The Role of Cardiopulmonary Exercise Testing for Identifying Possible Silent Myocardial Ischaemia in People with Coronary Heart Disease

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Abstract

This thesis investigates the utility of cardiopulmonary exercise testing (CPET) in assessing and managing patients with coronary artery disease (CAD), particularly focusing on the significance of oxygen pulse (O_2Pulse) inflections as a marker for myocardial ischemia. The research encompasses a comprehensive analysis of O_2Pulse morphology, inflection point identification, and the impact of exercise-based cardiac rehabilitation (exCR) programs, specifically high-intensity interval training (HIIT) and moderate-intensity steady-state (MISS) training, on patients with CHD.

Chapter 3 examines the reliability of CPET in detecting suspected myocardial ischemia through O_2Pulse and $\Delta\dot{V}O_2/\Delta WR$ inflections in chronic total occlusion (CTO) patients. This study was considerable hampered by poor recruitment and the outbreak of COVID-19. Subsequently only four patients were enrolled, three of whom exhibited no inflections in O_2Pulse. In the one patient who did have O_2Pulse inflections they occurred at similar work rates (10W) and heart rates (5bpm). Chapter 5 extends the inquiry into the short-term reliability and agreement of O_2Pulse curve parameters in a healthy cohort demonstrating that the mean percent minimal detectable change for filtered O_2Pulse was 13.5 ± 3.2. Building on these findings, Chapter 6 evaluates the inter- and intra-rater reliability in identifying O_2Pulse inflections, comparing subjective assessments with an objective algorithmic method. Almost perfect agreement between the algorithm and human raters was demonstrated, with a Fleiss' Kappa statistic of 0.89. Chapter 7, a subset analysis from the HIIT or MISS UK trial, delves into the rate of O_2Pulse inflections in outpatient cardiac rehabilitation (16%) and how different exercise interventions affect O_2Pulse inflections in CAD patients.

The results highlight a considerable potential for CPET, particularly O_2Pulse inflections, in the diagnosis, treatment, and management of CAD. The research underscores the potential reliability of O_2Pulse as a diagnostic tool, the effectiveness of exCR in improving cardiopulmonary fitness, and the relevance of O_2Pulse inflections as a surrogate marker for myocardial ischemia. The findings suggest that both HIIT and MISS can positively influence O_2Pulse inflections, offering a non-invasive means to monitor and potentially improve the health outcomes of CAD patients.

This thesis contributes to the understanding of CPET in clinical settings, advocating for its broader application in cardiac rehabilitation. It identifies areas for further research,

including the exploration of different exercise modalities, to optimize exCR programs and enhance patient care.

Thesis Publications

Nickolay, T., Nichols, S., Ingle, L., & Hoye, A. (2019). Exercise Training as a Mediator for Enhancing Coronary Collateral Circulation: A Review of the Evidence. *Current cardiology reviews*.

Publications Under Review

Sport Sciences for Health : The Morphology and Stability of the Oxygen Pulse Curve During Cardiopulmonary Exercise Testing

PLOS ONE : Inter- and Intra-Observer Reliability and Agreement of O_2Pulse Inflection during Cardiopulmonary Exercise Testing in Patients with Coronary Artery Disease: A Comparison of Subjective and Novel Objective Methodology

International Journal of Medical Reviews and Case Reports : Stability of the Oxygen Pulse Inflection During Cardiopulmonary Exercise Testing in the Presence of a Chronic Total Coronary Occlusion: A Case Report

"The greater the difficulty the more glory in surmounting it. Skilful pilots gain their reputation from storms and tempests".

Epictetus

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Preface and Personal Reflection

I am sure there are countless personal reflections in PhD theses that detail the difficulties, both personal and academic, brought about by the COVID-19 pandemic. I hope my writing about my experiences does not appear as a call for a reduction in the academic rigour with which you will evaluate this work. I include this only because I believe it is pivotal to understanding the trajectory and narrative of this thesis, as well as my overall growth as a scientist.

I began my PhD in October 2017 at the age of 30, after being awarded a full-time scholarship for a project entitled, "A Pilot, Feasibility Study of Exercise Therapy for Patients with Coronary Artery Disease (CAD)". Having only graduated in 2016, with a first-class honours degree in Sport and Exercise Science, I was a timid and novice researcher with minimal practical experience. The experience I did have, came for the most part from supporting the research of others. For example, I assisted in the running of many clinical cardiopulmonary exercise tests (CPETs) and processing of blood samples for the HIIT or MISS UK trial.

The first 12 months of my PhD were spent designing and gaining Health Research Authority (HRA) ethical approval for a clinical trial entitled, "Exercise in Patients with a Total Coronary Occlusion (EChO)" (see Chapter 3). My primary supervisor Dr Angela Hoye, is an interventional cardiologist specialising in the field of chronic total coronary occlusions (CTO), therefore the decision was taken to make this patient group the focus of my research. Patients with a CTO are unique in that, by definition, they have a completely occluded artery. Survival and functional capacity in this group is dependent upon the location of the occlusion and development of the collateral network supplying the area of myocardium no longer being perfused by the occluded vessel. In the above-mentioned clinical trial, I was hoping to determine what percentage of the cohort exhibited oxygen pulse (O_2Pulse) inflections during CPET, as these are believed to mark the onset of myocardial ischaemia. I would then retest those with inflections to observe their repeatability, before finally having patients exercise just below this threshold for 20 minutes, firstly to see if it was safe, and secondly, to see if it elicited wall-motion abnormalities consistent with ischaemia. As a novice researcher, this first year was at times overwhelming, speaking in front of patient groups and ethics meetings, as well as publishing my first paper (a narrative review on exercise mediating coronary collateral formation - Chapter 4). However, I managed to obtain

NHS Health Research Authority Ethical approval for my first study (EChO - Chapter 3) in January 2019.

Recruiting a population of n=12 to my first study was anticipated to be relatively straightforward, given the database of eligible patients and access to the clinic of Dr Hoye. However, recruitment was poor, and at the time of the COVID-19 outbreak in late 2019, I had only managed to get four participants through testing. Recruitment was believed to be poor due to my inclusion criteria accepting only patients with single vessel disease. Therefore, I began designing a second study that would look at the effects of resistance exercise on multiple parameters of functional capacity (including movement economy) in CTO patients, this time accepting those with multi-vessel disease (REACTOr - 11.5). Knowing that I was coming to the end of my allotted three years and had only minimal data, I also designed a healthy version of this study to look at the response in older sedentary patients, as they represent a group with increased risk of developing CAD and share some similar baseline characteristics (RARE - 11.6). my plan at this time was to continue collecting data on EChO and RARE until the very end of my three years. I would then spend 12 months writing up both studies and publish REACTOr as a protocol paper if it did not recruit.

I was granted ethical approval to begin testing for RARE and REACTOr in November and December of 2019 respectively. At the end of January 2020, the first confirmed UK cases of COVID-19 were recorded in York, at the time I was eight months from the end of my last year of paid scholarship and had three studies open to recruitment. By the time the World Health Organisation declared COVID-19 a global pandemic, and the government mandated a national lock-down (March 2020), institutions such as Hospitals and Universities had already instated strict restrictions on unnecessary face-to-face contact. Essentially this meant my data collection ended between February and March 2020.

National lockdowns were at the time unprecedented, and understanding of the virus was evolving each day. With this uncertainty in mind, I knew I needed to try and keep working on progressing the thesis where possible. I had begun thinking extensively about whether exercise could increase movement economy and thus functional, not necessarily maximal capacity in CTO patients. Although it did not fit neatly into the intended narrative of my thesis, I had an idea for a retrospective data analysis of current exercise-based cardiac rehabilitation for which I was granted access to the

CARE-CR dataset by my supervisor Dr Simon Nichols. I subsequently spent the majority of the first lockdown processing CPET data and writing a manuscript.

After the first lockdown I was awarded a four-month paid extension to my scholarship. However, my data collection in CAD patients was still not permitted, and due to the continuing uncertainty around the virus, recruitment to my healthy study had ceased. At this time, I was becoming increasingly concerned that I would be left with no novel contributions with which to fulfil the requirements of a PhD. In my personal life, I had been married during my first year and had my first son in my second year. I had a mortgage and two dependents to consider whilst still in the midst of a global pandemic. With my funding coming to an end, I took the difficult decision to take a 12-month leave of absence from my PhD and take up full-time employment at the University as a Laboratory Manager. My time away from the PhD was spent trying to devise a path to completion that would also restore some narrative and structure. I returned to the concept of identifying ischaemia through inflections in O_2Pulse. Given that it was no longer feasible for me to collect data, I could not, as had been my intention, determine the repeatability of these inflections in CTO or CAD patients. However, I was aware of a previous CPET repeatability study that had been completed in a healthy cohort by a colleague (Dr Damien Gleadall-Siddall). I subsequently reached out to him to see if he would permit me access to the data so that I could at least establish the repeatability of the O_2Pulse curve in healthy populations. At the same time, it occurred to me identifying inflections in the literature was always done subjectively, which I believed to be suboptimal. Having assisted in data collection on the HIIT or MISS UK trial I knew O_2Pulse was a parameter they collected but did not intend to use as a primary outcome. Therefore, I reached out to Professor Gordon McGregor (PI for the HIIT or MISS UK trial) to ask for access to the data to answer two research questions, those being: could an objective method of inflection identification be proposed, and did HIIT or MISS alter the point of inflection in those for whom one occurred. When I returned, my PhD was converted to part-time study, and I set to work on completing analysis of hundreds of CPET files.

Poor recruitment and the global pandemic disrupted the planned trajectory of this thesis, and as a result I had to generate additional research questions that could be answered through retrospective analysis of existing datasets. One thing that remained constant from the outset of the thesis was my overall concern with how research impacted the patient. My PhD journey is neither unique nor extraordinary; it is simply

my journey, and, difficult as it has been, upon reflection, it is probably not one I would trade. Doubtless, a straightforward path to completion would have sheltered me from the stress and anxiety that this thesis has imposed. However, without the trials and tribulations, setbacks, and disappointments, I would not be the scientist nor man I am today.

Acknowledgements

I extend my gratitude to my supervisory team, Dr. Angela Hoye, Dr. Simon Nichols, and Professor Lee Ingle, for their support throughout. Special thanks go to Dr. Simon Nichols, whose support and guidance were particularly vital during the challenging early stages of my PhD. I am also grateful to Professor Lee Ingle for his valuable insights in the later stages of my research. His constructive feedback on my manuscripts and enriching conversations have greatly improved my work.

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To my Mum, my first love; Dad, my hero; and Sister, my first friend, thank you for absolutely everything! Your love and support in everything I do is a blessing I could not do without.

Philippa May Nickolay, my wife, how can I ever thank you? We have been through more in the last seven years than some couples go through in a lifetime. Despite that, you have selflessly taken on more responsibilities to allow me the freedom to complete this PhD. Now, you can finally have your husband back and put your feet up. I loved you then, I love you now, and I will love you forever. Thank you for everything!

Finally, to my boys, Stanley and Henry (Biggie and Smalls). As far back as I can remember, I never wanted to be a footballer, a singer, an astronaut, or scientist; the only job I ever wanted was to be a dad. Being ***your*** dad is the greatest thing that has, or will ever, happen to me. I love you to the moon and back, no matter what, no matter where, no matter when!

Author's declaration

I confirm that this work is original and that if any passage(s) or diagram(s) have been copied from academic papers, books, the internet or any other sources these are clearly identified by the use of quotation marks and the reference(s) is fully cited.

I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in examinations.

I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources.

I confirm that any patient information obtained to produce this piece of work has been appropriately anonymised.

Contributions

I would like to take this opportunity to acknowledge the contributions made to this thesis by collaborators.

During Chapter 3 I was supported in data collection by Dr Angela Hoye and Chief Cardiac Physiologist Sarah Hurren, who undertook phlebotomy and echocardiology respectively.

In chapter 5 I was provided retrospective access to data by Dr Damien Gleadall-Siddall and Dr Andrew Garrett.

In chapter 6 & 7 I was again assisted with retrospective access to data by Professor Gordon McGregor, Dr Stefan Birkett, Dr Richard Powell and Dr Brian Begg. I would like to thank James Metcalfe for assisting me with O_2Pulse interpretation during Chapter 6.

Abbreviations

1RM - One Repetition Maximum

ACC - American College of Cardiology

ACCF - American College of Cardiology Foundation

ACS - Acute Coronary Syndrome

ACSM - American College of Sports Medicine

AE - Aerobic Exercise

AHA - American Heart Association

ARIC - Atherosclerosis Risk in Communities Study

ASMR - Age-Standardised Mortality Rate

AUC – Area Under the Curve

a-vO_{2diff} - Arteriovenous Oxygen Difference

bpm – Beats Per Minute

BMI - Body Mass Index

CABG - Coronary Artery Bypass Graft

CAC - Coronary Artery Calcification

CAD - Coronary Artery Disease

CCS - Chronic Coronary Syndrome

CCTA - Coronary Computed Tomographic Angiography

CDC - Centers for Disease Control and Prevention

CFI - Collateral Flow Index

CHD - Coronary Heart Disease

CI - Confidence Interval

CTCA - Computational Tomography Coronary Angiography

CR - Cardiac Rehabilitation

CRP - C-Reactive Protein

CTO - Chronic Total Occlusion

CT - Computed Tomography

CVD - Cardiovascular Disease

EACPR - European Association for Cardiovascular Prevention and Rehabilitation

EAPC - European Association of Preventative Cardiology

EAS - European Atherosclerosis Society

ECG - Electrocardiogram

EECP - Enhanced External Counter-Pulsation

EQ-5D - European Quality of Life 5 Dimensions

ESC - European Society of Cardiology

ETT - Exercise Treadmill Time

FBG - Fasting Blood Glucose

FGF - Fibroblast Growth Factor

FH - Familial Hypercholesterolemia

FIRST - FGF Initiating RevaScularization Trial

FSS - Fluid Shear Stress

GM-CSF - Granulocyte-Macrophage Colony-Stimulating Factor

HbA1c - Glycated Haemoglobin

HDL-C - High-Density Lipoprotein Cholesterol

HF - Heart Failure

HIIT - High Intensity Interval Training

HIF1-α - Hypoxia-Inducible Factor 1-Alpha

HR - Hazard Ratio

HRR – Heart Rare Reserve

IHD - Ischaemic Heart Disease

ICAM-1 - Intracellular Adhesion Molecule-1

IL-6 - Interleukin-6

IQR - Interquartile Range

LAD - Left Anterior Descending (artery)

LBBB - Left Bundle Branch Block

LCx - Left Circumflex (artery)

LDL - Low-Density Lipoprotein

LV – Left Ventricle

LVEF - left Ventricular Ejection Fraction

MACE - Major Adverse Cardiac Events

MACCE - Major Adverse Cardiovascular or Cerebrovascular Events

MCP-1 - Monocyte Chemotactic Protein-1

MDCT-CA - Multidetector Computed Tomography Coronary Angiography

MET - Metabolic Equivalent

MI - Myocardial Infarction

MISS – moderate Intensity Steady State NIH - National Institutes of Health

MM - Mitochondrial Myopathy

MUGA - Multi-gated Equilibrium 99mTc Radionuclide Cineangiography

NACR - National Audit of Cardia Rehabilitation

NSTEMI - Non-ST-Elevation Myocardial Infarction

NST-ACS - Non-ST Elevation Acute Coronary Syndrome

OMT - Optimal Medical Therapy

ONS - Office for National Statistics

PAH - Pulmonary Arterial Hypertension

PO_2 - Partial Pressure of Oxygen

PCI - Percutaneous Coronary Intervention

PCO_2 - Partial Pressure of Carbon Dioxide

Q - Cardiac Output

QoL – Quality of Life

RCA - Right Coronary Artery

RCT – Randomised Controlled Trial

RE - Resistance Exercise

RER - Respiratory Exchange Ratio

RR – Relative Risk

ROC - Receiver Operating Characteristic

SAQ - Seattle Angina Questionnaire

SMC - Smooth Muscle Cell

SPECT - Single-Photon Emission Computerized Tomography

STEMI - ST-Elevation Myocardial Infarction

SDS - Summed Difference Score

SV - Stroke Volume

SYNTAX - Synergy Between PCI with Taxus and Cardiac Surgery

TIMI - Thrombolysis in Myocardial Infarction

T2DM - Type 2 Diabetes Mellitus

TNF-α - Tumor Necrosis Factor Alpha

TnT – Troponin T

TnI – Troponin I

UK - United Kingdom

VCAM-1 - Vascular Cell Adhesion Molecule-1

VE/VO_2 - Ventilatory Equivalents of Oxygen

VE/VCO_2 - Ventilatory Equivalents of Carbon Dioxide

VEGF - Vascular Endothelial Growth Factor

VIVA - Vascular Endothelial Growth Factor in Ischaemia for Vascular Angiogenesis

$\dot{V}O_{2peak}$ - Peak Oxygen Uptake

VT1 - Ventilatory Anaerobic Threshold: Literature Review

WHO - World Health Organisation

ΔVO2/ΔWR - Change in Oxygen Consumption per Work-rate

Chapter 1 General Introduction

Coronary artery disease (CAD) is the most common form of cardiovascular disease, impacting over 110 million people worldwide (1). Characterised by the accumulation of atherosclerotic plaque in the coronary arteries (2,3,3–5), CAD represents a major global health concern (6), and is a significant contributor to morbidity and mortality, particularly in the developed world (7).

Cardiac rehabilitation is a multifaceted and interdisciplinary approach to managing cardiovascular diseases, including CAD. It encompasses educational, behavioural, psychological, in combination with exercise interventions with the aim of reducing risk factors and enhancing patients' quality of life (8–10). The European Society of Cardiology (ESC), American Heart Association (AHA), and American College of Cardiology Foundation (ACCF) consider exercise-based cardiac rehabilitation (exCR) as a Class 1 Grade A therapy (4,11). Both aerobic and resistance training, unless contraindicated, are recommended for comprehensive exCR by the ACPICR and AHA/ACCF (11,12). Moderate aerobic exercise, defined as exercise performed between 40 and 70% HRR (13), is the generically recommended by the Association of Chartered Physiotherapists in Cardiovascular Rehabilitation (ACPICR) (12) as training intensity for exCR in the UK. For CAD patients with residual myocardial ischemia, exercise prescription guidelines suggest maintaining an intensity ≈10 beats below the ischaemic threshold (13–15). This recommendation is based on the established association between acute myocardial ischemia and the risk of life-threatening arrhythmias (16–21).

Cardiopulmonary exercise testing (CPET) is regarded as the 'gold standard' for the non-invasive quantification of cardiopulmonary fitness and functional capacity in people with CAD and or heart failure (22,23). The diagnostic and prognostic utility of CPET in these contexts has been widely acknowledged (22–26). In particular, an early plateau or inflection in the normal linear progression of oxygen pulse (O_2Pulse) and oxygen consumption ($\dot{V}O_2$) despite an increasing work-rate (WR) are suggested to be indicative of inducible and reversable ischaemia (23,25,27–30). O_2Pulse, reflects left ventricular stroke volume (SV) as per the Fick principle, suggesting that any plateau or inflection in its progression, despite an increase in work-rate (WR), could indicate a pathological limitation in the progression of SV due to myocardial ischemia (22,23,25)

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Research has shown that myocardial wall-motion abnormalities, and subsequent reductions in SV often precede ECG changes and angina symptoms, making inflections in O_2Pulse and the $\Delta\dot{V}O_2/\Delta WR$ slope potentially more sensitive markers of ischemia (31). Indeed, the seminal work of Belardinelli and colleagues in 2003 demonstrated that such inflections could occur 265 ± 33 seconds prior to a 2mm ST segment depression during CPET, highlighting their potential diagnostic value (29). In light of these findings the guidance for those with residual myocardial ischaemia, possibly even silent myocardial ischaemia, to remain ≈10 beats below the ischaemic threshold would appear to be problematic.

The main aim of this thesis was to explore the potential use of CPET in interpreting cardiovascular function and adaptation in patients with CAD, especially those with chronic total coronary occlusions (CTO). The research sought to investigate how analysing abnormalities in important CPET derived parameters like O_2Pulse and $\Delta\dot{V}O_2/\Delta WR$, can indicate changes in cardiac function that may be related to myocardial ischemia. The overall objective was to improve the application of CPET in clinical practice, focusing on its ability to provide better patient care through personalised exCR prescriptions. These aims and objectives were pursued through a series of specific chapter aims addressing various aspects of CPET's role in CAD assessment and management.

Chapter 2 Literature Review

2.1 Coronary Artery Disease

The term CAD is often used interchangeably with coronary heart disease (CHD) or ischaemic heart disease (IHD) (3,32–34), for greater clarity reference to all three will be grouped as CAD for the remainder of this thesis. CAD which is typified by atherosclerotic plaque accumulation along the lumen of the coronary arteries (2,3,3–5) is the most common form of cardiovascular disease (CVD), with over 110 million cases worldwide (1). CAD is a progressive condition, often taking decades to mature into its most established incarnations (4,35). This is evidenced by the fact that both fatty streaks (the precursors to atherosclerotic lesions), and raised fibrous-plaque lesions have been documented within the coronary arteries of cadavers ranging in age from 2-39 years whose death was a consequence of non-cardiac related conditions or trauma (36). The gradual process of coronary calcification and arterial occlusion often results in several decades of asymptomatic and stable CAD (37). Indeed, patients may present with asymptomatic CAD even in the presence of total vessel occlusion (38). In patients for whom CAD remains clinically stable the asymptomatic period may eventually be concluded by exertional angina and its associated feelings of chest tightness (39). However, gradual erosion or sudden rupture of coronary plaque can result in rapid thrombus formation and subsequently unstable angina, myocardial infarction (ST and non-ST elevation) and ultimately death (3,5,39–41).

