment in healthcare science	20	P

B8	Interventions in respiratory and sleep physiology	15	P
B9	Adult sleep disordered breathing and respiratory muscle physiology	20	P
C	Research, Development, and Innovation	270	P
	TOTAL	**540**	

Appendix F – Interpreting the coefficients

Arm Ergometry $\dot{V}O_2$

Using the results of the multiple regression model the equation for predicting $AEVO_2$ is as follows:

$$\textbf{AE}\dot{\textbf{V}}\textbf{O}_2\textbf{max} = \text{Constant} + (b1 \times \text{age}) + (b2 \times \text{sex}) + (b3 \times \text{weight})$$

Sex was defined as:

Male = 0

Female = 1

The following is a worked example for a male, aged 30 years with a weight of 80kg

$AE\dot{V}O_2$ max = 1930.803 – (12.651 x 30) + (10.507 x 80)

= 1930.803 – 379.53 + 840.56

= 2391.06 ml.min

Using the 95% confidence intervals, the upper and lower limit of normal can also be calculated and a worked example for the same individual can be found below.

LLN = 1304.155 – (20.270 x 30) + (3.890 x 80)

= 1304.155 – 608.10 + 311.20

= 1007.255 ml.min

ULN = 2557.452 – (5.024 x 30) + (17.123 x 80)

= 2557.452 – 150.72 + 1369.84

= 3776.572 ml.min

Anaerobic Threshold

Using the results of the multiple regression model the equation for predicting anaerobic threshold is as follows:

Anaerobic threshold = Constant + (b1 x age) + (b2 x sex) + (b3 x weight)

Sex was defined as:

Male = 0

Female = 1

The following is a worked example for a male, aged 30 years with a weight of 80kg

Anaerobic threshold = 888.898 – (6.235 x 30) + (5.178 x 80)

= 888.898 – 187.05 + 414.24

= 1116.088 ml.min

Using the 95% confidence intervals, the upper and lower limit of normal can also be calculated and a worked example for the same individual can be found below.

LLN = 492.971 – (11.054 x 30) + (0.998 x 80)

= 492.971 – 331.62 + 79.84

= 241.191 ml.min

ULN = 1284.825 – (1.416 x 30) + (9.359 x 80)

= 1284.825 – 42.48 + 748.72

= 1991.065 ml.min

Peak Work Rate

Using the results of the multiple regression model the equation for predicting peak work rate is as follows:

Work rate = Constant + (b1 x age) + (b2 x sex) + (b3 x weight)

Sex was defined as:

Male = 0

Female = 1

The following is a worked example for a male, aged 30 years with a weight of 80kg

Work rate = 96.003 – (0.511 x 30) + (0.533 x 80)
= 96.003 – 15.33 + 42.64
= 123.313 watts

Using the 95% confidence intervals, the upper and lower limit of normal can also be calculated and a worked example for the same individual can be found below.

LLN = 70.078 – (0.827 x 30) + (0.260 x 80)
= 70.078 – 24.81 + 20.80
= 66.068 watts

ULN = 121.928 – (0.196 x 30) + (0.807 x 80)
= 121.928 – 5.88 + 64.56
= 180.608 watts

Peak Heart Rate

Using the results of the linear regression model the equation for predicting peak heart rate is as follows:

Heart rate = Constant + (b1 x age)

The following is a worked example for a male, aged 30 years with a weight of 80kg

Heart rate = 191.833 – (0.916 x 30)
= 191.833 – 27.48
= 164.35 bpm

Using the 95% confidence intervals, the upper and lower limit of normal can also be calculated and a worked example for the same individual can be found below.

LLN = 180.999 – (1.186 x 30)
= 180.999 – 35.58
= 145.419 bpm

ULN = 202.667 – (0.646. x 30)
= 202.667 – 19.38
= 183.287 bpm