2.1.1 Pathology

Historically, the identification of cholesterol contained within coronary plaques led researchers to conclude that CAD was simply a disease of excessive cholesterol storage (2). However, more resent research has begun to implicate inflammation as having a causal role in the pathogenesis of atherosclerosis (42,43). Therefore, CAD is now seen as an immunoinflammatory disease, manifest through augmented cellular adhesion molecule expression by the endothelium (Figure 1) (44).

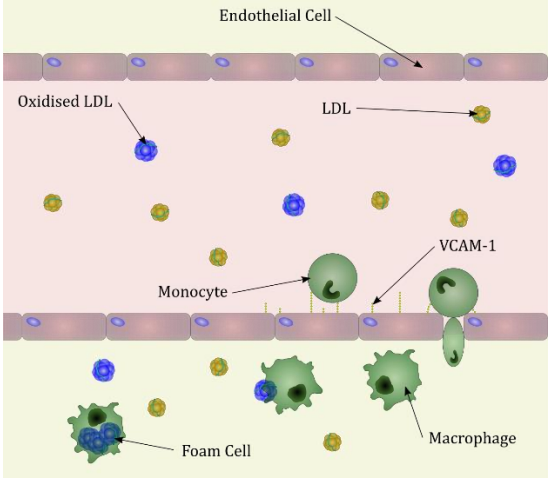

Figure 1. Simplified example of the atherosclerotic process in which there is an increase in leukocyte adherence to, and subsequent migration past the endothelium into the tunica intima

Leukocyte adherence to the vascular endothelium is ordinarily limited (45). However, sections of the endothelium can be exposed to a myriad of potentially harmful external influencers, ranging from inflammatory cytokines produced by excess adipose tissue storage, to bacteria and advanced glycation end products, often as a result of hyperglycaemia. This can result in the exposed section of endothelium exhibiting both an increase in permeability and expression of vascular cell adhesion molecules (Figure 1) (VCAM-1) (2,44). Once this dysfunctional section of endothelium begins to overexpress VCAM-1, blood leukocytes that would ordinarily flow freely past are stimulated to adhere via their corresponding counter receptors (46). Adherence alone however is not the fundamental cause of atheroma. Once bonded to the arterial endothelium these leukocytes (monocytes) are stimulated to migrate between adjoining endothelial cells into the tunica intima by chemotactic molecules, such as oxidised LDL and Monocyte chemotactic protein-1 (MCP-1) (46,47). After chemotaxis has occurred these monocytes differentiate into macrophages and begin scavenging to devour innate and oxidised LDL through macropinocytosis (48). These macrophages can now be classified as macrophage-derived foam cells, and as such they continue to internalise atherogenic lipoprotein molecules (49). This accumulation and subsequent conversion of lipoproteins into free cholesterol and fatty acids within the cell, eventually becomes uncontrolled (50). The resulting cytotoxicity may trigger the apoptotic death of the cell (44,49). Upon the demise of these cells their cellular content is released, perpetuating the cycle of inflammation and lesion formation by contributing to the necrotic lesion core, and recruiting more macrophages to the tunica intima (49,51).

2.1.2 Epidemiology

CAD is one of the foremost causes of death and disability in the developed world (7). The World Health Organizations Global Health Estimate ranks CAD (IHD) as the single largest cause of global mortality, accounting for 16% of deaths (6). Global mortality resulting from CAD is increasing, raising by over 2 million deaths in 2000 to 8.9 million in 2019 (6). However, CAD mortality has been decreasing in the England and Wales, falling by 48.1% between 2001 and 2019 (52). This is likely multifactorial but is consistent with the literature which suggests high income countries, such as the UK exhibit a decrease in prevalence, whilst Central and Eastern European countries exhibit high prevalence (53).

In 2019 the Office for National Statistics (ONS) in the United Kingdom (UK) reported 55,064 deaths due to CAD, accounting for 10.4% of annual mortality (52). Mortality is significantly influenced by age, therefore the age-standardised mortality rate (ASMR) introduced by the World Health Organisation (WHO) perhaps provides a more informative outcome measure with which to view disease specific mortality (54). The ASMR for CAD deaths the in UK in 2019 was 96.1 per 100,000 people (52). A recent systematic review on premature CVD mortality found a higher ASMR for CAD (IHD) (15.57) than for stroke (12.36) (55). Considerable differences were also found for subgroup analysis with sex as a factor, ASMR for males was 27.51 whilst females was 9.30, furthermore when correcting for outliers these values changed to 45.07 and 11.18 respectively (55).

In 2022 the European Society of Cardiology (ESC) released their comprehensive compilation and evaluation on CVD statistics up to 2021. The report indicates that in 2019 there were 5.8 million new cases of CAD (referred to in this instance as Ischaemic Heart Disease (IHD)) across their 57 member nations (56). The median age-standardised incidence estimate given per 100,000 people of 293.3 (IQR = 195.8 – 529.5) corresponds to an incidence rate of 0.29%, this does however range from <0.15% in Cyprus, Luxembourg, Portugal, and Poland to >1% in Uzbekistan. The Centers for Disease Control and Prevention (CDC) has reported on the findings of the American Heart Association (AHA) (57), suggesting that CAD is the most prevalent form of CVD in the United States, with 1 in 20 adults (≥20 years of age) having CAD (58). As of 2019 an estimated 47.6 million people across the ESCs member nations were reported to be living with CAD (IHD), this equates to an incidence rate of 2.89% (56).

2.1.3 Risk Factors

The premature death of sitting US President Franklin D. Roosevelt in 1945 owing to hypertensive heart disease and a subsequent stroke is often cited as one of the driving forces behind the establishment of the Framingham Heart Study (59). The Framingham study is one of a number of large epidemiological research projects that together generated a foundational scientific understanding of the "risk factors" that predispose an individual to the development of CVD (59).

Risk factors for CVD can be divided into two distinct classes; those that are amenable to change (modifiable), and those that are not (non-modifiable) (4,60) (Table 1).

Table 1. Modifiable and Non-modifiable risk factors for cardiovascular disease

Modifiable	Non-modifiable
Hypertension	Age
Dyslipidaemia	Sex
Smoking	Family history
Diabetes mellitus	Ethnicity
Sedentary lifestyle	
Overweight / obese	

2.1.3.1 Hypertension

Epidemiological studies have highlighted a significant positive association between CVD outcomes and hypertension (61,62). However, generating a definitive threshold value for diagnosing hypertension is difficult, as arterial pressure exhibits a continuous relationship to cardiovascular risk from 115-110/75-70mmHg upwards (63). Nonetheless, having a reproducible means of classifying the severity of hypertension allows for simplified and accurate diagnosis and treatment (63) (Table 2).

Table 2. Arterial blood pressure classification taken from the European Society of Hypertension and the European Society of Cardiology 2007 task force statement

Classification	Arterial blood pressure (mmHg)
Optimal	<120/<80
Normal	120-129/80-84
High Normal	130-139/85-89
Grade 1 hypertension	140-159/90-99
Grade 2 hypertension	160-179/100-109
Grade 3 hypertension	≥180/≥110
Isolated systolic hypertension	≥140/<90

Hypertension leads to endothelial dysfunction (64), which by definition impairs vasodilatory capacity and generates a pro-inflammatory pro-thrombotic environment (65). One meta-analysis approximated the prevalence of hypertension within economically developed countries to range from 20-50% (66). According to a recent report cardiovascular disease mortality may account for 1 in 36 deaths (286/10300) amongst normotensive, versus 1 in 8 (245/1915) untreated hypertensive US adults (HR 1.77, 95%CI = 1.34-2.35) (67).

Aerobic exercise training has been shown to reduce resting arterial blood pressure in both normotensive and hypertensive individuals (68). However, the decrease in hypertensive pressure appears significantly more pronounced than that of normotensives (hypertensive = systolic, -6 mm Hg, 95% CI, -8 to -3; diastolic, -5 mm Hg, 95% CI, -7 to -3 versus normotensive = systolic, -2 mm Hg, 95% CI, -3 to -1; diastolic, -1 mm Hg, 95% CI, -2 to -1) (69). Reducing systolic blood pressure by as little as 5mmHg could confer an approximate 9% reduction in CHD mortality (70).

2.1.3.2 Dyslipidaemia

Dyslipidaemia is a prominent risk factor for both the development and progression of cardiovascular disease, its existence is typified by abnormally elevated concentrations of lipids within the blood (71). This diagnosis can encompass hyper- and hypo-lipidaemias, of which the former is more prevalent (72). The ESC and the European Atherosclerosis Society (EAS) recommend screening for dyslipidaemia in those already manifesting symptoms of cardiovascular disease, with conditions associated with elevated cardiovascular disease risk, or any instance in which risk factor

screening is conducted (73). Furthermore, dyslipidaemia screening is recommended in all men >40 and women >50 years of age (or post-menopausal) (73). The ESC/EAS baseline recommended analysis for dyslipidaemia consists of evaluating triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) (73). According to the National Heart Lung and Blood institute (NIH) healthy blood cholesterol levels for those over 20 are; total cholesterol 125-200mg/dL, non-HDL-C <130mg/dL, LDL-C <100mg/dL and HDL-C >40 and >50mg/dL for men and women respectively (74).

It is understood that some dyslipidaemias, such as familial hypercholesterolemia (FH), are primarily caused by autosomally inherited mutations in lipoprotein receptor genes (LDL-C receptor gene in FH) (75). However, dyslipidaemia in the absence of autosomal inheritance has been the subject of multiple hypotheses, perhaps the earliest of which is the 'Cholesterol Hypothesis'. In 1913, Dr Anitschkow postulated that dietary cholesterol was responsible for atherosclerosis; he arrived at this conclusion after feeding rabbits a mixture of egg yolk and sunflower oil (76). Whilst Anitschkow appears to have generated a profound understanding of the atherosclerotic process, transferring his rabbit model to humans does not hold up to scrutiny, as the animal is known to be a habitual herbivore not in possession of the metabolic machinery necessary to synthesis large quantities of cholesterol.

2.1.3.3 Smoking

It was estimated in 2010 that 36.6% of men and 7.5% of women were smokers (77). Smoking is reported to be the most prevalent cause of CVD (78) and its related morbidity and mortality (79). Globally CVD accounts for approximately one third of all smoking related deaths (77). Furthermore, almost one third of CAD related deaths due to smoking can be attributed to smoking exposure, both active and passive (second-hand) (80). It has been estimated that 41,000 preventable deaths each year in non-smokers are caused by second-hand exposure to cigarette smoke (80). There is no known safe lower limit of smoke exposure as the chance of plaque rupture is increased, thus even brief exposure may prompt acute myocardial infarction (MI) (77,80–83). Therefore, reducing and not eliminating cigarette smoke does not totally mitigate the risk. Smoking is a strong independent risk factor for CAD (80), with risk remaining apparent even after controlling for other known risk factors (78). The risk factors associated with CAD are believed to have a multiplicative interaction, whereby the presence of multiple factors together drastically increase the associated CAD risk (78).

Indeed, smoking itself has a negative synergistic interaction with other factors, contributing to endothelial dysfunction (84), central adiposity (85), serum lipoprotein levels (86), and hypertension (87). Smoking has previously been shown to accelerate the progression of existing coronary lesions, and the formation of new lesions during repeated angiography (88). Smoking cessation leads to increase in endothelium-dependent vasodilatory function and is associated with a reduction in excess risk even in older adults (77,89). The risk of death 12 months post smoking cessation is approximately half that of a current smoker (77), risk of death and heart failure (HF) after >15 years of smoking cessation is comparable to someone who has never smoked (90).

2.1.3.4 Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) is characterised by a continual state of hyperglycemia that occurs as a result of poor insulin sensitivity, this is followed by an increase in insulin secretion that eventually leads to tissues becoming insulin resistant (91). T2DM is considered to be one of the largest global health crisis, once impacting only older adults it is now increasingly prevalent amongst children and adolescents (91,92). T2DM is a major risk factor for CAD and CAD is a major cause of death in T2DM, accounting for approximately 75% of deaths (93,94). Whilst T2DM is often associated with other known risk factors, perhaps most notably dyslipidaemia (3,60,95), it continues to be a significant and independent cardiovascular risk factor, even after adjusting for age, smoking, BMI, and hypertension (96,97). Coronary artery calcification (CAC), which represents an independent risk factor of adverse outcomes and is correlated to total plaque burden, is higher amongst patients with T2DM than amongst healthy cohorts (96,98,99). A recent epidemiological analysis of 2682 middle aged Finish men, followed since the 1980s, highlighted fasting blood glucose (FBG) as having the highest hazard ratio (HR) for CAD development (60). The authors used a simple multiplicative survival model, which yielded a HR of 2.69 for diabetes (FBG ≥7.0 mmol/L) versus normoglycemia (FBG 5.6 mmol/L) (60). Similarly, there is estimated to be up to a 16% increase in cardiovascular events for every 1% increase in HbA1c (glycated haemoglobin) (96). There is evidence to suggest the CAD risk associated with T2DM is amplified in females (100). In a meta-analysis of 37 prospective cohort studies, women with T2DM were found to have a 50% higher risk of fatal CAD than men with T2DM (101).

2.1.3.5 Physical Inactivity and Sedentary Behaviour

Physical inactivity can be defined as not meeting current physical activity guidelines (102). The WHO recommended guidelines for adults is to undertake a minimum of 150 – 300 minute of moderate; or 75 – 150 minutes of vigorous activity (or equivalent combination of the two) per week (102). In this context moderate intensity would equate to between 3 and 6 Metabolic equivalents (METs), whilst vigorous activities would elicit ≥6 METs. Multiple large population-based studies have determined that physical inactivity is an independent risk factor for (1,103,104), and predictor of future CAD development (105). The link between physical activity, sedentarism, and CAD began to be elucidated between the 1950s and 1970s when Morris and colleagues (106,107) reported that middle aged men performing vigorous physical activity ≥2 days per week had one third the CAD risk of their physically inactive peers. In a prospective cohort study of 130,843 participants (free from CAD at entry) the rate of MI per 1000 person years was 1.71 for those achieving recommended physical activity, and 2.64 for those who did not (108). The risk from physical inactivity appears to be somewhat dose dependent, with those engaging in the least amount of moderate to vigorous activity having the highest risk (80). A recent systematic review and meta-analysis suggests there may be a 22% lower mortality rate associated with CAD for each 10 MET (task hours) increase in physical activity per week (109). Similarly a meta-analysis of 44 studies which includes >1.5 million participants shows an inverse association between moderate and vigorous physical activity and CVD mortality (110).

As with physical inactivity, sedentary behaviour can be categorised by MET energy expenditure, in this instance ≤1.5 whilst sitting, reclining or lying (102). Sedentary behaviour is now recognised as a distinct risk factor for CVD apart from physical inactivity (103). In contrast with physical activity, sedentary behaviour is positively, and not negatively related to CVD risk (111). An in crease in sedentary time is associated with a worsening of other known CAD risk factors (80). In 1953 Morris and colleagues published the results of a landmark study which showed that physically active bus conductors had a considerably lower incidence of CAD events (1.9) when compared to their seated and sedentary bus driver counterparts (2.7 per 1000) (107). More recent evidence indicates that clinical outcomes in patients with established CAD are worse with greater sedentary time (1). A prospective observational study recruiting >100,000 MI patients demonstrated a 62% greater incidence of mortality in those with 4-8 hours per day of sedentary activity, versus those with <4 hours per day (112). Similarly, a prospective study of women post-acute coronary syndrome (ACS)

indicates that each additional hour of sedentarism associates with a 9% greater mortality (113).

2.1.3.6 Overweight and Obesity

An increase in the availability of affordable, palatable, and calorie dense food sources, and a reduction in the physical demand of work have combine to ignite an obesity epidemic (80). Obesity, defined as a BMI equal to, or greater than 30 kg/m^2 is associated with multiple CAD risk factors, such as hypertension, T2DM, and dyslipidaemia (114). In 1995 the 27th Bethesda conference classed obesity as an independent risk factor for CVD (115). In 1996 results publishes as part of the Muscatine Heart Study demonstrated that obesity was strongly associated with coronary artery calcification as detected through computed tomography (CT) scan (116). Studies of obesity often include sub-groups of overweight (BMI 25 – 29.9 kg/m^2) as it has become ever more apparent over the last 50 years that both are associated with CAD (114). Increasing body mass seems to provide a spectrum within which there exists a positive linear relationship with CAD risk. Multivariate analysis results from a study of 13874 CAD patients undergoing coronary computed tomographic angiography (CCTA) show a significant ($P < 0.001$) positive association between BMI and all CAD (117). Furthermore, there was also a significant association between BMI and the number of diseased vessels and risk of MI (117). BMI should be interpreted with caution, especially in the presence of Asian ancestry, older adults and those with muscular physiques (80). In these instances and in cases of BMI <35 kg/m^2 it would be advisable to include a measure of waist circumference to increase sensitivity (80). Many studies have now suggested the apparent existence of what has been termed the obesity paradox, so called as a result of a paradoxical reduction in CAD mortality in obese patients (118). Studies using an array of adiposity measures, from BMI to body fat percentage and waist circumference have all reported these paradoxical findings (119). One suggested explanation for the paradox is the presence of confounding and unmeasured variables, such as genetic expression, which may result in an alternate CAD etiology in lean patients, potentially leading to a worse prognosis (119).

2.1.3.7 Ethnicity

The prevalence of CAD has proven to be variable amongst different ethnicities (120,121). Indeed, an established body of literature points to a disproportional burden of CAD morbidity and mortality amongst ethnic minorities (122,123). For example, South Asian men and women, typically defined as having ethnic heritage in India,

Pakistan, Bangladesh, Sri Lanka, Nepal, Bhutan and the Maldives, exhibit earlier CAD development, hospitalisation, and mortality compared to white counterparts (124,125). Data from the Coronary Artery Calcium Consortium showed that in a model adjusted for traditional risk factors, and with Whites as a reference, Black and Hispanic individuals had greater mortality risk, with sub-distribution hazard ratios of 3.4 and 2.5 respectively (126). However, coronary calcium scans following by electron-beam CT point to non-significant differences between Black men and women and White men and women (121). A recent UK based prospective cohort study of over 450,000 participants found a higher risk of CVD amongst Black and South Asian participants than amongst White participants, even after adjusting for age and sex (127). Nonetheless, when adjustments were made to the model to account for deprivation, the increase risk experienced by Black participants was attenuated (127). The variability in CAD risk associated with ethnicity has, by some, been attributed to persistent socio-economic as well as cultural differences (98). These differences are suggested to result in "risk factor clustering" (121). In the US, data from the Dallas Heart Study suggests the incidence of smoking, T2DM, and hypertension are significantly more common amongst Black Americans (121,128). Similarly, earlier evidence from the Atherosclerosis Risk in Communities (ARIC) Study showed that risk factor clustering, in this context referring to obesity, hypertension, diabetes, smoking, hypercholesterolemia, hypertriglyceridemia, and low HDL cholesterol, was considerably more prevalent amongst Black Americans than amongst White Americans (129). The contribution of risk factor clustering has also been suggested as an explanation for the increase risk of CAD in South Asian populations, with T2DM, dyslipidaemia, and physical inactivity all occurring with greater frequency and at an earlier age (124).

2.1.3.8 Sex

The most consistent sex-based differences in adult mortality rates are associated with CAD, which consistently results in higher mortality and risk for men (130). In general women typically tend to experience their first cardiac event 10 years after their male counterparts (131). Data preceding the advent and widespread use of medications for hypertension, dyslipidaemia, and hormone replacement, indicated that the male to female ratio (2.5 – 4.5) of mortality resulting from CAD was remarkedly similar across 52 nations, irrespective of the total CAD incidence (132). This apparent universal ratio was taken as an indicator of inherent male risk and female protection from CAD (130). One unfortunate consequence of this assumption has been the underestimation of

female CAD risk (133). Heart disease is in fact still the largest cause of female mortality globally, with one in ten deaths attributable to CAD (134,135). Moreover, in 2014 CAD claimed almost three times more female lives than breast cancer (135). Over the last three decades there has been an increase in MI in women aged 35 – 54, whilst similar aged men have experienced a decline (133).

The question of whether sex results in an independent predisposition to CAD remains a topic of some debate, with some attributing female risk to gender specific characteristics, such as vessel size, pregnancy and hormonal milieu (130,133,135), and male risk to a greater level shared risk factors (130). It has been assumed that oestrogen exposure in the first half of life may prevent CAD in women (133). Oestrogen has an impact on the regulation of many known CAD risks, such as inflammation, coagulation, vasodilation, and circulating lipids (133). Indeed, menopause is associated with an increased risk profile (133,136), whilst menopause occurring before the fourth decade of life (early menopause) is accompanied by a two year reduction in life expectancy (133,137). However, research into women receiving hormonal replacement therapy to counter menopausal decreases in oestrogen demonstrate no reduction in CAD risk (138). Another possible reason for the seeming disparity between male and female CAD risk is the deceleration of male risk past the age of 45 years (130). In 2011 Vaidya and colleagues looked at the census data from three different birth cohorts in the US and UK (139). From the data they determined that linear mortality rates from heart disease peaked in men by age 45, with shallowing rates were seen thereafter. In contrast there was a consistent linear increase in women, with no upsurge in risk post menopause (50 years). This led the authors to conclude that it was in fact the deceleration in male mortality post 45 years that explained the pattern of sex difference in risk (139).

2.1.3.9 Age

Age is a major risk factor for CAD, as, by definition, longer life allows for prolonged exposure to other known CAD risk factors (140,141). In the US it has been estimated that 10.9% of those over 45 years old have CAD, with this number increasing to 17% in those over 65 (142). Epidemiological evidence from the Framingham Heart Study indicates that age is more strongly associated with cardiac events than any other factor in men, whilst it is second only to hypertension in women (143). As mentioned in section 2.1.1 CAD is an inflammatory condition, and ageing is known to result in an increase in reactive oxygen species and pro-inflammatory compounds, such as,

interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), and c-reactive protein (CRP) (131). Additionally aging is associated with an increase in prevalence of hypertension, hyperlipidaemia, and diabetes, all of which are known to contribute to an increase in the risk of CAD (144).

2.1.3.10 Family History

Having a family history of CAD is itself a risk factor for CAD, particularly if the male relative with CAD was diagnosed before 55 or the female relative was diagnosed before 65 years of age (141). The risk associated with a family history of CAD has been reported to increase in relation to a greater number of diseased relatives (3). The mendelian inheritance of certain genetic disorders, such as hypercholesterolaemia (see section 2.1.3.2), has been associated with CAD development (145). In 2014 Cohen et al performed a subset analysis of 3185 participants from the Multi-Ethnic Study of Atherosclerosis cohort. The chosen participants had a zero CAC score at baseline and were followed-up for a median of 10 years. The results highlight an approximate 70% increase in CAD risk to those with family history of CAD versus those without (146). Furthermore, this disparity persisted despite of adjustment for age, gender, and ethnicity (146). CAD risk is multifactorial and the increased risk associated with family history of CAD is believed to stem not only from genetic predisposition but also heritability of conventional and environmental risk factors (147,148).

2.2 Clinical Manifestations of CAD

Due to the progressive and sometimes dynamic nature of its development CAD may remain asymptomatic and thus undiagnosed for many years. The pathophysiological mechanisms that underpin CAD (see section 2.1.1) do not present with clinical uniformity across those who are afflicted, with some experiencing chronic and some acute onset. In recent times guidelines have changed to reflect this and advocate two main categories of CAD, those being chronic coronary syndrome (CCS) and acute coronary syndrome (ACS) (4). Anyone presenting with signs or symptoms commonly associated with CAD, such as chest pain (radiating to the neck, jaw or left arm), dyspnoea, palpitations, nausea etc. should be administered with and ECG and have levels of troponin tested at first medical contact (149,150).

2.2.1 Acute Coronary Syndrome (ACS)

ACS covers a range of clinical presentations characterized by new or changing symptoms or signs, which may or may not be accompanied by alterations in a 12-lead ECG and may or may not involve a rise in cardiac troponin levels (149). Estimates

suggest that 7 million people are diagnosed with ACS every year (151). Following evaluation patients presenting with ACS might ultimately be diagnosed with either ST-elevation MI (STEMI), non-ST-elevation MI (NSTEMI) or unstable angina (149,151). Although unstable angina and NSTEMI are separate conditions, they are often considered together and homogenised under the classification of non-ST elevation ACS (NST-ACS). The proportion of ACS attributable to NST-ACS is estimated to be 70%, with the remainder diagnosed as having STEMI (151).

2.2.1.1 ST-Elevation Myocardial Infarction (STEMI)

The pathological definition of MI is myocardial cell death resulting from prolonged ischaemia (152). Clinical criteria for MI involves evidence of acute myocardial injury as detected by abnormal troponin levels in the presence of evidence of myocardial ischaemia (ECG) (152). STEMI are MI caused by acute thrombotic occlusion (complete or near complete) of epicardial coronary arteries, which result in transmural (full thickness of myocardium) ischaemia (153,154). In clinical terms a STEMI is diagnosed when there is a ≥2 mm elevation of the ST segment alongside prominent T-waves during ECG (155). Timely diagnosis and treatment of STEMI has been shown to reduce mortality, positively influence prognosis, and reduce duration of inpatient care (156).

2.2.1.2 Non-ST-Elevation Myocardial Infarction (NSTEMI)

Patients presenting with ACS in the absence of ST-elevation may instead have ST-depression (31.3%), T-wave inversion (11.7%), both together (15.7%), or neither (41.2%) (157). Normally, NSTEMI presents following the incomplete thrombotic occlusion of an epicardial coronary artery (151,158,159). ECG abnormalities in the T-wave or ST-segment are typically caused by myocyte injury which can usually be attributed to tissue hypoxia (160). Testing for elevated levels of cardiac troponin in systemic circulation has become mandatory for all patients presenting with NST-ACS (149,159). The ESC guidelines for the management of ACS also recommend that a secondary troponin measurement be taken 1-2 hours after the first (149). The change in concentrations between samples will inform the clinical decision-making process.

2.2.1.3 Unstable Angina

The presence of myocardial ischaemia at rest or during minimal exertion, absent of myocardial necrosis can be defined as unstable angina (149). In this context unstable angina can be seen as a transitionary condition resulting from atherosclerotic plaque disruption (161). Unstable angina has three clinical presentations, that is, at rest (characteristic angina symptoms for >20 minutes), new onset (≤2 months) of moderate

to severe angina (as per CCS grade II or III; see Table 3), and crescendo angina (increase in severity and duration of previous angina with reduced provocation) (4). The presenting symptoms and ECG features of unstable angina and NSTEMI are difficult to differentiate as they both often include chest pain and ST-segment depression with or without accompanying T-wave inversion on ECG (162). As a consequence the two diagnosis are often separated by the presence (NSTEMI) or absence (unstable angina) of significant and consistent elevations in the levels of the biomarker troponin (162).

2.2.2 Chronic Coronary syndrome (CCS)

CCS can be differentiated from ACS by the presence of disease stability and lack of non-ST-elevated MI (NSTEMI) and ST-elevated MI (STEMI) (163). The term CCS can be seen as an umbrella term that most commonly encompasses a variety of conditions, such as angina, new onset heart failure (HF), and patients with stabilised symptoms (symptomatic or asymptomatic) following ACS or revascularisation (4). The full range of conditions covered by the CCS classification is extensive and exceeds the scope of this review, therefore I will focus only on angina, its subclassification of stable angina and silent myocardial ischaemia.

2.2.2.1 Angina

The below is a passage written in 1772 by William Heberden. It stands today as likely one of the most articulate and poetic description of angina pectoris (angina).

> *« But there is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, which deserves to be mentioned more at length. The seat of it and the sense of strangling and anxiety with which it is attended, may make it not improperly be called angina pectoris. Those who are afflicted with it, are seized while they are walking (more especially if it be uphill, and soon after eating) with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life if it were to increase or to continue; but the moment they stand still, all this uneasiness vanishes. In all other respects, the patients are, at the beginning of this disorder, perfectly well, and in particular have no shortness of breath, from which it is totally different. It likewise*

very frequently extends from the breast to the middle of the left arm ». (164).

Angina is viewed as the most common clinical symptom of underlying CAD (165–167). Angina has been estimated to have a prevalence of 3-4% in UK adults, with over 20,000 new cases diagnosed each year (167). Following the initial assessment of presenting symptoms and clinical investigations angina may be partitioned into two main forms, which are termed 'stable' and 'unstable' (4).

2.2.2.1.1 Stable Angina

Angina is defined as 'stable' if symptomatic episodes are seen unchanging for 3-6 months (168). The primary cause of stable angina is myocardial ischemia, which typically arises from an imbalance between the oxygen demand of myocardium, and the supply it is provided (169). The underlying cause of ischaemia in most instances is flow limiting stenosis due to coronary plaque accumulation (168,169). Even in cases of advanced CAD the demand for, and supply of myocardial O_2 may be matched at rest. However, with an increase heart rate, either from physical or emotional stress comes an increase in demand which may outweigh the coronary capacity to supply ("*Those who are afflicted with it, are seized while they are walking (more especially if it be uphill, and soon after eating) with a painful and most disagreeable sensation in the breast*" (164)). Angina is often graded using the four stage Canadian Cardiovascular Society (CCS) system first proposed in 1976 (Table 3) (170).

Table 3. Canadian Cardiovascular Society angina grade system

Grade	Description
One	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation
Two	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions
Three	Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace
Four	Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest

Whilst angina has its origin in the myocardium it symptoms are only felt when signalling reaches the frontal cortex, if this does not occur angina can be considered 'silent' (165).

2.2.2.2 Silent Myocardial Ischaemia

Silent myocardial ischaemia can be defined in the presence of quantifiable ischaemia and absence of related symptoms (171–174). Quantification of ischaemia may be undertaken in a variety of ways, such as through ECG stress testing, ECG halter monitoring, nuclear imaging, stress echocardiography, and coronary catheterisation (174). It has been estimated that silent myocardial ischaemia may occur in 25-50% of people with CAD, and that for every episode of symptomatic ischaemia (angina) there are 20 silent episodes (174). In 1976 Froelicher and colleagues (175) reported performing ECG stress tests on 1390 asymptomatic men from the US Air Force. The authors identified positive stress test results in 111 (≈8%) cases, from which 34 (2.5%) were later found to have >50% coronary occlusions (171). Similar findings have more recently been reported by Thaulow et al (176) in the Oslo Ischemia study. The study recruited 2014 male office workers (age 40-59 years) between 1972 and 1975. ECG stress testing identified 115 (≈6%) patients as having signs of myocardial ischaemia, 105 of whom went on to undergo angiographic assessment. The results demonstrated that 69 of the 105 patients had >50% coronary stenosis in at least one vessel. Of the 69 patients with both positive ECG stress test and angiographically confirmed CAD, 50 patients reported being completely asymptomatic, which represents approximately 2.7% of the entire cohort.

2.2.3 Coronary Chronic Total Occlusion

Coronary chronic total occlusions (CTO) are a subdivision of CAD, exemplified by the mass accretion of atherosclerotic plaque, culminating in the absolute obstruction of blood flow through the vessel (Figure 2) (177). For a lesion to truly be classified as a CTO the atherosclerotic burden should adhere to certain criteria. Firstly, the antegrade flow in the occluded section of the vessel must generate a thrombolysis in myocardial infarction (TIMI) flow score of zero (178–182). Secondly, although the age of an occlusion can be difficult to establish, it should be estimated to be three months or older before being considered chronic (181,183).

Figure 2. Example of a flow limiting stenosis (top) and a chronic total occlusion (bottom)

CTOs are not an uncommon occurrence within CCS where retrograde blood supply is sufficient enough to adequately perfuse the distal myocardium at rest (184,185). Indeed, various studies have estimated that within a population of patients who have significant coronary artery disease on coronary angiography, approximately 35-52% will have at least one CTO (186,187). Somewhat unfortunately there is currently less consensus understanding on the pathophysiology of CTO lesion development, then there is expertise on resolving the problems posed by the (184). Whilst the majority of researchers will concede that the process is a function of plaque rupture, the mechanism separating this rupture from those resulting in acute coronary syndromes is less evident. It is believed that following the initial rupture CTO's undergo a process of remodelling and organization that includes the replacement of cholesterol and foam cells in the necrotic core with fibrocalcific material, contributing to the lesions enhanced structural stability (184,188). The exact relationship between lesion age, composition, and severity is unclear. Some evidence indicates a correlation between lesion age and its increased calcific and fibrous composition, whilst other findings suggest little to no relationship between composition or severity of stenosis (188).

2.2.3.1 Coronary Collateral Arteries

The topic of human coronary collateral vessels is covered in Chapter 4 and has been published in full elsewhere (189). Therefore, this section of the literature review will add some additional depth to the topic by focusing on proposed mechanisms of development and augmentation mentioned only briefly in the published work.

In summary, the coronary arteries do not, as was once believed, function as "terminal arteries" (190), they are instead interconnected by an extensive network of inter and intra-arterial anastomosis (Figure 3) (191,192).

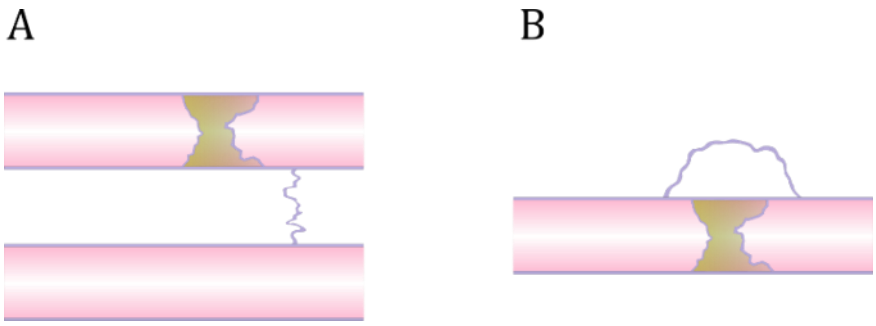

Figure 3. Example of both inter-arterial (A), and intra-arterial (B) collateral arteries

These anastomosis are believed to be remnants of a dense arterial network that develops during embryonic vasculogenesis (192). Subsequently, collateral arteries are present in those with, and without CAD (193,194).

Collateral arteries can, if sufficiently well developed, be visualised during coronary angiography, as a consequence angiography has historically been used to grade these vessels qualitatively, using scoring systems such as the Rentrop classification (195). Unfortunately, these scoring systems are limited by the special resolution of angiography, resulting in small diameter vessels (often imperceptible to the technology) not being acknowledged (196). The gold standard measure of collateral flow is now accepted to be the collateral flow index (CFI), which is the ratio of mean occlusive coronary pressure – central venous pressure, and mean aortic pressure – central venous pressure, all measured during a 1-minute balloon occlusion (197).

In the presence of CAD well developed collateral vessels have been shown to confer a 36% reduction in mortality risk when compared to less developed vessels (198). Angiographically visible collaterals have been associated with reduce infarct territory and less extensive microvascular damage in those suffering ST-elevation MI (STEMI) (199). Furthermore, in ¼-⅕ of healthy participants undergoing brief vascular occlusion, the presence of "recruitable" collaterals prevents signs of ischaemia during intracoronary ECG (194). Research suggests a CFI of >0.20-0.25 is required to cause such ischemic absence during occlusion (192).

Whilst their presence in healthy hearts has been established, their functional prevalence increases with the severity of CAD, being highest in those with CTO's (189,192). Early investigations during the 1950s by Fulton (1956) (200) and Zoll et al (1951) (201), revealed that whilst collaterals were evident in 63% of hearts with significant CAD, they were even more prevalent (95%) in the presence of a CTO.

2.2.3.1.1 Ischaemic signalling and collateral development (Angiogenesis)

The two physiological mechanisms most commonly proposed to be responsible for postnatal collateral development are angiogenesis and arteriogenesis. Angiogenesis refers to the *de novo* formation of capillaries from pre-existing vessels (190,192). The resulting capillaries are endothelial cell structures devoid of smooth muscle or additional stabilizing wall assemblies (202). Due to the structural composition of these vessels they are fragile and prone to rupture (203). The primary trigger for angiogenesis in the context of arterial occlusion is tissue hypoxia (204). Hypoxic conditions result in the expression of numerous cytokins, chemokines and growth factors; such as, hypoxia-inducible factor 1-α (HIF1-α) and vascular endothelial growth factor (VEGF) (190,192,204). Whilst angiogenesis likely does occur in ischaemic myocardium, research suggest it is not the primary cause of collateral artery growth (203). As previously mentioned, collateral arteries have been extensively observed to varying degrees in the hearts of heathy individuals, which should preclude any significant myocardial ischaemia. Furthermore, maximal collateral adaption is attributable to slowly progressing stenosis that culminate in eventual chronic occlusion, which produce only minimal levels of ischaemia (205). The complex structural changes that take place during angiogenesis take time. Angiogenesis therefore cannot not be expected to occur rapidly enough to prevent signs of ischaemia during sudden coronary occlusion. However, research suggests that ST-segment changes indicative of myocardial ischaemia are absent in 20% of healthy participants undergoing brief balloon occlusion of a coronary artery (194). This resilience to brief occlusions in healthy participants is likely due to the presence of pre-existing arteriolar bypasses capable of accommodating sufficient flow. Capillaries are reported by numerous investigations to have a luminal diameter of between 4 and 9 μm, whilst native coronary arteries are reported to be between 1.9 ± 0.4 – 4.5 ± 0.5 mm (206). Therefore, the sheer volume of capillary growth that would be required to adequately perfuse a myocardial region at risk after CTO would likely exceed the volume of the tissue at risk (207).

2.2.3.1.2 Collateral development (Arteriogenesis)

The main epicardial arteries (coronary arteries) function to deliver oxygen and nutrients to the myocardium (208). During foetal development the immature coronary plexus (a complex network of small thin vessels) migrates towards, and eventually connects with the aorta (209). After this connection is made the mechanical forces resulting from the influx of coronary blood flow (Shear stress, circumferential wall

stress) drive arterial remodelling that results in the development of functional coronary arteries (210). Once fully formed the coronary arteries provide the most efficient path for coronary flow, allowing maximal perfusion of myocardium (211). Under pathological conditions in which a coronary artery becomes stenosed, and eventually occluded, the pressure in the distal portion of the vessel will be reduced, thus establishing a pressure gradient across the site of occlusion (189). If a "dormant" anastomosis (left over from the coronary plexus), is positioned such that it terminates at the low-pressure segment, and originates at a higher-pressure segment, it will, in accordance with Ohm's law, be forced to accommodate an increase measure of coronary flow.

$$Flow = \frac{\Delta\, Pressure}{Resistance}$$

Concomitant with an increase in flow through the anastamosis, is an increase in the mechanical stresses acting upon the endothelium (212,213). These mechanical stresses; namely, fluid shear stress (FSS) and circumferential wall stress (CWS), provide the primary stimulus for the anastomosis to remodel into a more robust and functional collateral artery (213). Initially, these pre-existing anastamosis are microvascular in size (30–50 μm), comprising a lining of endothelial cells bordered by an elastic lamina encased in one to two layers of smooth muscle cells (SMC's) (207,214). The increasing levels of FSS cause the intimal endothelial layer of the collateral arteriole to become "activated". Once activated the vessel passes through four stages of vascular remodelling that includes an increase in vascular permeability, digestion of extracellular scaffolding, reconstruction of the SMC coat (along with production of a larger vascular scaffolding), and pruning of additional collateral vessels (203,215,216). After as little as 7 days a microvascular arteriole, can be repurposed into a collateral artery that is up to 20 fold larger and more robust (Figure 4) (207,217).

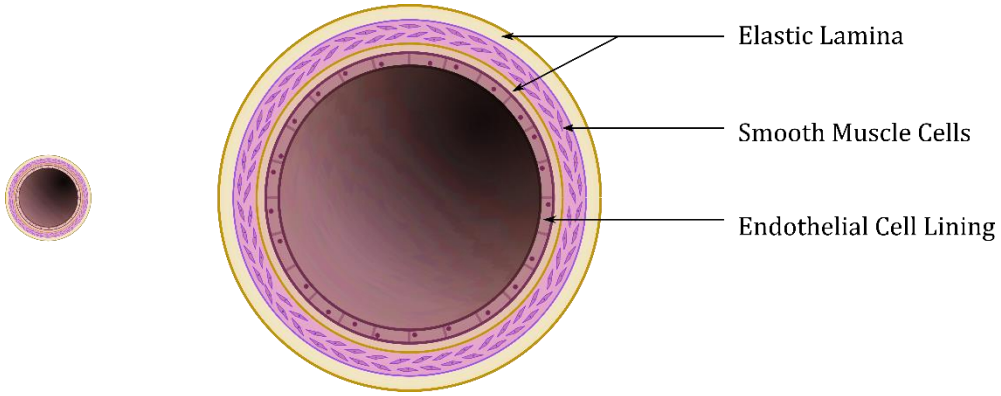

Figure 4. Comparison of an arteriole before (left) and after (right - collateral) arteriogenesis

This collateral development (termed Arteriogenesis) is very significant, as according to Poiseuille's law even minor increase in vessel diameter can result in large increases in flow (218).

$$Q = \frac{\pi P r^4}{8\eta l}$$

(Q = Flow, P = Pressure, r = radius, η = Viscosity, l = Length).

For example, if the pressure gradient, blood viscosity, and vessel length are taken to be constant, a mere 25% increase in luminal diameter after remodelling, would yield an approximate 144% increase in flow. However, in vivo all other variables in the equation are not constant; for example FSS falls to the third power of the collateral radius (219). Therefore, as the diameter of the collateral vessel increases the pressure `gradient "normalises" to a nadir, at which point the threshold mechanical stimulus for growth is no longer sustained, and thus luminal growth ceases (219). Research suggest that under usual conditions there is a physiological limit (30-40% native vessel conductance) to the amount of flow that collateral arteries can enlarge to accommodate (205). This threshold is sufficient enough to restore resting conductance but not dilatory reserve (219). Therefore, whilst this level of development may help to reduce, or even eliminate myocardial ischaemia at rest, it may not be adequate to maintain perfusion above resting levels (220).

2.2.3.1.2.1 Hind Limb Model of Arteriogenesis

The inability of collateral arteries to develop beyond this proposed threshold was hypothesised to result from the premature restoration of proximal pressure, and thus the reduction of FSS (219). To test this hypothesis Pipp and colleagues (2004) (213)

added an arteriovenous “shunt” to the standard hind limb experiment, in which the femoral artery of an animal (usually rabbit or dog) is surgically occluded to induce collateral development (Figure 5). In doing so, the pressure in the distal section of the occluded artery is not permitted to increase past the threshold at which FSS is sufficiently reduced. Maintaining an elevated level of FSS across the collateral network for one week, resulted in a 2.3 fold increase in maximal collateral conductance when compared to the standard ligature only model (213). The authors estimated that such marked increases above normal development may be sufficient to equal the maximal conductance of the native (unobstructed) vessel (213).

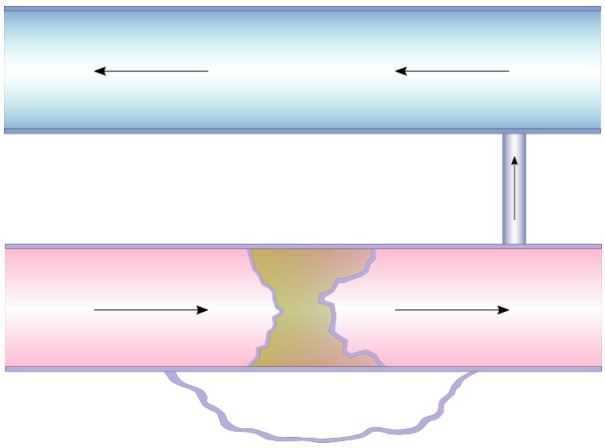

Figure 5. Example of the arteriovenous shunt used to modify the hind limb model of arteriogenesis

2.2.3.1.2.2 Pharmacological Arteriogenesis

The ability to stimulate arteriogenesis is an enticing proposition, especially when considering the ≈20% of CAD patients for whom revascularisation is not a viable option (221). As highlighted above collateral arteries do not passively dilate to accommodate increased coronary flow; instead, they remodel by active cellular proliferation (222). The biochemical cascade that ensues after activation of the collateral endothelium, has given rise to the field of pharmacologically enhanced arteriogenesis (222). Numerous growth factors and signalling molecules have been investigated as potential mono- and combination therapies to augment arteriogenesis (221). These therapies have been well reviewed by various authors (221–224) and thus the topic will only be briefly summarised in this section.

Following the mechanical stimulation of arteriogenesis by FSS, the microvascular collateral undergoes substantial remodelling. Research has demonstrated that this is largely instigated by monocyte infiltration and differentiation (224,225). Therapeutic

targeting of monocyte adherence has therefore formed the cornerstone of clinical arteriogenic research, with binding molecules such as monocyte chemoattractant protein-1 (MCP1), intracellular adhesion molecule-1 (ICAM-1) and vascular cellular adhesion molecule-1 (VCAM-1) studied extensively. After migrating into the perivascular space monocytes generate growth factors that further the proliferative cascade, leading researchers to investigate numerous growth factors; such as, fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) (221,222).

Whilst this field of research has found success in many animal models (221), transfer to humans has proven less successful. For instance, the VIVA (Vascular Endothelial Growth Factor in Ischaemia for Vascular Angiogenesis) trial examined the effects of administering VEGF in a placebo-controlled trial of n=178 stable CAD patients. The studies primary endpoint was exercise treadmill time (ETT) measured 60 days from baseline. Upon completion of the study no significant differences in ETT between groups following treatment were found, moreover ETT had slightly increase in the placebo group (+48 versus +30 seconds) (226). Similarly, the multicentre, randomized, double-blind, placebo-controlled FIRST (FGF Initiating RevaScularization) trial, sought to measure the effects of a single intra-coronary bolus of fibroblast growth factor-2 (FGF2) in n=337 CAD patients. Again the primary outcome was ETT measured from baseline to 60 days and again there was no significant difference between treatment and placebo groups (all groups increase ETT) (227).

These finding are perhaps further proof of the primary role FSS plays in collateral development. Providing a biochemical milieu that is pro-arteriogenic should perhaps only be considered beneficial in the presence of increased FSS.

Pharmacological arteriogenesis research is further hampered by what has been termed the “Janus Phenomenon” (228). This phenomena describes the seemingly dichotomous ability of some compounds (growth factors and adhesion molecules) to simultaneously contribute to arterogenesis and arteriosclerosis (228). For example, Zbinden et al (2005) (229) were forced to prematurely terminate a double-blind placebo control trial, in which n=7 stable CAD patients were receiving subcutaneous granulocyte-macrophage colony-stimulating factor (GM-CSF) injections. After only 12 days of the study two members of the treatment group had experienced an acute coronary syndrome (1 = LAD occlusion; 1= RCA occlusion) versus none in the placebo group. The researchers suggested in their conclusions that this could be a by-product of GM_CSF

increasing MCP-1 (229). Their rational for this suggestion stems from animal research by van Royen and colleagues (2003) (230), in which mice infused with MCP-1 exhibited an increase in plaque area and a decrease in plaque SMCs versus control. These findings are not surprising given the processes of atherosclerosis outlines in section 2.3.1.

2.2.3.1.2.3 Enhanced External Counter-Pulsation (EECP) and Arteriogenesis

As described in section 2.2.3.1.2 the increased luminal diameter of collateral arteries following coronary occlusion is believed to prematurely halt arteriogenesis by reducing FSS. Experimental research has demonstrated that if FSS is reintroduced (through arteriovenous shunt); collateral arteries are capable of supporting significantly larger levels of coronary blood flow. One possible method of restoring the pressure gradient, and thus FSS, is enhanced external counterpulsation (EECP). Enhanced External Counterpulsation (EECP) is a non-invasive procedure used in the treatment of refractory angina (231). During EECP three sets of inflatable pneumatic cuffs are placed around the lower limbs (Figure 6), the cuffs are then sequentially inflated to an external hydraulic pressure of 300 mmHg during diastole (gated by ECG), before being rapidly deflated prior to systole (232).

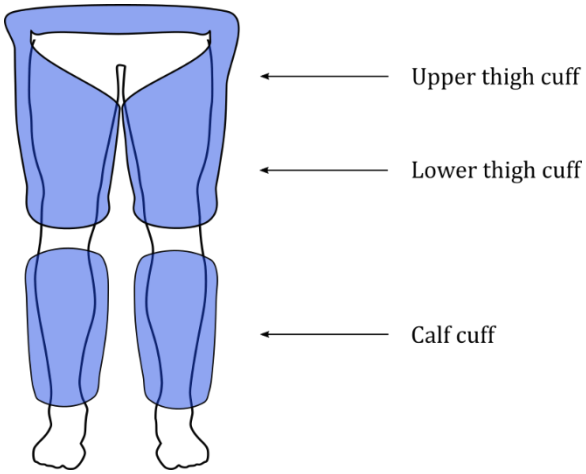

Figure 6. Schematic representation of EECP cuff placement

This cuff inflation augments diastolic blood pressure and cardiac output, increasing pressure across all branches of the coronary tree (233). In principle, this transiently replicates the changes in physical forces (FSS) that are usually localised to collaterals terminating distal to an arterial stenosis. Clinical studies have demonstrated that EECP does improve myocardial perfusion in CAD patients (234).

In a cohort of 10 Patients referred for diagnostic coronary angiography, intra-arterial diastolic blood pressure was monitored during EECP cuff inflation, and was found to increase by 92% from baseline (71±10 mmHg to 136±22 mmHg / p<0.0001) (235). This translated to a 16% increase in mean intracoronary pressure (88±9 to 102±16 mmHg) and resulted in a 150% increase in peak intracoronary diastolic blood velocity (18±7 cm/s to 45±14cm/s, p=0.0004) (235). In a randomised controlled trial EECP significantly increased collateral flow, as measured by the gold standard collateral flow index (CFI) in a group of CAD patients (p=0.006), this improvement was not observed in a group receiving sham EECP treatment (p=0.14) (236). Although EECP has shown promise in treating CAD it is not suitable for every patient. EECP is contraindicated in the presence of congestive heart failure, peripheral arterial disease, atrial fibrillation, and frequent ventricular ectopic heart beats (237). Other factors limiting the utility of EECP are the bruising and discomfort caused by the high pressure cuff inflations (237), the amount of time needed to undergo treatment (one hour attendance at the clinic five days a week for 7 weeks), and the per patient cost, estimated to be £4347.0 per standard 35 hour treatment block (238).

2.2.3.1.2.4 Resistance Exercise and Diastolic Blood Pressure

The haemodynamic response to resistance exercise was illustrated by MacDougall et al in 1985. The authors recruited n=5 healthy male bodybuilders (22-28 years of age) to undertake resistance exercises whilst cannulated with a pressure transducer (brachial artery). Participants were required to perform single arm biceps curls and overhead presses (both with the non-catheterised arm) for the upper body, and uni and bilateral seated leg presses for the lower body. Exercises were performed to concentric failure at successive intensities corresponding to 80, 90, 95 and 100% of the maximal weight achieved prior to testing (1RM). Each participant was permitted 2 minutes of rest between efforts. The maximal blood pressure recorded during testing was 480/350 mmHg achieved during the bilateral leg press at 90% of 1RM. The authors reported a consistent haemodynamic pattern across all participants, namely an extreme elevation in systolic and diastolic pressure in response to lifting the weight, followed by a rapid reduction to near baseline values when the weight is lowered. The peak elevation then becomes progressively larger through each subsequent repetition of the set, with the highest values recorded during the final repetition. Following completion of the set both systolic and diastolic values immediately fall below those recorded prior to exercise, returning to normal after approximately 10 second.

Whilst this research is informative and data was collected using the gold standard measure of arterial pressure, the findings should be interpreted with caution before being extrapolated to the wider population. The authors recruited a small, specific and homogenous cohort with substantial experience of resistance training. Experienced weightlifters will often briefly perform the Valsalva manoeuvre during resistance exercise, especially when lifting loads in excess of 80% 1RM, or when lifting lighter loads to concentric failure (240). The Valsalva manoeuvre has been shown to dramatically increase the inter-arterial pressure when preforming resistance exercise (leg press) at 80 and 100% 1RM (198/175-311/284 & 178/156-267/239 mmHg respectively) in a similar but not identical cohort (241). MacDougall and colleagues (1985) reported observing no obvious signs of Valsalva unless participants were performing the lifts at 1RM intensity, however they did not explicitly coach against this breathing technique and therefore its occurrence cannot be ruled out.

The pattern of rapid increase and subsequent decrease in blood pressure with each repetition during resistance exercises renders standard manual and digital sphygmomanometers obsolete. As previously mentioned, the gold standard measure of beat-to-beat arterial pressure is cannulation (242), however the invention of finger photo-plethysmography machines by Wesseling and colleagues in the early 1980s has permitted the non-invasive measure of beat-to-beat arterial pressure in clinical and research environments (242).

In research by Featherstone and colleagues (1993) (1) 12 men with stable CAD performed RE (bench press, shoulder press, biceps curl, quadriceps extension) for maximal repetitions using 40, 60, 80 and 100% of their one repetition maximum weight. The researchers non-invasively observed diastolic blood pressures as high as 138 mmHg, however values were predominantly below 126 mmHg (243). In contrast to the indirect measure of diastolic blood pressure by Featherstone et al (1993), research using intra-arterial pressure measures after cannulation in healthy cohorts report figures as high as 156 mmHg during RE (244). These values are comparable to the increases observed during EECP (136±22 mmHg) and are likely to provide similar increases in FSS.

Resistance exercise has also been shown to result in a lower heart rate than traditional AE (245).Resistance exercises have been shown to transiently and significantly increase diastolic blood pressure (239,244,246). When viewed in combination, these two factors could indicate that RE has the potential to influence perfusion pressure and

time more favourably than does traditional AE (Figure 9). It is therefore theorised that RE has the potential to replicate the therapeutic arteriogenic effects of EECP.

2.2.3.1.2.5 Resistance exercise and Arteriogenesis

Resistance exercise (RE) can be defined as the structured contraction of one or more skeletal muscles with the aim of overcoming, balancing or slowing the effects of an external resistance, such as; gravity, elastic bands, free weights or cable pulley machines. At the time of writing there is only one study that has investigated the acute effects of RE on collateral arteries, with no research into possible longer-term outcomes.

Lin and colleagues (2012) recruited 65 single vessel CAD patients undergoing PCI, randomly allocating them to either an isometric exercise (n=33), or sedentary group (n=32). CFI was measured pre and post 1-minute balloon occlusion at the site of stenosis. During occlusion, the exercise group performed isometric handgrip exercise at 50% maximal voluntary contraction, whilst the sedentary group remained still. CFI post occlusion was significantly greater than pre-occlusion in the isometric exercise group (0.16 – 0.20; p=0.01), whilst there was no difference in the sedentary group (0.14 – 0.15). The researchers did not report blood pressure or heart rate during the RE, however previous results suggest this exercise modality will have increased both (248).

2.3 Front line detection of CAD

2.3.1.1 Troponin

The gold-standard biomarker for myocardial damage is troponin (249). When there is a suspicion of unstable or acute CAD, isoforms for either troponin T (TnT) or troponin I (TnI) should be measured (4). TnT and TnI, are key components of myocytes contractile apparatus and are predominantly expressed in the heart. (152). However, elevated TnT levels can occur with skeletal muscle damage, a phenomenon not observed with TnI (152). In recent decades high sensitivity assays have been developed that can now detect low levels of troponin even in those patients with stable CAD (80). A raise and/or fall of troponin, with at least one value >99th percentile is seen as clinical criteria for diagnosing MI (152). Although troponin has proven to be a useful prognosticator, it is not yet a recognised tool for CAD diagnosis (4).

2.3.1.2 Electrocardiogram (ECG)

As previously mentioned (section - 2.2) ECG is recommended in the first line assessment of suspected CAD, and has been a mainstay in this regard for decades (4,149,150,250). ECG traces are used to detect abnormal repolarisation patterns associated with ischaemia, including but not limited to, ST-segment elevation or depression, wide or deep Q-waves, biphasic, flat, inverted, and/or hyperacute T-waves (4,80,251). Current guidelines rely primarily on changes in the amplitude of the ST-segment to detect and classify MI (covered in more detail in sections 2.2.1.1 and 2.2.1.2) (152). However, research suggests that the sensitivity and specificity of ST-segment changes can vary substantially (250). In a meta-analysis pooling over 24,000 patients the reported sensitivity and specificity of ECG for the detection of CAD was reported to be 68% and 77% respectively (252).

2.3.2 Angiography

The first recorded coronary angiogram was performed in 1958, since then it has become the gold-standard for diagnosing CAD (253,254). It is estimated that 250,000 coronary angiograms are performed annually in the UK (254). However, in spite of its wide spread use, coronary angiography has multiple limitations, such as its invasive nature, two dimensional anatomical nature, the operators technical proficiency, the patients anatomical presentation, and the subjective nature of lesion classification (253,254). In recent years, technology and techniques have advanced to the point where the ESC now recommends computational tomography coronary angiography (CTCA) where possible (4). CTCA is a far less invasive alternative to traditional coronary angiography. During CTCA the patient has a contrast dye injected intravenously before undergoing computed tomography. The resulting data is used to generate a three-dimensional rendering of the coronary arteries, which, when coupled with the laws of fluid dynamics can be used to generate virtual measures of blood flow, such as fractional flow reserve (FFR) (254).

2.3.3 ECG Stress test

ECG stress testing was established around the principle that exercise, or pharmacological stimulation where exercise is not possible, increases myocardial oxygen demand. In the presence of flow limiting stenosis, this increase demand may not be met, and thus myocardium perfused by this stenotic lesion may incur ischaemia that is evident in the pattern of repolarisation (255). The first description of transient repolarisation abnormalities (T-wave and ST-segment changes) during exercise is often credited to Fiel and Seigal in 1928 (256). In 1941, Masters and Jaffe combined

ECG with the standardised Master's two step exercise test to elicit ECG changes (257). However, this was a demanding test, requiring the patient to complete 30 steps up a nine-inch step in a three-minute window. Due to the demanding nature of the test, most people gravitated to the alternative treadmill protocol proposed by Bruce and colleagues in 1956 (258), which is to this day still one of the most commonly cited protocols in the field of clinical exercise testing (257). The sensitivity and specificity of ECG stress testing in the identification of obstructive CAD has been reported extensively in the literature (252,255,256,259–262). The values reported are not consistent, but are reported to range from 58 – 81% (259,260) for sensitivity, and – 84% (29,260) for specificity. It is now widely considered that ECG stress testing in isolation is inferior to ECG stress testing in combination with medical imaging, or indeed with medical imaging alone, either through CTCA (see section 2.3.2), stress echocardiography, or single-photon emission computerised tomography (SPECT) (256,260). Moreover, Belardinelli and colleagues (29) demonstrated that, when using a two-variable model consisting of O_2Pulse and $\Delta VO_2/\Delta$ work-rate, CPET could provide greater sensitivity (48 – 88%) and specificity (75 – 98%) than ECG stress testing in the identification of myocardial ischaemia.

2.4 Alternative Testing

2.4.1 Cardiopulmonary Exercise Test (CPET)

Cardiopulmonary exercise testing, commonly known as CPET, facilitates the non-invasive evaluation of the integrated cardiac, respiratory, and skeletal muscle response to ramped incremental exercise (23,263). During CPET, patients pedal a stationary cycle ergometer whilst wearing a respiratory face mask which is connected to a metabolic cart. This configuration allows for the breath-by-breath analysis of oxygen utilisation (VO_2), carbon dioxide production (VCO_2), and minute ventilation (VE). CPETs are usually ramped and incremental in nature, meaning that the load on the ergometer increases gradually over the course of each minute. In clinical populations the ramp increments are usual applied between 5 and 15 Watts per minute, with tests lasting 8-12 minutes. Tests are usually taken to volitional exhaustion, unless they are stopped prematurely due to the development of clinical symptoms (264).

Over the last two decades evidence for the diagnostic and prognostic use of CPET in CAD has increased substantially (22,27–30,265–275,275–287). The basis of its use centres around the Fick principle, which states that;

$$\dot{V}O_2 = Q \times a - vO_{2diff}$$

With Q representing cardiac output and a-vO_{2diff} denoting the arteriovenous oxygen difference (275,288). By rearranging the equation, and supplementing cardiac output with the product of stroke volume and heart rate, O_2Pulse can be used as a surrogate for stroke volume (289). The O_2Pulse exhibits a linear increase in response to graded exercise in healthy cohorts (290). This is because O_2Pulse is the product of both heart rate and a-vO_{2diff}, and, whilst stroke volume usually plateaus around mid-exercise in graded CPET, a-vO_{2diff} increases linearly to peak exercise (291). The result is a linear, or curvilinear morphology when O_2Pulse is expressed against work-rate or time. However, a premature flattening or decline in the slope of O_2Pulse has been proposed to represent left ventricular wall motion abnormality, secondary to myocardial ischaemia (27,29,30). Moreover, when the ischaemic threshold is surpassed, the rate of VO_2 may be impaired, which can manifest as a decrease in the $\Delta VO_2/\Delta$ work-rate slope (290). A sudden increase in heart rate above the ischaemic threshold appears to be an innate mechanisms to counter the reduction in cardiac output, and has been reported to be a useful diagnostic tool for CAD (277,292). Indeed, two of the three above mentioned variables, O_2Pulse flattening and $\Delta VO_2/\Delta$ work-rate slope, are included in both the original 2012 (293), and updated 2016 versions of the (294) joint EACPR and AHA scientific statements universal reporting form for CPET data.

2.4.1.1 CPET markers of CAD and Myocardial Ischaemia

O_2Pulse is perhaps the most studied variable related to myocardial ischaemia collected during CPET. The first report of an abnormal O_2Pulse morphology during exercise came from Patterson and Remole in 1981 (295). The authors compared the O_2Pulse response of CAD patients to healthy controls. They reported that in some patients with CAD the O_2Pulse reduced toward the end of exercise to a value approaching that at the beginning of the test.

The first study to use O_2pulse slope morphology in the identification of left ventricular dysfunction was performed by Klainman and colleagues in 2002 (296). The authors recruited 46 patients with CAD (n=39 male; mean age 59.2), each of whom performed CPET and multi-gated equilibrium 99mTc radionuclide cineangiography (MUGA) to measure left ventricular (LV) ejection fraction (LVEF) at rest and during exercise. Since this was the first study to investigate the O_2Pulse slope morphology, it was by default the first to rate the slope categorically. The authors graded the O_2Pulse curve during CPET on a 10-point scoring system; as either normal (10-points), normal shape but low values (8-points), flat curve with low values (5-points), or descending curve (3-points).

Results of the MUGA were also ranked according to the degree of ischaemia, as either: normal diastolic function (control), mild-ischaemia, LV dysfunction, and significant ischaemia with systolic dysfunction. Correlation analysis yielded a Pearson correlation coefficient of r=-0.89, which was accompanied by a Fisher's exact test of p <0.001.

To date the most cited work in the field of O_2Pulse morphology (2023 = 178 citations) is that of Belardinelli and colleagues in 2003 (29). The authors sought to identify the variables from CPET that were most predictive of myocardial ischaemia. They prospectively recruited 202 (173 men; mean age 55.7 ± 10.8 years) patients with CAD to undertake (ECG) CPET with myocardial scintigraphy. The CPET parameters were compared against a group of healthy controls (n=196; 172 men; mean age 57.2 ± 12). The results of ECG were used to sub-divide those with CAD into an ischaemic (n=62) and non-ischaemic (n=140) group. Similarly, myocardial scintigraphy results were grouped according to the summed difference score (SDS) as no perfusion defects (n=62) or ≥1 perfusion defect (n=140). Those with perfusion defects were further subdivided according to severity (mild = 29; moderate = 52; severe = 59). The authors assessed the following CPET parameters for their use in identifying myocardial ischaemia; peak ventilation (VE_{peak}), peak oxygen utilisation (VO_{2peak}), ventilatory anaerobic threshold (VT_1), end-tidal partial pressure of oxygen (PO_2) and carbon dioxide (PCO_2), ventilatory equivalents (VE/VO_2 & VE/VCO_2) taken at VT_1 and VO_{2peak}, peak respiratory exchange ratio (RER), the ratio of dead space to tidal volume, rest and peak O_2Pulse, and the $\Delta VO_2/\Delta$ work-rate slope. Logistic regression analysis, with scintigraphy results as the dependent variable, identified O_2Pulse flattening duration (p<0.001) and $\Delta VO_2/\Delta$ work-rate slope (p = 0.0001) from the point of O_2Pulse flattening as significant predictors of a positive scintigraphy. The beta coefficient for O_2Pulse flattening duration was $\beta = 0.02$, indicating that the longer the flattening duration the greater the likelihood of ischaemia. Conversely, the $\Delta VO_2/\Delta$ work-rate slope had a negative beta value ($\beta = -0.54$), suggesting that shallower slope was more likely to indicate ischaemia. Subsequent receiver operating characteristics (ROC) curve analysis yielded an area under the curve (AUC) of 0.83. When compared to standard ECG stress testing the two variable model had greater sensitivity (87% Vs. 46%) and specificity (74% Vs. 66%), as confirmed by myocardial scintigraphy.

The early research into O_2Pulse morphology and myocardial ischemia, exemplified by the aforementioned studies, represents the genesis of the field. These studies highlight the potential of O_2Pulse analysis as a diagnostic tool to detect and differentiate the

degree of myocardial ischemia, thus contributing to its future use in clinical settings. An exhaustive review of each subsequent study in this rapidly expanding field is beyond the scope of this literature review. Therefore, Table 4 has been compiled to highlight the key findings and methodological differences in the available literature.

Table 4. Research relating to the use of CPET variables in detecting and quantifying the degree of CAD induced myocardial ischaemia

Author & Year	Aims	Population	Imaging	Medication	Binary or Categorical Abnormal Slope Identification	Variables of Interest Reported	Results
Contini et al., 2006 (297).	Report the CPET results of a patient with critical right coronary lesion.	Referred for exercise testing due to chest pain during physical activity. 54-year-old male (BMI 31.1).	MDCT-CA	No medication reported.	Binary: defined as abnormal due to early plateau.	$\Delta VO_2/\Delta$work-rate, O_2Pulse curve, and $\Delta HR/\Delta$work-rate	No ECG changes but abnormal $\Delta VO_2/\Delta$work-rate and O_2Pulse morphologies which coincided with a flattening of the $\Delta HR/\Delta$work-rate. Subsequent MDCT-CA revealed critical stenosis to the mid portion of the right coronary artery. Following PCI with stent CPET was repeated and all variables exhibited normal linear progression.
Bussotti et al., 2006 (274).	Determine CPET pattern of ischaemia.	Patients without angina symptoms but with ST-segment changes during exercise. n=48. Healthy age and sex matched controls. n=35.	Coronary Angiography	No medication reported.	Binary; inflection point taken as appearance of ST-segment changes.	$\Delta VO_2/\Delta$work-rate and O_2Pulse	$\Delta VO_2/\Delta$work-rate slope showed sig flattening above VT_1 in those with significant lesions and not in those with nonsignificant lesions or controls (p<0.01). $\Delta VO_2/\Delta$work-rate slope was sig flattened above the ischaemic threshold in those with significant coronary lesions (p<0.01).
Munhoz et al., 2007 (298).	Compare O_2Pulse response using treadmill CPET in those with and without myocardial ischaemia.	Patients referred for exercise myocardial perfusion scintigraphy. n=87.	Myocardial Perfusion Scintigraphy	Medications withheld for ≥3 days prior to testing.	Slope not analysed.	O_2Pulse	O_2Pulse taken at 25, 50, 75 and 100% of PCET were not significantly different in those with (n=31) and without (n=56) perfusion defects.
Inbar et al., 2008 (299).	Determine whether PCI alters CPET variables in those with obstructive CAD.	Patients referred for PCI due to results suggestive of myocardial ischaemia. n=14.	Coronary Angiography	Nitrates (24 hours), calcium-channel blockers (48 hours), and beta-blockers (5 days) stopped before testing.	Categorical: 10-point system as normal, low peak, flat, down sloping.	O_2Pulse	In those with successful PCI peak O_2Pulse and O_2Pulse slope category were all significantly improved (p<0.005).
Chaudhry et al., 2009 (27).	Demonstrate the potential value of CPET to detect macro and microvascular ischaemia.	Asymptomatic 49-year-old male fire fighter (healthy). 68-year-old female with peripheral arterial disease patient with dyslipidaemia and hypertension (CAD).	Coronary Angiography	Medications included valsartan, hydrochlorothiazide, rosuvastatin, ezetimibe, niacin, and venlafaxine. Medication was not reportedly stopped.	Binary: defined as abnormal due to early inflection.	$\Delta VO_2/\Delta$work-rate, O_2Pulse curve, and HR	Abnormal CPET response (inflection) in the patient with CAD but with no ST-segment changes. Subsequent angiography revealed a critical (>95%) stenosis in the right coronary artery.

Chaudhry et al., 2010 (28).	Track the progression of suspected ischaemia through repeated CPET.	Asymptomatic 36-year-old male with strong family history of premature CAD (BMI 27.8).	None	Test one = no medication Test three = atorvastatin and niacin.	Binary: defined as abnormal due to early inflection.	$\Delta VO_2/\Delta$work-rate, O_2Pulse curve, and HR	The patient performed three CPETs over the course of 3.3 years. The severity of abnormality in the $\Delta VO_2/\Delta$work-rate, O_2Pulse slope, and HR during CPET increased between test one and two. More aggressive medical therapy commenced after test two (atorvastatin and niacin). CPET three was completed wit no inflection or flattening in $\Delta VO_2/\Delta$work-rate, O_2Pulse slope, or HR.
Chaudhry et al., 2011 (276).	Track the CPET response in suspected microvascular ischaemia before and after anti-ischaemic therapy.	Symptomatic 59-year-old female with hypertension, exertional chest pain and dyspnoea and ST-segment changes.	Coronary Angiography, Echocardiography, Myocardial Scintigraphy	Atenolol, oestrogen, and aspirin. Started ranolazine after CPET one.	Binary: defined as abnormal due to early inflection.	$\Delta VO_2/\Delta$work-rate, O_2Pulse curve, and HR	CPET were repeated 3 weeks apart. During test one the $\Delta VO_2/\Delta$work-rate, O_2Pulse, and HR were all characteristically abnormal and suggestive of myocardial ischaemia. Subsequent imaging revealed no evidence of flow limiting stenosis and no structural disease. The patient was started on ranolazine, which was taken for three weeks prior to CPET two. A rightward shift in O_2Pulse inflection, $\Delta VO_2/\Delta$work-rate, HR and ST-depression were all observed during CPET two.
Zimarino et al., 2013 (300).	Compare ST/HR hysteresis to CPET variables for identifying myocardial ischaemia.	Symptomatic patients referred for ECG stress testing. n=56.	Myocardial Scintigraphy	Nitrates (24 hours), calcium-channel blockers (48 hours), and beta-blockers (5 days) stopped before testing.	Binary: all had ST-segment changes that were used to demarcate the onset of ischaemia.	$\Delta VO_2/\Delta$work-rate, O_2Pulse curve	All patients had ST-segment changes during exercise and thus were separated as to the presence or absence of ischaemia based on myocardial scintigraphy results. The slope of $\Delta VO_2/\Delta$work-rate after the ischaemic threshold (point of ST-segment change) was significantly (p=0.005) lower in those with versus without ischaemia. O_2Puls flattening duration (taken simply from the noted point of ischaemia on ECG) was not significantly different.
Belardinelli et al., 2014 (30).	Determine whether CPET can improve diagnostic accuracy of ECG.	Symptomatic patients referred for ECG stress testing. n=1265.	Myocardial Scintigraphy, Coronary Angiography	Medications stopped for four times the drugs half-life prior to testing.	Binary: defined as abnormal due to early inflection.	$\Delta VO_2/\Delta$work-rate, O_2Pulse curve	CPET significantly improved the sensitivity, specificity, PPV and NPV of ECG stress testing (88%, 98%, 73%, 99% Versus. 48%, 55%, 33%, 95% respectively) Additional criteria on top of inflections, such as $\%VO_2$ predicted ≤90 were able to rule out occlusive CAD with 100% accuracy.
Ahmad et al., 2015 (301).	Evaluate the diagnostic utility of O_2Pulse parameters.	Symptomatic patients referred for exertional dyspnea and fatigue or for presurgical evaluation. n=54.	None.	Bronchodilators were stopped one day prior to testing. all other medications were taken as per prescription.	Categorical; normal, plateau, decline.	O_2Pulse curve	The O_2pulse curve pattern was suggested to have 61% accuracy to differentiate between cardiac and no-cardiac causes of CPET limitation. Inter-rater agreement for curve categorisation ranged from κ=0.43 to κ=0.63 (p<0.0001).
Chaudhry et al., 2017 (277).	Quantitative comparison of HR responses between healthy and CAD patients.	Symptomatic patients with exercise intolerance. n=208. Healthy controls. n=116.	Coronary Angiography.	Medications not withheld.	Continuous: acceleration of HR as determined by an objective mathematical model.	ΔHR/Δwork-rate slope	The novel ΔHR/Δwork-rate slope had significantly greater sensitivity but similar specificity to ECG to detect undertreated CAD. In men the slope increased area under the ROC curve from 60% - 94% for non-obstructive CAD and 64% - 80% for obstructive CAD. In women, AUC increased from 64% - 85% for non-obstructive CAD and 66% - 90% for obstructive CAD.
De Lorenzo et al., 2017 (283).	Assess how the O_2Pulse curve morphology correlates with clinical, angiographic, and	Patients with known or suspected CAD recruited following elective coronary angiography. n=40.	Coronary Angiography, Myocardial Scintigraphy.	Nitrates (24 hours) and calcium-channel blockers (48 hours) stopped before testing.	Categorical; normal (A), probably normal (B), probably abnormal (C), definitely abnormal (D).	O_2Pulse curve	The prevalence of angiographically documented CAD or scintigraphically evident ischaemia was not significantly different for those with A/B or C/D curves.

	scintigraphy during CPET.						
Yoshida et al., 2017 (292).	Investigate how compensatory HR increase during myocardial ischemia affects oxygen uptake with or without beta-blocker.	Symptomatic patients referred for CPET due to chest pain. n=42.	Coronary Angiography.	Medications (beta-blocker) not withheld.	Binary: inflection (ischaemia) identified through ST-segment changes.	$\Delta VO_2/\Delta$work-rate, O_2Pulse curve, and $\Delta HR/\Delta$work-rate	Patients were split into three groups: A) ≥1 stenotic lesion taking beta-blocker. B) significant coronary stenosis not taking beta-blocker. C) no stenotic lesions and no beta-blocker. Above the ischaemic threshold, A = higher O_2Pulse increase but lower $\Delta VO_2/\Delta$work-rate and $\Delta HR/\Delta$work-rate than Group B.
De Lorenzo et al., 2018 (282).	Evaluate O_2Pulse curve for diagnosis in patients with known coronary anatomy who underwent CPET with myocardial perfusion scintigraphy	Patients with CAD and known coronary anatomy. n=40.	Coronary Angiography, Myocardial Scintigraphy.	Nitrates (24 hours) and calcium-channel blockers (48 hours) stopped before testing.	Categorical; normal (A), probably normal (B), probably abnormal (C), definitely abnormal (D).	O_2Pulse curve	O_2Pulse curve C/D in combination demonstrate sensitivity 38.5%, specificity 78.6%, positive predictive value 76.9%, and negative predictive value 40.7% when compared to angiography.
Degani-Costa et al., 2019 (291).	Compare O_2Pulse curve in patients with Pulmonary Arterial Hypertension (PAH) and Mitochondrial Myopathy (MM).	MM patients referred for CPET. n=15. PAH patients referred for CPET. n=21.	None.	No medication reported.	Binary; flattening or decreasing slope of O_2Pulse.	$\Delta VO_2/\Delta$work-rate, O_2Pulse curve, and $\Delta HR/\Delta$work-rate	In the clinical population (MM) characterised by a high a-vO_{2diff} the trajectories of O_2pulse and heart rate were abnormal in n=3 cases (20%). This is significantly lower (p<0.001) that the occurrence in the PAH group (n=14; 67%) who are typically characterised by low or abnormal SV.
Popovic et al., 2019 (302).	Investigate CPET ability to predict CAD severity and prognosis.	Patients with CAD lesions ≥50%. n=40.	Coronary Angiography.	Nitrates (24 hours), calcium-channel blockers (48 hours), and beta-blockers (3 days) stopped before testing.	Binary: $\Delta VO_2/\Delta$work-rate, O_2Pulse curve flattening.	$\Delta VO_2/\Delta$work-rate, O_2Pulse curve	$\Delta VO_2/\Delta$work-rate, O_2Pulse curve flattening duration were not significantly different between those with 1-2 diseased vessels (n=30) or 3 diseased vessels (n=10). $\Delta VO_2/\Delta$work-rate was significantly correlated (r=−0.46, p=0.01) with cumulative cardiovascular event occurrence, and was a significant predictor during univariate analysis (F=7.57, p=0.01).
Bechsgaard et al., 2019 (272).	Investigate differences in CPET parameters between women with microvascular disease (angina) and asymptomatic sex matched controls.	Asymptomatic women with no evidence of obstructive CAD (<50% stenosis) during angiography. n=99. Asymptomatic women with no CTCA evidence of occlusive CAD (<50% stenosis). n=27.	Coronary Angiography, CT angiography.	Medications paused for 24 hours.	Binary: $\Delta VO_2/\Delta$work-rate, O_2Pulse curve flattening.	$\Delta VO_2/\Delta$work-rate, O_2Pulse curve	There were no plateaus or inflections in O_2Pulse and $\Delta VO_2/\Delta$work-rate.

Parasuraman et al., 2020 (303).	Describe the usefulness of CPET in the diagnosis of CAD.	Case 1) Symptomatic 64 -year-old male with exertional breathlessness. Case 2) Symptomatic 61-year-old woman with non-exertional chest pain.	Coronary Angiography.	No medication reported.	Binary: $\Delta VO_2/\Delta$work-rate, O_2Pulse curve flattening.	$\Delta VO_2/\Delta$work-rate, O_2Pulse curve	Case 1 exhibited no ECG changes indicative of ischaemia but did have an abrupt flattening of O_2Pulse and a deceleration in $\Delta VO_2/\Delta$work-rate progression. Later angiography revealed significant right coronary stenosis, successful stenting of which eradicated exertional breathlessness. Case 2 demonstrated ECG and echocardiographic evidence of left bundle branch block (LBBB). There were no abnormnalities during CPET.
Petek et al., 2021 (304).	Determine whether qualitative and quantitative O_2Pulse metrics could diagnose occlusive CAD.	Patients referred for CPET with known coronary anatomy. n=104.	Coronary Angiography, CT angiography.	No medication reported.	Categorical; normal (A), flat (B), plateau (C), decline (D). Continuous: percentage change in O_2Pulse slope from test to final 2 minutes.	O_2Pulse curve	The diagnostic performance of both O_2Pulse metrics in the diagnosis of occlusive CAD was poor. The C/C slopes had ROC curve AUC of 0.51 with sensitivity of 33% and specificity of 67%. The percentage change in the slope yielded an AUC of 0.55 with sensitivity = 91% and specificity = 18%.
Huang et al., 2022 (305).	Investigate the CPET indicators of CAD and compare O_2Pulse response across CAD severity.	Symptomatic patients referred for CPET and angiography. n=138.	Coronary Angiography, Intravenous ultrasound.	Medications not withheld.	Continuous: Difference between O_2Pulse at peak versus VT_1. ($\Delta VO_2/HR_{(Peak-AT)}$).	O_2Pulse	Patients with a greater CAD severity had a significantly greater reduction in $\Delta VO_2/HR_{(Peak-AT)}$ compared to those with less severe CAD (p=0.004). The AUC of ROC analysis for $\Delta VO_2/HR_{(Peak-AT)}$ was 0.80; p=0.005, with sensitivity and specificity of 95.7% and 62.5% respectively.
De Assumpção et al., 2022 (22).	Examine association between O_2Pulse curve changes and stress echocardiography in refractor angina.	Symptomatic patients with refractory angina. n=31.	Exercise Stress Echocardiogram.	Medications not withheld.	Binary; flattening or decreasing slope of O_2Pulse.	O_2Pulse curve	In total 77% of the cohort had either a plateau or inflection in O_2Pulse. There was a significant (p=0.019) association between the heart rate at ischaemic onset, when determined via exercise stress echocardiogram, and the heart rate at the beginning of O_2pulse abnormality (r=0.48).

The studies presented in Table 4 are heterogeneous in nature with divergent methodologies, aims and population characteristics. The table contains five descriptions of O_2Pulse morphology in isolated case studies or case series (27,28,276,297,303). In all these studies O_2Pulse morphology was reported to be abnormal, with either a premature plateau or decline during CPET.

Subsequent coronary angiography in three of these studies (27,297,303) revealed critical, defined in only one study as >95% (27), or significant stenosis (undefined) (303). In the case study with critical stenosis (undefined) by Contini et al (297) the vessel was successfully stented and CPET repeated. The secondary CPET was completed two weeks later, during which the patient was able to exercise for longer and had no inflections or plateaus in VO_2 or O_2Pulse. The study indicates that the inflections observed in the patient's initial CPET were caused by the occlusion, and that O_2Pulse morphology could thus be used to track the progression of CAD. As this is a case study the results cannot be generalised to apply to all patients with CAD.

Nevertheless, the O_2Pulse curve was also used by Inbar and colleagues (299) to show that revascularisation through PCI could restore normal O_2Pulse morphology. In the study n=14 patients referred for coronary angiography (with PCI where appropriate) were divided in to an experimental (n=8) group, who had PCI, and a control group (n=6) who did not. Participants in the control group were not revascularised due to lack of necessity or feasibility. Each participant completed CPET ≈2 week prior to and ≈3 weeks post angiography. In contrast to the earlier work of Contini et al (297) who used simple binary classification of O_2Pulse morphology (normal or abnormal), the authors used a categorical approach, in which two examiners graded the O_2Pulse morphology as either normal (10), low peak but up-sloping (8), flat (5), or down-sloping (3). The results revealed a statistically significant (p<0.05) change in test duration, VO_{2peak}, VT_1, O_2Pulse peak, and O_2Pulse slope in those who had been revascularised, with no significant change occurring in the control group.

CPET was also used to monitor the progression of suspected CAD in a case series reported by Chaudhry and colleagues (28). Their case series focused on an asymptomatic 36-year-old male with a strong family history of premature CAD. The authors performed three CPETs over the course of 4.3 years. The first two CPETs (separated by 12 months) highlighted a worsening of O_2Pulse plateau which coincided with a greater deceleration in the ΔVO2/Δwork-rate slope, and a steepening of the ΔHR/Δwork-rate slope. In the 3.3 years between test two and three the patient was

prescribed ‘aggressive’ medical therapy. Test three revealed that each previously abnormal variables was now exhibiting a normal linear or curvilinear increase.

Collating and critically appraising the literature on the use of CPET in CAD is a difficult task, owing to the diversity of application. For example, variables derived from CPET, such as O_2Pulse, the O_2Pulse curve, ΔVO2/Δwork-rate and ΔHR/Δwork-rate, have been used to identify the presence or absence of CAD, the presence or absence of myocardial ischaemia, the degree of myocardial ischaemia, the ischaemic threshold, and the progression and or regression of CAD / myocardial ischaemia. Moreover, there are key methodological differences between studies. Whilst some recruit asymptomatic participants, others recruit symptomatic patients with diagnosed CAD and or known coronary anatomy. In some studies, the definition of CAD is left vague and undefined, whilst in others it is explicit and given as diameter of occlusion. Some grade the performance of CPET variables as to their ability to differentiate between patients with and without stenosis, whilst others opt for contractile dysfunction through nuclear imaging. Inherently the patients in the population under investigation are often receiving aggressive pharmacotherapy, with the aim of slowing disease progression and relieving and or reducing symptoms. Many of the drug classes used in these patients directly or indirectly interfere with the normal chronotropic response, such as beta-blockers and calcium-channel blockers, or with cardiac pre and after load, such as in the presence of oral nitrates. The decision to discontinue medications prior to CPET in these studies requires both methodological and ethical consideration and is ultimately at the discretion of the research team and regional ethics board. It does however mean caution must be used when comparing findings, as these compounds exert a clear impact on the majority of the CPET variables under consideration.

Most studies in Table 4 applied either a subjective approach to the identification of O_2pulse, ΔVO2/Δwork-rate and ΔHR/Δwork-rate slope abnormality, in which one or more members of the research team identifies the point at which they believe abnormality begins. Studies that did not do this did not identify the point of abnormality in the data, but rather opted to use the onset of ST-segment changes or VT_1. The studies that subjectively interpreted variables can be further classified into binary, categorical or continuous groups. Binary meaning simply normal or abnormal, categorical meaning arranged, usually into four groups depending on morphology, and continuous, as the difference between slope inclinations.

This collective body of work underscores the need for standardisation were possible. Study aims and cohorts will inevitably remain diverse, as will the decision to pause or continue medication. However, it should be possible to formalise an objective algorithmic means of quantifying the abnormal O_2Pulse response.

2.5 Treatment

When considering treatment options for CAD, two primary strategies are considered: one is invasive, which includes procedures such as Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Graft (CABG). The other is non-invasive, typically involving lifestyle modifications or pharmacotherapy, often referred to as Optimal Medical Therapy (OMT) (306,307).

2.5.1 Optimal Medical Therapy

The use of OMT requires the layering of several drug classes that in combination impact multiple biological processes to retard the progression of atherosclerosis, alleviate the symptoms of angina, and improve the prognosis for patients suffering from coronary syndromes. OMT commonly consists of a statin, beta-blocker, antiplatelet, renin angiotensin system blocker and nitrate (308,309). OMT is advocated by several agencies including the American College of Cardiology Foundation (ACCF), the AHA, and The ESC (310). In a prospective analysis of myocardial infarction patients by Bramlage and colleagues (311)**,** patients receiving OMT experienced a 74% reduction in mortality at 12 months when compared to those not receiving OMT. A recent met-analysis of over 12,000 patients concluded that combining OMT with PCI did not amount to a greater reduction in mortality or MI occurrence (312). However, the addition of PCI was associated with improvement in anginal symptoms.

2.5.2 Percutaneous Coronary Intervention

Percutaneous coronary intervention (PCI), undertaken by interventional cardiologists, involves the catheterisation of either the femoral or radial artery, which then allows for a guidewire to be advanced into position at the site of lesion being treated. Once in position the catheter can be deployed over the guidewire and angioplasty with or without stent implantation performed (313). The success of percutaneous coronary intervention (PCI) is dependent upon using the catheter to re-establishing the flow between proximal and distal sections of the occluded artery (184). This is affected by a multitude of factors, including the amount of calcification present at the fibrous lesion caps, the level of tortuosity within the vessel, and the age and length of the offending

occlusion (179,314). Over 100,000 PCIs were performed in the UK in 2020, this equates to over 5 times the number of CABGs (313).

A meta-analysis of randomised controlled trials (RCT), which included 37,757 patients from 46 studies, found PCI significantly reduced CAD mortality (RR, 0.69 [95% CI, 0.53–0.90]; p=0.007) and MI (RR, 0.74 [95% CI, 0.62–0.90]; p=0.002) in patients with unstable CAD (315). However, PCI did not have the same impact in the presence of stable CAD with RR=0.89 (95% CI, 0.71–1.12) for CAD mortality (p=0.33) and RR=0.96 (95% CI, 0.86–1.08) for MI (p=0.54) (315). The improvement in quality of life (QoL) following PCI can be predicted by the severity of angina and functional magnitude of occlusion (316).

From a clinical perspective CTO's rank amongst the most challenging lesions to treat (317). Due to the perceived procedural complexity and inferior success rates, CTO's have historically been a prognosticator against PCI (183,317). In 2017 only 3-4% of PCI's undertaken in the United States were been performed to revascularize CTO's (318). Even within a population highly scrutinised and carefully selected, the successful recanalization of a CTO via PCI only occurs in approximately 50-70% of cases (317). However, successful implementation of PCI to treat CTO's has been shown to associate with increased ten-year survival when compared with unsuccessful PCI revascularisation (182). A meta-analysis in 2010 also found that successful versus non-successful PCI amongst CTO patients significantly reduced the incidence of angina after 6-year follow-up (319).

2.5.3 Coronary Artery Bypass Graft

Coronary artery bypass graft (CABG) surgery involves opening of the chest cavity through sternotomy, which allows the surgeon optimal access to the heart. Donar vessels, or grafts are then carefully selected, either from the wider arterial or venous circulation. These vessels are used to connect proximal and distal sections of coronary artery, thereby bypassing the section or sections of the artery or arteries that are stenotic (320). A recent systematic review and meta-analysis, which included five studies and 94,399 patients reported on the short (in-hospital and 30-day) and long term mortality of CAD patients following CABG (321). For analysis patients were divided into those with reduced (<50%) and preserved (≥50%) LVEF. The risk of early mortality following CABG was significantly (p<.0.05) greater (RR, 2.14, [95% CI, 1.50 - 3.06]) in those with reduced ejection fraction as was long term mortality (RR, 1.67, [95% CI, 1.35 - 2.08]) (321). A prospective study of 272 CABG patients used the short form

(SF36) healthy survey to examine the long term (up to 10 years) impact the procedure had on QoL (322). At five years post-surgery there was a significant increase in the physical components score (p<0.01) compared to pre-surgery. This component was significantly reduced at 10 years (p<0.01) when compared to 5 years but remained significantly higher than baseline values (p=0.004).

Historically, revascularisation of CTO's was most commonly attempted using CABG (323,324). This was especially true of the more complex CTO cases, such as in the presence of multi-vessel disease, multiple CTO's, and left main stem or left anterior descending occlusions (324,325). The preferential use of CABG over PCI for the treatment of CTO's exists despite a scarcity of literature on their comparison (323). The influence of CTO on CABG outcomes was investigated by Banerjee and colleagues (2012). CTOs were present in 256 of 605 consecutive CABG patients recruited. Revascularisation was successful in 92% of occlusions occurring in the circumflex (LCx) and right coronary (RCA) artery, as well as 100% of left anterior descending (LAD) occlusions. Furthermore, of the 26.2% of patients with multiple CTOs, 85.2% were completely revascularized. After a mean follow-up 348.9 ± 4.5 days a composite of all cause death and myocardial infarction had occurred in 7.1% of CTO and 7.4% of non-CTO patients (P=0.97). When the CTO group were divided and compared according to occlusion length (<20mm, 20-40mm and ≥40mm), cumulative survival was significantly greater only for those with lesions <20 compared with ≥40mm (P=0.04).

2.6 Exercise-based Cardiac Rehabilitation

Cardiac rehabilitation is comprehensively defined by the British Association for Cardiovascular Rehabilitation (BACPR) as.

> *"The coordinated sum of activities required to influence favourably the underlying cause of cardiovascular disease, as well as to provide the best possible physical, mental and social conditions, so that the patients may, by their own efforts, preserve or resume optimal functioning in their community and through improved health behaviour, slow or reverse progression of disease."* (327).

Cardiac rehabilitation is complex and multi-disciplinary, involving a variety of therapeutic interventions: such as, education, behavioural change, psychological support, risk factor reduction and structured exercise (8–10). Exercise is consistently

identified in clinical guidelines as an integral part of cardiac rehabilitation, i.e., exercise-based cardiac rehabilitation (exCR) (328), and is recommended as a Class 1 Grade A therapy by the ESC, AHA and ACCF (4,11). The ACPICR and AHA/ACCF recommend performing both aerobic and resistance training, unless contraindicated (11,12).

Exercise capacity, often quantified through maximal or peak oxygen utilisation (VO_{2max}/VO_{2peak}), is a strong independent predictor of both all cause and CVD mortality in patients with CAD (9,329). Increases in VO_{2peak} of 1 $mL \cdot kg^{-1} \cdot min^{-1}$ have been associated with decrease in risk of mortality of ≈15% (330). The most recent systematic review and meta-analysis reported a 26% reduction in CVD mortality (RR, 0.74, 95% CI, 0.64–0.86), a 23% reduction in hospital admissions (RR, 0.77, 95% CI, 0.67–0.89) and an 18% reduction in MI (RR, 0.82, 95% CI, 0.70–0.96) for patients with CAD following exCR versus no-exercise as a control (331).

2.6.1 Current Exercise Guidelines in the UK

In the UK exCR provision is administered locally by the associated NHS trust. Whilst guidance suggests that exCR should be delivered by a multidisciplinary team (MDT) (327), this cannot always be guaranteed. Indeed, the 2017 annual statistical report undertaken by The National Audit of Cardia Rehabilitation (NACR), found that 97% of sites had nurses, 71% physiotherapists, 9% doctors, 15% health care assistants, 26% occupational therapists, and only 53% dedicated exercise specialists (332).

The BACPR describe a face-to-face assessment of functional capacity as essential for each person entering into exCR to aid in risk stratification and exercise prescription (327). If the gold standard CPET is not possible they recommend submaximal testing in the form of the 6-minute walk, incremental shuttle walk, step test, or sub-maximal cycle ergometer test. Despite these recommendations the NACR found less than one third of patients received any baseline assessment of functional capacity (332).

The ACPICR recommend training intensities of between 40 and 70% heart rate reserve (HRR) for exCR in the UK (12). Initially, exercise sessions are prescribed in an interval fashion, split between periods of aerobic exercise and periods of active recovery (333). The goal is to progress from this interval style prescription towards a moderate intensity steady-state (MISS) style session (334). As has been established less than one third of patients are afforded baseline testing, therefore it must be assumed that most of the exercise prescription in UK exCR is done from an estimated HRR. Exercise

prescribed between 40 and 70% HRR is classified by the European Association of Preventative Cardiology (EAPC) and ESC as moderate aerobic exercise (13). Multiple large scale observational studies indicate that relative exercise intensity is of greater importance than exercise duration to reduce the risk of chronic disease and extend life expectancy (1,2). These studies have sparked debate and criticism of the %HRR method, shifting preference towards a threshold-based approach focused on VT_1 (333).

In 2020 Pymer and colleagues (336) recruited 112 patients with CAD referred for community based exCR to compare the estimated %HRR with CPET derived measures. The authors found only a modest correlation between HRR derived from CPET (72±15 bpm) and estimated HRR (78±20 beats per minute [bpm]; r=0.32; *p*=0.001). The mean difference of 6.74 bpm (95% CI, 2.99–10.49 bpm) between CPET derived and estimated HRR was statistically significant (*p*=0.001). Furthermore, VT_1 occurred at less than 40% estimated HRR in 45% of patients, and over 70%HRR in 9.8% of patients. When the cohort were divided into tertiles of baseline fitness, 35.8% of those with the lowest fitness had VT_1 occur within the 40-70%HRR recommendation, by comparison this was 50% for those in the moderate and high tertiles.

Adherence to the prescribed 40-70%HRR exercise intensity has recently been drawn into question. Khushhal and colleagues demonstrated that in one community based exCR programme (8-weeks) the mean %HRR achieved by patients during exercise was 37.1±10.1% (333). It should be noted that the minimum and maximum %HRR recorded were 17% and 62% respectively. Similarly, during periods of active recovery the mean %HRR was reported to be 31.5±12.6%. Furthermore, in a later paper discussing the same data set, the authors demonstrated that mean exercise intensity only exceeded 40%HRR (42±12%) in the last week (week-8) of exCR (337). Similar findings were reported by Ibeggazene et al for n=60 patients undertaking routine UK exCR (338). In the study by Khushal and colleagues, total exercise time was increased from 17±6 minutes in week one, to 32±8 minutes in week eight. However, session RPE remained low throughout, peaking in week-8 at 3.3±0.6, which corresponds to only moderate effort on the Borg CR-10 scale.

2.6.2 High Intensity Interval Training (HIIT)

Exercise is ubiquitously used in cardiac rehabilitation settings, with the overall intention of improving cardiorespiratory fitness (339). Increases of 1 $mL \cdot kg^{-1} \cdot min^{-1}$ in VO_{2peak} are viewed as clinically meaningful, as they have been associated with an approximate 15% decrease in risk of mortality (330,334,340). Increases in VO_{2peak}

following an exercise intervention are believed to be dependent upon its combined intensity, frequency, and duration, as well as the length of intervention (341). At present there is no scientific consensus as to the optimal training intensity for exCR (342). However, the efficacy of a training intervention is generally increased incrementally with an increase in intensity (327). Moreover, large scale observational studies now suggest that, at least in primary prevention, the intensity of exercise - more so than duration - may increase life expectancy and reduce the risk of chronic disease (13). For example, the Copenhagen City Heart Study (343) analysed the cycling habits of 5000 participants over a 20-year period, observing that those who reported cycling fast lived longer, had lower BP, cholesterol, and incidence of T2DM than those who cycled slowly. Furthermore, the authors noted that the total amount of cycling per day was not related to either the amount of risk factors or life expectancy.

The past two decades have seen an increase in both the interest, and evidence for prescribing high intensity interval training (HIIT) as an adjunct or alternative to traditional exCR (344–347). Whilst there is no consensus on the optimal training intensity for HIIT in CAD, evidence for the effectiveness of higher intensity prescriptions is mounting (347). Recommendations often call for repeated bouts of vigorous activity (>85% VO_{2peak}, max HR, max work rate, or RPE 15-18) alternated with periods of active, or even passive recovery (334,340,348,349). Various structures have been proposed within the literature, but two commonly seen are 4 x 4 and 10 x 1, in which patients complete four bouts of vigorous activity lasting four minutes with three minutes recovery, or ten bouts of vigorous activity lasting one minute with one minute recovery (349).

Evidently, exercise can only be sustained for short durations when performed at sufficiently high, or vigorous intensity (334). Therefore, by alternating between relatively short periods of high and low intensity efforts, HIIT allows individuals to accumulate a greater overall time spent at a higher intensity, which would otherwise not be possible with continuous training (10,327,350,351). There are putative cellular differences in the response to HIIT and MISS that engender different adaptations. For example, when compared to MISS, there is a greater increase in calcium released from the sarcoplasmic reticulum, a greater turnover of adenosine triphosphate, and a greater reliance on carbohydrates for metabolism during HIIT (352). Consequently, metabolites, ions and free radicals accumulate at a greater rate during HIIT, which increases the activation of kinases Ca^{2}+/calmodulin-dependent protein kinase II and

AMP-activated protein kinase. Increasing the activation of these signalling proteins leads to an rise in the rate of mitochondrial protein synthesis, which is likely to be the reason HIIT protocols demonstrate greater increases in mitochondrial density than MISS protocols (350,352).

In the past decade there have been multiple systematic reviews and meta-analyses summarising the effects of HIIT in various CAD populations, for a comprehensive evaluation the reader is directed to these resources (342,344,346,353–359). To date the majority of findings suggest HIIT generates a greater increase in VO_{2peak} than MISS, with mean differences ranging from 1.35 – 1.83 $mL \cdot kg^{-1} \cdot min^{-1}$ (346,360) and weighted mean differences from 1.30 – 1.6 $mL \cdot kg^{-1} \cdot min^{-1}$ (354,359). However, most studies included in these analyses did not employ isocaloric matching for HIIT and MISS interventions. Previous meta and multi-level linear regression analysis have indicated that total energy expenditure, more so than frequency, intensity or duration, is the primary determinant of increase in exercise capacity (361,362). To this end Gomas-Neto and colleagues performed a sub-analysis of four studies (n=137) that did prescribe isocaloric exercise, finding a non-significant difference of 0.7 (95% CI, 0.1–0.9) $mL \cdot kg^{-1} \cdot min^{-1}$ between HIIT and MISS (354).

Increases in VO_{2peak} reported in the aforementioned analyses are similar to those from a recent large multi-centre randomised controlled trial (HIIT or MISS UK). The study recruited 382 patients referred for exCR to undertake 8-weeks of low volume HIIT (10 x 1, >85% HR max) or usual care (MISS). After adjusting for age, sex and study site, low volume HIIT increased VO_{2peak} by a significant (p=0.002), and clinically meaningful margin (1.04 $mL \cdot kg^{-1} \cdot min^{-1}$ (95% CI, 0.38 - 1.69) when compared to MISS (334). The magnitude of the VO_{2peak} difference between HIIT and MISS in this study is marginally smaller than previously reported mean differences from meta-analyses. However, the studies included in these analyses tend to examine small cohorts in laboratory-controlled environments. In contrast, the HIIT or MISS UK study was pragmatic in nature, with interventions delivered in standard NHS cardiac rehabilitation sites by practitioners not researchers (334).

Fidelity and adherence are often cited as concerns when prescribing HIIT in patients with CAD. The previously mentioned HIIT or MISS UK study reported that ≥13 sessions, from a possible 16, were completed by 75% of patients in the HIIT group and 84% in the MISS group. The per-protocol analysis for the proportion of patients in each group completing < or ≥13 sessions was not significantly different (334). Patients in the HIIT

group exercised over the prescribed 85%HR max in 76% of sessions. By contrast, those in the MISS group completed only 45% of sessions within their prescribed 60-80%HR max range, with the remaining 55% of sessions completed above 80%HR max. These findings indicate that higher intensities of exercise, including low volume HIIT, are well tolerated by patients referred for exCR across multiple NHS centres, and that lower, not higher intensities are less likely to be adhered to.

2.6.3 Uptake and Adherence

Despite a robust evidence base for the efficacy of exCR, uptake and adherence amongst eligible patients remain poor (363). The 2020 and 2021 NACR quality and outcomes reports have been unable to determine the rates of exCR uptake due to staffing limitations caused by the COVID-19 pandemic. However, in the 2019 report the overall mean uptake to exCR in the UK was 50% (364). In England the overall number of patients undertaking exCR increased by 2,126 between 2018 and 2019, however this was proportional to the increased number of patients eligible in 2019 (364). Barriers related to exCR uptake are diverse, but it has been shown that participation is lower amongst older, female, unemployed, single, less educated, higher comorbidity, and lower income groups (365). However, self-reported disinterest was the main reason for not partaking in exCR during the 2017 NACR survey (332). The results indicate lack of interest is the dominant reason for not participating in all four phases of exCR, with the percentage of respondents reporting disinterest increasing from 14% in phase two to 54% in phase four (332).

Adherence to exCR has been shown vary substantially, with dropout rates prior to completion of between 10 and 50% (366,367). UK statistics for 2017 indicate 77% of patients who started exCR went on to complete the phase two (332). Factors influencing adherence are reported to be psychological wellbeing, location, transport access, and not wanting to participate in group-based sessions (363). In an attempt to combat these factors, and increase both uptake and adherence, home-based exCR alternatives have been proposed (368). However, whilst home-based interventions appear to yield similar increases in capacity (368), recent evidence indicates that rates of adherence are not improved (369).

2.6.4 Evidence of Efficacy

A change in aerobic capacity, either as directly determined $VO_{2peak/max}$ (during CPET), or through an estimated surrogate, is often the primary outcome for studies that involve an exercise intervention. This is clearly a valid clinical marker of change, as

increases of as little as 1 mL·kg^{-1}·min^{-1} in VO_{2peak} have been associated with an approximate 15% decrease in risk of mortality (330,334,340). Increases in measured VO_{2peak} following exCR vary, with studies in the US reporting increases of 1.9-2.6 mL·kg^{-1}·min^{-1} (370,371), whilst more modest increases of 0.5-1.2- mL·kg^{-1}·min^{-1} have been reported in UK studies (334,372,373). In recent years the efficacy of UK exCR has been drawn into question, with cohort studies published in 2018 and 2020 finding no significant increase in measured VO_{2peak} (373,374). Furthermore, the same authors demonstrated that whilst measured VO_{2peak} did not significantly increase (p=0.332) following routine community-based exCR, estimated VO_{2peak} did (p=0.006) (373). The reported mean bias for estimated versus directly determined VO_{2peak} was 0.7 mL·kg^{-1}·min^{-1} (373).

Increases in maximal capacity alone may not necessarily provide a tangible subjective benefit to patients' daily life unless baseline capacity is very low. Activities of daily living are undertaken at a greater percentage of VO_{2peak} or VO_2 reserve in patients with CAD when compared to controls (375). However, even the most vigorous and high energy expenditure activity recorded (ascent and decent of a 20-step staircase) required only 61±26% VO_{2peak} (375), which is close to the reported VT_1 of patients entering exCR (336). Therefore, it may be hypothesised that increasing sub-maximal capacity, quantified as VT_1, could better translate to patient felt increases in physical capacity. Nichols et al found that a median of 15 routine exCR sessions significantly increased VT_1 by 1.4 mL·kg^{-1}·min^{-1} (95% CI, 0.5 - 2.3 mL·kg^{-1}·min^{-1}; p=0.005) despite VO_{2peak} increasing by only 0.5 mL·kg^{-1}·min^{-1} (p=0.332). However, more recent evidence indicates that VT_1 may be increased by as little as 0.66 mL·kg^{-1}·min^{-1} following 8-weeks of routine exCR (twice weekly) (334).

It has been suggested that exCR should be graded on its ability to 'add life to years', rather than simply adding 'years to life' (376). In this regard quantifying the change in a patients QoL following exCR is paramount. Whilst many exCR studies do report QoL as an outcome measure, it is often not possible to pool large numbers of them for accurate meta-analysis due to the variation in questionnaires and or domains used (377). A recent meta-analysis by Dibben and colleagues reported increases in both the mental (MD; 2.14, 95% CI 1.07 – 3.22) and physical component (MD; 1.7, 95% CI -0.08 – 3.47) score of the SF-36 following exCR in six trials (331). However, it should be noted that the proportion variation attributed to the heterogeneity of studies was greater for the physical component (I^2=73%) than for the mental component score (I^2=21%). The

same study also found that there was no evidence of an increase in the pooled EQ-5D visual analogue scores for the three studies in which it was reported (MD; 0.05, 95% CI -0.0 – 0.10), again the proportion of heterogeneity was relatively high (I^2=69%). An earlier meta-analysis by McGregor and colleagues reported increases in QoL following exCR, with six short-term (>6 months) and five medium-term (8-12 months) domains of the SF-36 favouring exCR versus control (376). In a longitudinal study involving 4,570 UK patients who underwent exCR post-acute MI, improvements in QoL were observed for up to 12 months following discharge (378). The authors used the EQ-VAS for which previous research has established 6.9-points of difference to be clinically meaningful (379). The authors found a EQ-VAS difference of 14.9 when comparing those who attended exCR and performed additional activity to those who did neither, and differences of 6.5 when simply comparing those who attended and did not attend exCR (378).

2.6.5 Safety in Cardiac Rehabilitation

Exercise-based cardiac rehabilitation is widely regarded as a safe and effective therapy for the secondary prevention of CAD (13,360,380–383). In a study of 25,420 patients, across 65 exCr centres in France, the rate of severe cardiac events was reported to be 1 per 49,565 patient-hours (2.02/100,000), in the study this amounted to 15 events over the course of 743,471 hours of exCR (383). Of the 15 events recorded, eight were chest pain and four were ventricular tachycardia, with the remaining three events being heart failure, weakness, and cardiac arrest. There were no deaths as a result of the reported cardiovascular events. A similar study conducted in Japan analysed data from 383,096 patients undergoing exCR, reported non-life threatening adverse event rates of 12 per 383,096 patient hours (3.13/100,000) (381). They classified acute MI, cardiac arrest, cardiac tamponade and death as life-threatening adverse events, for which the reported rate of occurrence was 1 (acute MI) per 383,096 hours (0.26/100,000) (381).

A 2007 scientific statement from the AHA outlined that, in some susceptible patients, vigorous activity acutely and transiently increases the risk of MI and sudden cardiac death (384). This is of particular relevance, given the previously mentioned interest in HIIT as an alternative or adjunct to routine exCR. With the growing interest is in HIIT, there is a growing need to assess its safety, especially in comparison to that of MISS (usual care).

The risk of adverse events during HIIT and MISS was compared by Rognmo and colleagues in 2012 (385). The authors found that over the course of 175,820 total hours of exCR (Norway), in which each patient undertook both HIIT and MISS session, there was one fatal cardiac arrest during MISS (or ≤1 hour after), and 2 non-fatal cardiac arrests during HIIT (or ≤1 hour after). However, it should be taken into consideration that the total duration of exercise during HIIT was approximately 33-minutes (386), compared with 60-minute sessions of MISS. Therefore, amongst 4,846 CAD patients, across three exCR sites, the adverse event rate in MISS was 1 per 129,456 hours (0.77/100,000), compared with 1 per 23,182 (4.31/100,000) hours in HIIT. The rate of adverse events was also compared during the recent FITR heart study by Taylor and colleagues (372). As with the study of Rognmo et al FIRT employed a 4 x 4 HIIT protocol in which 4-minutes of exercise at high intensity (15-20 RPE (387)) were interspersed with 3-minutes of active recovery (RPE 11-13 (387)), this was compared to 40-minutes of MISS at the same intensity as active recovery. Whilst the authors report nine adverse events, six for HIIT and three for MISS, only one in which a patient experienced post-exercise (HIIT) hypotension, was deemed related to the study intervention. The results of the previously mentioned HIIT or MISS UK trial also point to the relative safety of HIIT when compared to MISS in exCR. This large-scale pragmatic study reported five serious adverse events in 382 patients (HIIT=187; MISS=195) over the course of 8-weeks and 4,863 session (HIIT=2288; MISS=2575) (334). Of the five serious adverse events (HIIT=3; MISS=2) only one incidence of new-onset atrial fibrillation was considered possibly related to exercise, the remaining events occurred at participants homes and were not related to the intervention. Two meta-analyses published in 2022 (357,360) also suggest HIIT is a safe and effective alternative to MISS in patients with CAD. The risk difference calculated for eight studies and 387 patients was reported by Qin and colleagues to be 0.01 (95% IC, -0.02-.004; p=0.53).

2.6.5.1 Avoiding Myocardial Ischaemia

Guidelines for exercise prescription in patients with CAD state that, in those with residual myocardial ischaemia, exercise should be undertaken at an intensity that is sufficient to remain ≈10 beats below the ischaemic threshold (13–15). This guidance stems from a long established association between acute myocardial ischaemia and the onset of life threatening arrhythmias (16–21). The concept of myocardial ischaemia proceeding cardiac arrest and sudden cardiac death has been around in the literature since the early part of the twentieth century (17). However, it was demonstrated experimentally, but not fully understood in the middle of the nineteenth century (17).

In 1842 Erichsen ligated a coronary artery in a live dog, which the author reports resulted in ventricular action ceasing but for *"a slight tremulous motion"* (388). Multiple authors have since shown that myocardial ischaemia causes changes at the cellular level, these changes alter the usual path of action potentials, which generates a pro-arrhythmic condition (16,18,20,21). However, these studies are often not referring specifically to exercise-induced myocardial ischaemia, and are instead talking about the early stages of ischaemia following acute MI.

There is some evidence to suggest that periods of exercise-induced myocardial ischaemia proceed ventricular abnormalities. Rinaldi and colleagues demonstrated that for patients with chronic stable CAD (angina), exercising with 1mm of ST-depression resulted in wall-motion abnormalities and significant reductions in LVEF (p<0.001) at 30-minutes post exercise (389). However, acute reductions in ST-segment abnormality have been recorded in patients with CAD following repeated bouts of balloon occlusion during angiography (390). This phenomenon, known as 'preconditioning', has been repeated multiple times in animal models, and is known to reduce the size of future infarction (391). It has been suggested that this may caused by vasodilatory or pressure mediated priming of collateral arteries (389) (see section 2.2.3.1).

In recent years researchers have begun to question the *"sacrosanct dogma"* of arbitrarily avoiding exercise at or even above the ischaemic threshold (392,393). For example, Guiraud and colleagues sought to compare different HIIT prescriptions in patients with stable CAD (393). However, in the process of doing so n=3 (16%) of their cohort experienced ischaemia during the intervention. Despite this the authors report significant ventricular arrhythmia, concluding that HIIT over the ischaemic threshold may be safer than MISS as the threshold is only intermittently, and not continuously surpassed (393). These findings were supported by a recent case report by Corre et al in 2021 (392). The report discusses the case of a 72-year-old male suffering from refractory angina despite receiving OMT. The patient performed three HIIT sessions, three times per week for seven weeks. Each session required him to perform six bouts of exercise above the ischaemic threshold (90% VO_{2peak}) with two minutes of active recovery below the ischaemic threshold. The patient increased VO_{2peak} by 35.7%, increased his ischaemic threshold from 40-80 watts, and reported a 32-point increase in QoL as per the Seattle Angina Questionnaire. Furthermore, the authors reported no adverse events or arrhythmia (392). There is also growing evidence to suggest longer

periods of continuous exercise above the ischaemic threshold are tolerable and safe in CAD patients with residual ischaemia. Noël and colleagues recruited n=22 patients with CAD, randomising them to receive either exercise prescribed above or below the ischaemic threshold (394). Patients exercised three times per week for six weeks, with exercise gradually increasing in duration from 20-60 minutes. During the 60-minute exercise sessions the patients in the above threshold group experienced 49.8±2.2 minutes of ≥1.0mm ST-segment depression. There were no recorded incidences of adverse events or ventricular arrhythmia throughout the study (394). Moreover, the authors measured TnT 18-24 hours after the first three 60-minute exercise sessions, none of which yielded a positive increase. This lack of biomarker evidence of myocardial damage following exercise above the ischaemic threshold was later corroborated by Juneau et al (390). The authors recruited n=21 patients with CAD to undertake two exercise session ≥72 hours apart. The first 20-minute session was performed below, and the second 20-minutes session above the ischaemic threshold. Despite exercising with a 1.4±0.5mm ST-segment depression, there were no adverse events or arrhythmia. Furthermore, analysis of multiple biomarkers (creatine kinase, creatine kinase MB isoenzyme, and TnT) taken at 6 and 12 hours post exercise showed no significant increase following exercise above or below the ischaemic threshold (390).

Remaining dogmatically obedient to guidance that may now be outdated and overly conservative could be problematic. Research is beginning to indicate higher, rather than lower intensity exercise is more beneficial for patients with CAD (333,334,395). However, some individuals may experience myocardial ischaemia at relatively low intensities, some even lower than the 40-70% HRR recommended for standard UK exCR (390). Given the current guidance these individuals are likely to be receiving a suboptimal, or even inadequate training stimulus (390). Furthermore, the most common way to prescribe exercise blow the ischaemic threshold is to determine either the work-rate or heart rate at which there is ≥1mm of ST-segment depression (396). However, research has demonstrated that exercise induced myocardial ischaemia may proceed ST-segment depression by as much as 265 ± 33 seconds (29).

Chapter 3 : Exercise in Patients with a Total Coronary Occlusion (EChO)

3.1 Abstract

Cardiopulmonary exercise testing (CPET) is essential in evaluating cardiopulmonary fitness in coronary artery disease (CAD) patients, including those with chronic total occlusions (CTO). This study focuses on assessing the utility of CPET variables, particularly oxygen pulse (O_2Pulse) and the rate of change in oxygen consumption relative to work-rate ($\Delta\dot{V}O_2/\Delta WR$), as non-invasive markers for myocardial ischemia.

A prospective, single-arm, single-centre pilot study was conducted, with recruitment aimed at CAD patients having single-vessel CTO. CPET was performed using standard protocols to collect key variables. The primary goal was to assess the feasibility of recruiting and retaining participants, and secondarily to examine if O_2Pulse and $\Delta\dot{V}O_2/\Delta WR$ inflections indicative of myocardial ischemia were present during ramped incremental exercise.

From April 2019 to June 2020, nine patients agreed to participate, with four completing baseline CPET. The rate of recruitment was slower than anticipated, and only one of the four participants exhibited inflections in O_2Pulse, suggesting myocardial ischemia. In this patient, inflections persisted across two CPETs, with minor variations in work-rate (10 W) and heart-rate (5 bpm) at the point of inflection. The study demonstrated a 100% retention rate but faced challenges due to COVID-19 restrictions.

The study highlights the challenges in recruiting a sufficient sample size for CTO patients within a single centre. The findings, though limited due to a small sample size, provide preliminary evidence of the potential utility of O_2Pulse as a marker for myocardial ischemia in CTO patients. However, the absence of inflections in most participants calls for further research to validate these findings and establish guidelines for exercise prescription in this patient population.

3.2 Introduction

Cardiopulmonary exercise testing (CPET) uses the principles of ventilatory gas exchange to facilitate the collection of variables such as: oxygen pulse (O_2 pulse), respiratory exchange ratio (RER), ventilatory anaerobic threshold (VT_1) and peak oxygen uptake ($\dot{V}O_{2peak}$) (263,397). CPET can be added to conventional ECG stress testing, thus providing a non-invasive method for clinicians to examine the function and capacity of the cardiopulmonary system during maximal or symptom-limited graded exercise (23,263).

The change in oxygen consumption as a function of work-rate ($\Delta\dot{V}O_2/\Delta WR$) during ramped incremental CPET reflects oxygen utilisation (mL·min) relative to external work (watts [W]) and is reported as mL·min·W. In healthy individuals free from cardiorespiratory disease, a linear increase in this relationship, with a slope of ≈10 $mL \cdot min^{-1} \cdot W^{-1}$ should be observed (27). Overall reductions in the linear progression of this slope from the start of exercise could be indicative of pathology such as chronic heart failure or chronic obstructive pulmonary disease (290). If the slope of $\Delta\dot{V}O_2/\Delta WR$ is initially normal but suddenly becomes reduced myocardial ischaemia could be present (290).

Similarly, O_2Pulse, expressed in $mL \cdot beat^{-1}$, is derived from the ratio of oxygen extracted per heart beat (290). The O_2Pulse allows for the estimation of stroke volume (SV) during CPET through a simple modification of the Fick equation, in which $\dot{V}O_2$ is equal to the product of cardiac output ($\dot{Q}$) multiplied by the arteriovenous oxygen difference ($_{a\text{-}v}O_{2diff}$) (290,304). Consequently, O_2 pulse can be seen as a non-invasive surrogate measure of SV.

The onset of myocardial ischaemia is frequently determined via standard (ECG) stress testing (29). During such tests, ST-segment depression is considered to be indicative of exercise induced myocardial ischaemia, secondary to obstructive coronary artery disease (CAD) (152). The heart rate corresponding to ST-depression is then used to prescribe the intensity of exercise-based cardiac rehabilitation (CR). However, research has demonstrated that exercise induced myocardial ischaemia may proceed ST-segment depression by as much as 265 ± 33 seconds (29).

Previous studies have examined the potential of variables like O_2Pulse and $\Delta\dot{V}O_2/\Delta WR$ to detect the presence of ischaemia and determine the severity of CAD, however the results are ultimately inconclusive

(23,25,27,28,266,272,274,276,277,282,283,291,292,296,298,300,302,304,398–407). The majority of these studies are influenced by, and make specific reference to a landmark study by Belardinalli and colleagues in 2003 (29). The authors performed CPET with ECG on 202 CAD patients, followed by myocardial scintigraphy as the 'gold-standard' for ischaemia detection. A two-variable model consisting of $\Delta\dot{V}O_2/\Delta WR$ slope changes and O_2Pulse curve flattening (independent predictors) were found to have the highest predictive accuracy for detecting ischaemia (29). The authors used this two-variable model again in 2014 to determine whether it could better the diagnostic accuracy of standard ECG stress testing (30). Indeed, the model had significantly ($p<0.0001$) better positive and negative predictive sensitivity and specificity (88%, 98%, 73%, 99%) than traditional ECG stress testing (48%, 55%, 33%, 95%) (30). Despite the success of this two-variable model the vast majority of subsequent studies have used these variables independently and concluded that they may only be useful in detecting extensive ischaemia (296,298,400).

Despite the conflicting evidence as to the efficacy of CPET in the diagnosis and categorisation of CAD its use is nonetheless advocated by both the European Association for Cardiovascular Prevention and Rehabilitation (EACPR) and the AHA. In 2012, the EACPR and the AHA published a joint scientific statement outlining their clinical recommendations for CPET interpretation (293). In the statement the authors support using O_2Pulse and $\Delta\dot{V}O_2/\Delta WR$ in the universal reporting of CPET, providing template forms in their appendix. The statement was revised in 2016 but the advice remained the same (294).

CAD patients may in some instances develop chronic total occlusions (CTO) (≈18%) (408). A CTO is defined as complete coronary occlusion with a thrombolysis in myocardial infarction (TIMI) flow score of 0, believed to be present for at least 3 months (409). In patients with a CTO the lumen distal to the occluded segment is perfused via pre-existing collateral arteries (410) (Figure 7).

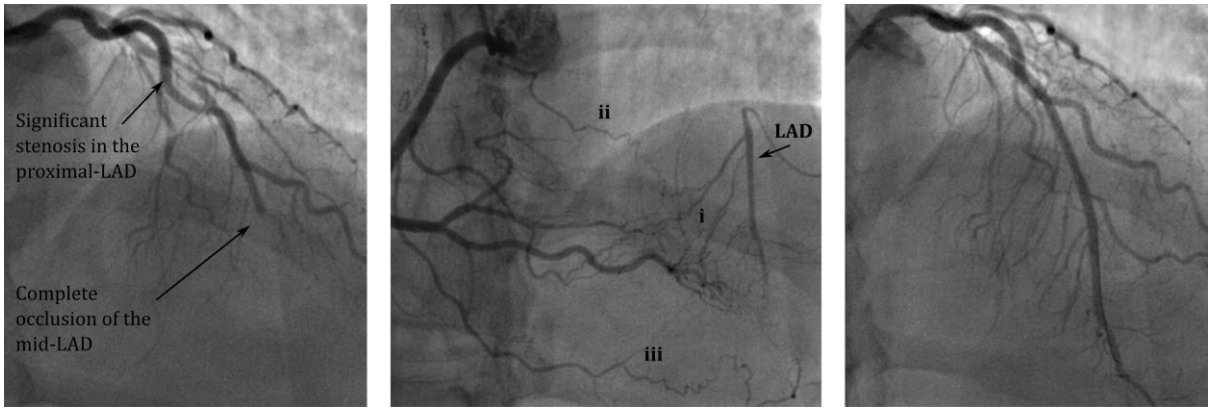

Figure 7. Coronary collateral filling of the distal left anterior descending artery via septal (i) and epicardial (ii, iii) channels (Angiogram supplied by Dr Angela Hoye)

In some individuals the collateral circulation is capable of supplying flow sufficient enough to prevent signs of myocardial ischaemia during brief coronary occlusion (410), and perhaps limit the area at risk after myocardial infarction (MI) (411). However, it is not likely to prevent symptomatic ischaemia during physical activity (411).

Cardiac rehabilitation (CR) is a collection of secondary prevention techniques offered to patients with heart disease, including CAD (412). CR is endorsed as a Class I recommendation by the AHA, American College of Cardiology (ACC) and the ESC (11,413). Exercise has been recommended as a key component of CR since 1993 (10,414), (exCR) and is still seen as a cornerstone of treatment (380).

However, at present there is no consensus training advice within exCR for CTO patients. Existing training guidelines presented by the American College of Sports Medicine (ACSM), recommend outpatient training intensities for exCR to be below the ischaemic threshold (<10 beats), or below a threshold that elicits the onset of angina symptoms (415). Unfortunately, some CTO patients may be asymptomatic during exertion (silent ischaemia) (416), therefore ceasing exercise prior to the ischaemic threshold would not be plausible.

Given that research suggests higher rather than lower training intensities confer greater cardio-protective benefits (417), the vague nature of exercise prescription for CTO patients could mean they are receiving suboptimal exCR. Furthermore, there is no evidence as to the reliability and agreement for the onset of ischaemia during exercise. Therefore, it is not clear that using this as a marker for exercise prescription is even possible. Accurate identification of myocardial ischaemia, coupled with a good

understanding of its repeatability through CPET could allow clinicians to provide patients with a more precise, personalised training intensity for exCR.

This study was designed as a prospective single arm, single centre pilot study. The primary aims of this study were to determine rates of recruitment and adherence to the study protocol amongst CTO patients in the local area. Recruitment was deemed feasible if all patients were enrolled within 18 months. Secondary aims were to determine whether CTO patients exhibit inflections in O_2Pulse and $\Delta\dot{V}O_2/\Delta WR$ indicative of myocardial ischaemia (previously described by Belardinelli et al., 2003(29)) during ramp incremental exercise. If inflections were present in this patient group, the reliability and agreement associated with their occurrence was to be determined via interclass correlation coefficients (ICC), Bland-Altman analysis and standard error of measure / minimal detectable change respectively. Finally, I sought to establish whether prolonged (20 minutes) fixed workload exercise at an intensity associated with previously described inflection(s) (minus 2/3 ramp rate) was safe, and whether it would elicit wall motions abnormalities representative of myocardial dysfunction identified through stress echocardiography.

3.3 Methods

An *a priori* determined sample size for this study was estimated to be n=12 based on the recommendations of Julious (418). Eligible patients were either awaiting angioplasty or being managed with medical therapy at the time of involvement. Inclusion criteria were as follows; 1) Single vessel CTO of the right coronary, left anterior descending or circumflex artery determined through angiography <24 months prior to recruitment, 2) Willingness to undertake symptom limited CPETs, 3) Resting systolic blood pressure <180 mmHg, 4) resting diastolic blood pressure ,100 mmHg, 5) Aged >18 years, 6) Normal resting left ventricular function, 7) Ability to provide written informed consent.

Exclusion criteria were; 1) Significant proximal left main stem stenosis, 2) Multi-vessel disease (>50% stenosis in another major epicardial coronary vessel), 3) Absence of exercise-induced myocardial ischaemia, 4) O_2Pulse inflection or $\Delta\dot{V}O_2/\Delta WR$ inflection at a respiratory exchange ration <1.05, 5) Change in cardiac medications <2 weeks, 6) Unstable angina, 7) MI <6 weeks, 8) Canadian classification system for angina class IV, 9) Chronic heart failure, 10) Significant valvular pathology, 11) Resting ejection fraction <40%, 12) Severe orthopaedic limitations, 13) Past history of complex arrhythmias, 14) Atrial fibrillation, 15) Severe chronic obstructive pulmonary disease.

Ethical approval for the research was provided by the National Health Service (NHS) Health Research Authority (HRA) (REC reference: 18/YH/0360). Written informed consent was obtained from all participants during their first visit.

Potential participants were approached and informed of the study by a member of their usual clinical care team. They were provided with a copy of the patient information sheet and asked if they would consent to be approached by a member of the research team. During this initial contact with the research team willing patients were invited to the laboratory to provide written informed consent before beginning the procedures in section 3.3.2.

3.3.1 Statistical analysis

The *a priori* intention was to use ICC, Bland-Altman analysis, %SEM and %MDC to quantify the variation in inflection occurrence. However, because of poor recruitment and early study cessation due to COVID-19 results are presented merely as frequencies and descriptive statistics (mean ± SD).

3.3.2 Procedures

Visit one included the collection of venepuncture blood samples pre and post a symptom limited CPET. These samples provided information as to the full blood count, biochemical profile and levels of Troponin T prior to, and immediately following CPET (Troponin T). Samples would be used to determine baseline biochemical differences between participants and monitor for evident myocardial damage. Each CPET was performed on an electronically braked cycle-ergometer (eBike, General Electrical Company, USA) using an individualised ramp protocol (10 – 25 watts·min). Prior to testing the breath-by-breath gas analyser (Jaeger, Wuerzburg, Germany) was calibrated in line with the manufacturer's recommendations. Patients were then fitted with a face mask (Hans Rudolf Inc, USA), 12-lead ECG (CareFusion, USA) and automated blood pressure cuff (SunTech Medical, USA).

Each test began with the patient sitting stationary on the ergometer for 3-minutes (reference phase), this was followed by a 3-minute period of cycling with no resistance at a cadence of 60 revolutions per minute (rpm) (reference phase). Beginning in the seventh minute, the resistance on the ergometer began gradually increasing until the patient reached volitional exhaustion, or the researchers made the decision to terminate the test. A twelve lead ECG was recorded throughout the CPET, with heart rate and RPE sampled every minute, and blood pressure sampled every 2 minutes. Following test completion, the data were exported for analysis by two researchers

working independently from one another. Each researcher subjectively identified the point in each graph at which they believed an inflection had occurred. Consensus was to be reached after discussion in cases of disagreement between researchers.

If no infections were apparent from the data collected during visit 1 the patient was thanked for their time and informed that no further involvement was required. However, if the aforementioned inflections in O_2Pulse or $\Delta\dot{V}O_2$/ ΔWR were visible the patient was invited back to attend visit 2, during which an identical CPET was performed.

The same data analysis process was completed following visit 2, firstly to determine if the inflection(s) persisted, and secondly (if observed) to compare the work-rate (W) and heart-rate (HR) at which inflection(s) occurred. Once this had been established the patient was invited back to complete the third and final visit in which they were asked to cycle for 20 minutes at a work rate corresponding to the onset of inflection(s) minus two-thirds of the ramp rate (419). If the onset of inflection(s) from visit 1 and 2 did not converge over the same load (watts), then visit 3 was prescribed at the load corresponding to the difference between visits. Following the completion of the submaximal test the patients were assisted into a supine position and a qualified technician performed an echocardiogram to check for any visual evidence of wall motions abnormalities. As with visit one levels of Troponin T were collected pre and post exercise to determine if any biochemical evidence of myocardial damage was present.

3.4 Results

Between April 2019 and June 2020 all patients diagnosed as having a CTO on coronary angiogram were screened for eligibility to participate in this study (Figure 8). During the 18 months this study was open to recruitment nine patients agreed in principle to join. At this rate of recruitment (two patients per month) it would have taken approximately 24 months to achieve a sample of twelve. Due to the outbreak of COVID-19 and the finite PhD timeframe the decision was taken to pause recruitment and write up what data had been collected.

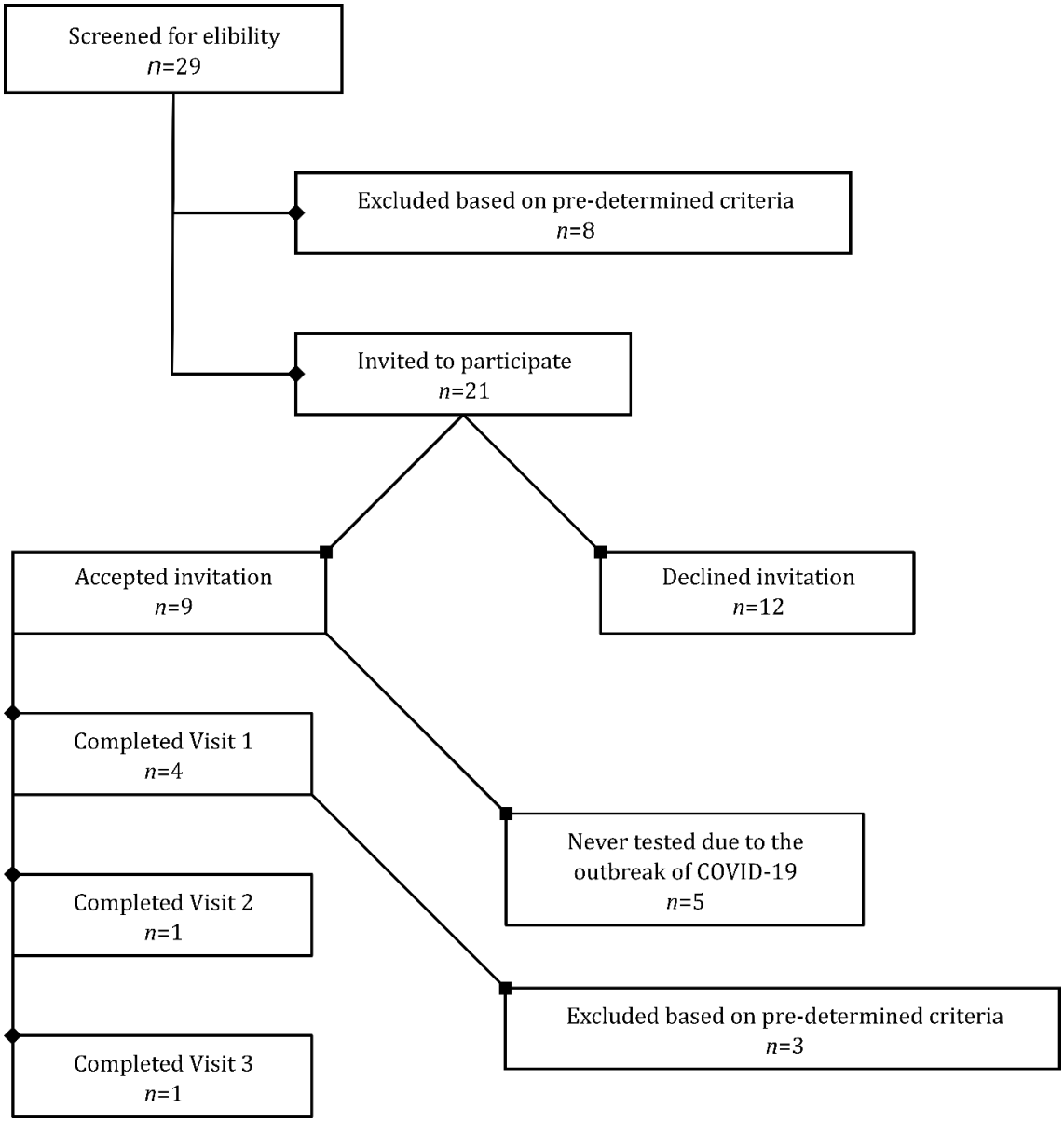

Figure 8. Schematic diagram of the participant recruitment process

None of the four recruited patients chose to drop out of the study of their own volition, thus this study had 100% retention rate. None of the four patients tested presented with ST-depression during CPET, and there were no adverse events due to testing procedures. Patient characteristics are presented in Table 5. All four patients were male with a mean age of 63.5 ± 5.4. The most commonly occluded vessel was the right coronary artery (RCA) (3/1). All patients were taking at least one medication to help relieve symptoms associated with their diagnosis.

Table 5. Baseline patient characteristics

Anthropometric Measurements	**ECHO1**	**ECHO2**	**ECHO3**	**ECHO4**	**Mean ± SD**
Sex	Male	Male	Male	Male	-
Age (years)	59	71	64	60	63.5 ± 5.4
BMI (kg·m^2)	25.2	19.4	29.1	22.6	24.1 ± 4.1
Wait to Hip Ratio	0.90	0.98	1.03	0.84	0.94 ± 0.08
Haemodynamic measurements					
Resting HR (bpm)	68	80	60	60	67 ± 9
Resting systolic blood pressure (mmHg)	138	111	133	131	128 ± 12
Resting diastolic blood pressure (mmHg)	100	75	77	71	81 ± 13
Presenting diagnosis					
Occluded vessel	RCA	RCA	RCA	LAD	-
CCS class	1	1	1	2	1.25 ± 0.5
Pack years smoked	0	50	18	5	18.25 ± 22.49
Diabetes (%)	No	Yes	No	No	-
PCI	Waiting	Failed	Not attempted	Waiting	-
Venepuncture Measures					
Haemoglobin (g/L)	155	151	157	(<)97	140 ± 28.77
White blood cell count (*10^{9}L)	5.5	6.7	7.5	4.7	6.1 ± 1.24
Platelets (*10^{9}L)	228	(<)107	337	273	236.25 ± 97.08
Sodium (mmol/L)	138	140	137	135	137.5 ± 2.08
Potassium (mmol/L)	4.2	4	4.5	4.2	4.23 ± 0.21
Urea (mmol/L)	6.1	(>)8.8	4.9	5.7	6.38 ± 1.7
Creatinine (umol/L)	0.083	0.092	0.081	0.077	83.25 ± 6.34
Glucose (mmol/L)	5.3	(>)7.6	5.6	(>)6.1	6.15 ± 1.02
Troponin T (ng/L)	8	14	6	<5	9.3 ± 4.2
Medication					
Antiplatelet	Yes	Yes	Yes	Yes	-
Beta Blocker	-	-	Yes	Yes	-
ACE inhibitor	-	-	Yes	Yes	-
Statin	-	Yes	Yes	Yes	-
Oral Nitrate	-	Yes	-	Yes	-
Calcium channel blocker	-	Yes	Yes	-	-

PCI: percutaneous coronary intervention; CCS class: Canadian Cardiovascular Society class; BMI: Body Mass Index; HR: Heart Rate; RCA: Right Coronary Artery; LAD: Left Anterior Descending: (</>) above or below normative values

3.4.1 Visit One

Cardiopulmonary exercise test variables from all visits are presented in Table 6.

Table 6. CPET data for all patients at visit one

Visit One					
Variable	**ECHO1**	**ECHO2**	**ECHO3**	**ECHO4**	**Mean ± SD**
$\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})	18.4	25.3	21.6	17.2	20.62 ± 3.60
Percent predicted $\dot{V}O_{2peak}$	43.93	112.8	87.48	57.68	75 ± 31
VAT (mL·kg^{-1}·min^{-1})	12.4	16.5	13.8	11.7	13.6 ± 2.12
VAT % $\dot{V}O_{2peak}$	67.40	65.22	63.89	68.02	66.13 ± 1.92
Peak HR (bpm)	112	120	136	111	120 ± 12
Percent predicted peak HR	91.28	105.6	114.09	90.98	100 ± 11
Peak WR (watts)	100	96	127	93	104 ± 16
Peak O2pulse (mL/beat)	11.6	12.6	14.5	12.9	12.9 ± 1.20
$\Delta\dot{V}O_2/\Delta$WR slope	8.51	10.74	10.72	8.85	9.7 ± 1.2
O2pulse at inflection (mL/beat)	-	-	13.7	-	-
WR at inflection (watts)	-	-	104	-	-
$\dot{V}O_2$ at inflection (mL·kg^{-1}·min^{-1})	-	-	19.1	-	-
HR at inflection (bpm)	-	-	113	-	-
Time elapsed at inflection (sec)	-	-	630	-	-
RER at inflection	-	-	1.1	-	-
Systolic BP at inflection (mmHg)	-	-		-	-
Diastolic BP at inflection (mmHg)	-	-		-	-
OUES	1.77	1.54	1.70	1.81	1.7 ± 0.12
CPET duration (secs)	396	566	753	550	566.25 ± 146.20
Peak RER	1.18	1.27	1.18	1.26	1.22 ± 0.05
Peak RPE	-	20	20	19	-
Δ Troponin T (ng/L)	-1	1	0	0	0 ± 0.8
Visit Two					
$\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})	-	-	21.7	-	-
Percent predicted $\dot{V}O_{2peak}$	-	-	89.19	-	-
VAT (mL·kg^{-1}·min^{-1})	-	-	13.7	-	-
VAT % $\dot{V}O_{2peak}$	-	-	63.13	-	-
Peak HR (bpm)	-	-	158	-	-
Percent predicted peak HR	-	-	133	-	-
Peak WR (watts)	-	-	121	-	-
Peak O2pulse (mL/beat)	-	-	15.2	-	-
$\Delta\dot{V}O_2/\Delta$WR slope	-	-	10.74	-	-
O2pulse at inflection (mL/beat)	-	-	13.7	-	-
WR at inflection (watts)	-	-	109	-	-
$\dot{V}O_2$ at inflection (mL·kg^{-1}·min^{-1})	-	-	19.4	-	-
HR at inflection (bpm)	-	-	116	-	-
Time elapsed at inflection (sec)	-	-	660		
RER at inflection	-	-	1.22	-	-
SBP at inflection (mmHg)	-	-		-	-
DBP at inflection (mmHg)	-	-		-	-
OUES	-	-	1.87	-	-
CPET duration (secs)	-	-	714	-	-
Peak RER	-	-	1.23	-	-
Peak RPE	-	-	18	-	-
Visit Three					
Average $\dot{V}O_2$ over the final 5min	-	-	11.50	-	-
Average $\dot{V}O_2$ as a % of peak	-	-	53.1	-	-
Average O2pulse over the final 5min	-	-	11.4	-	-
Average HR over the final 5min	-	-	124	-	-
Average HR as a % of peak recorded	-	-	78	-	-
Average SBP over the final 5min	-	-	193	-	-
Average DBP over the final 5min	-	-	85	-	-
Average RPE over the final 5min	-	-	17	-	-
Δ Troponin T (ng/L)	-	-	-1	-	-

Analysis of the $\Delta\dot{V}O_2/\Delta WR$ slopes revealed no discernible inflections, abnormal increases (<10 $mL \cdot min^{-1} \cdot W^{-1}$) were however present in two of the four patients tested (Figure 9).

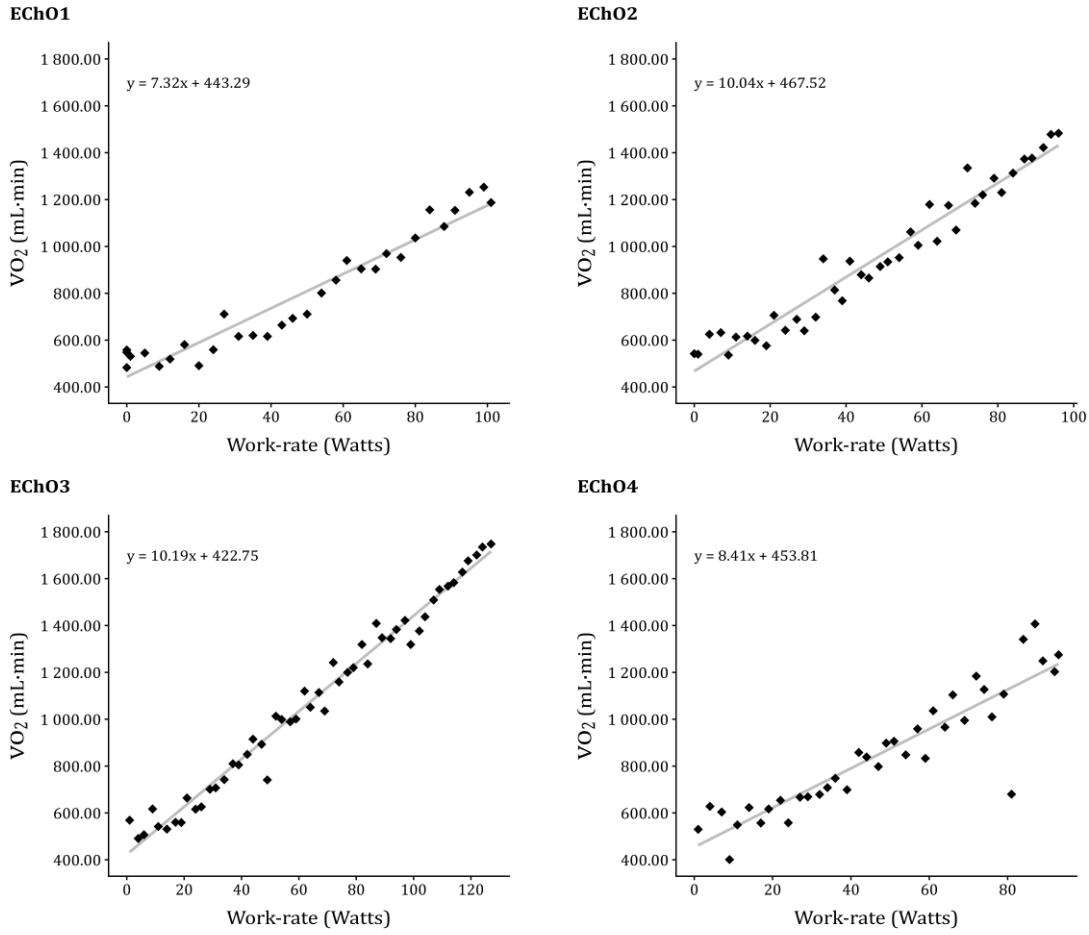

Figure 9. $\Delta\dot{V}O_2/\Delta WR$ slope plots from Visit 1 for all participants

Inflections in O_2Pulse were noted in only one of the four patients tested (EChO3) (Figure 10). In this patient the inflection was deemed to have occurred at a heart rate of 102 bpm and a work rate of 87 watts. This patient had a normal $\Delta\dot{V}O_2/\Delta WR$ slope. Troponin T was not abnormally elevated in any patients either at baseline or post CPET.

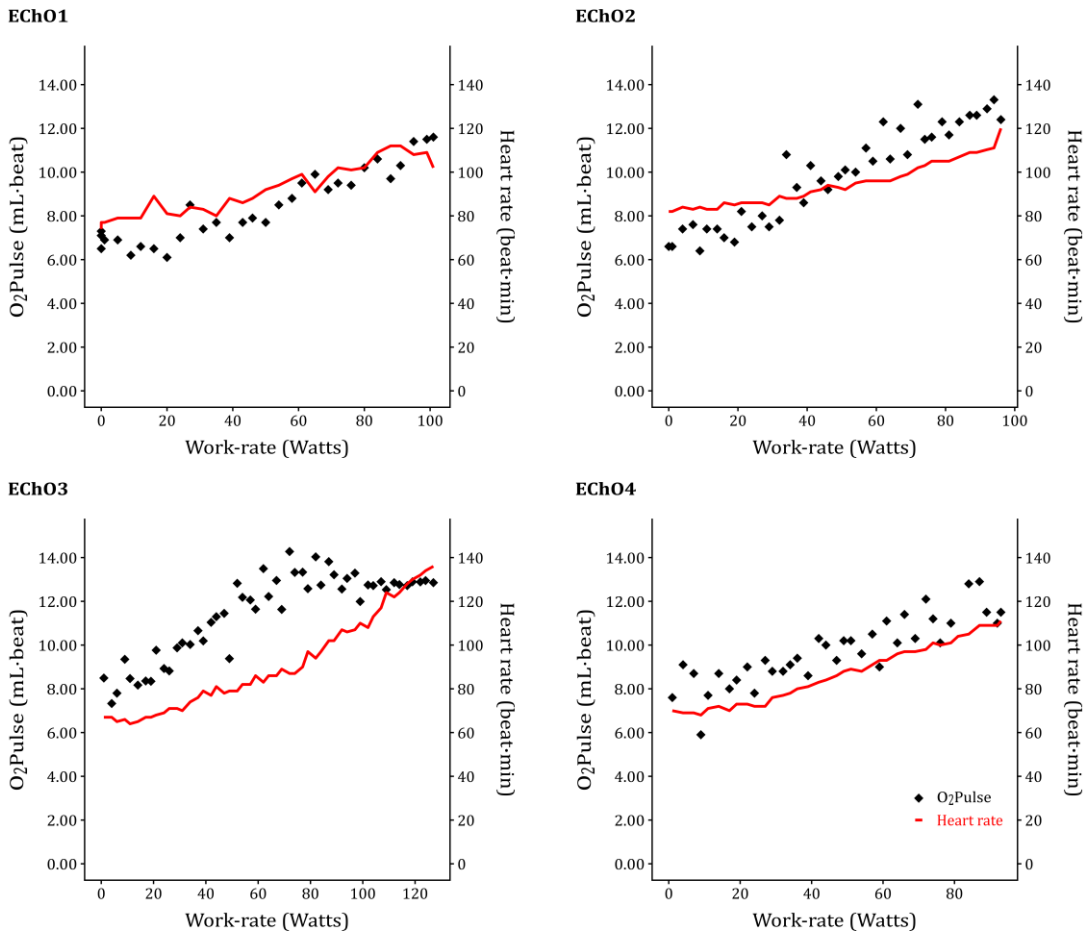

Figure 10. O_2Pulse and heart rate curve plots from Visit 1 for all participants

3.4.2 Visit Two

Three patients did not meet the extended inclusion criteria following visit one and were subsequently excluded from further participation. Consequently, only one participant progressed on to visit two.

As with visit one the participant exhibited no identifiable inflection in the $\Delta\dot{V}O_2/\Delta WR$ slope during visit two. The negative inflection in O_2Pulse, with concomitant positive inflection in HR observed during visit one persisted during visit two. The O_2Pulse inflection during visit two occurred at a heart rate of 107 and a work rate of 97 watts, this translates to an additional 60 seconds of work (Figure 11). The mean work rate at inflection across both visits was 92 W. As inflections were observed during visit one and visit two, the participant was invited back to undertake 20 minutes of continuous workload exercise during visit three.

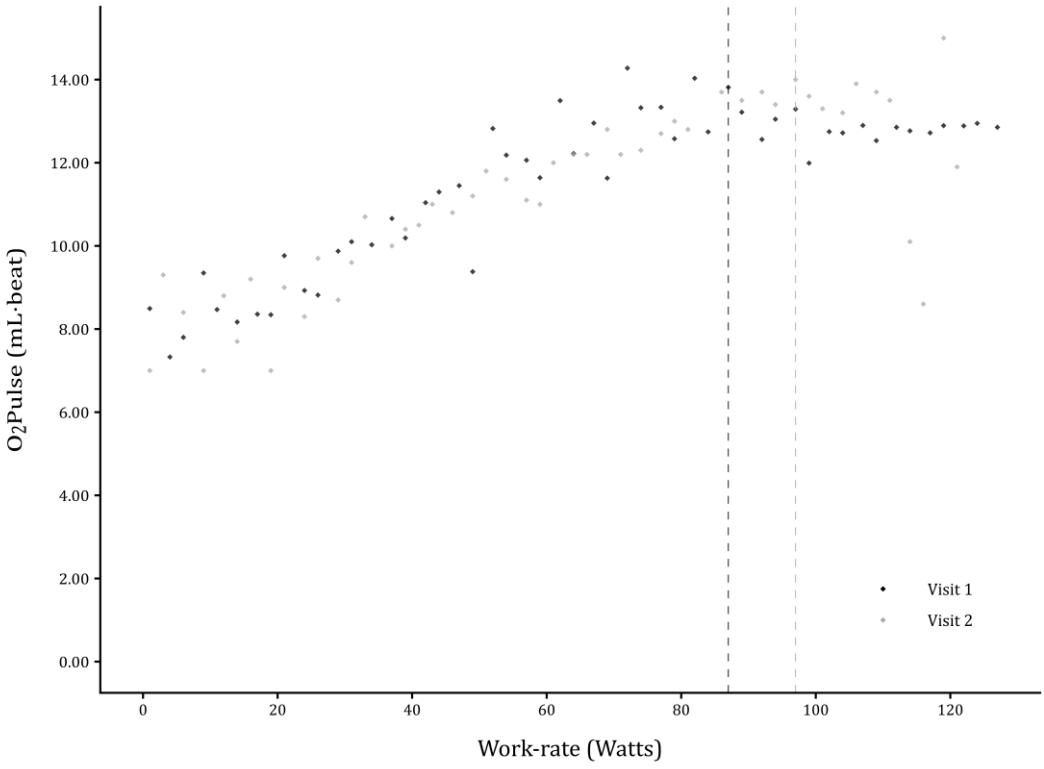

Figure 11. Inflections in O_2Pulse during visits one and two for ECHO3

3.4.3 Visit Three

Visit three entailed 20 minutes of continuous cycling at a workload of 85 W (mean WR at inflection minus 2/3 of the rap rate) (Figure 12). The mean oxygen pulse over the final five minutes of fixed workload exercise was 11.4 mL·beat^{-1}, this corresponds to 82% of the mean O_2Pulse inflection point from visits one and two. As with the initial CPET troponin T levels were not elevated post 20 minutes of continuous exercise in this patient.

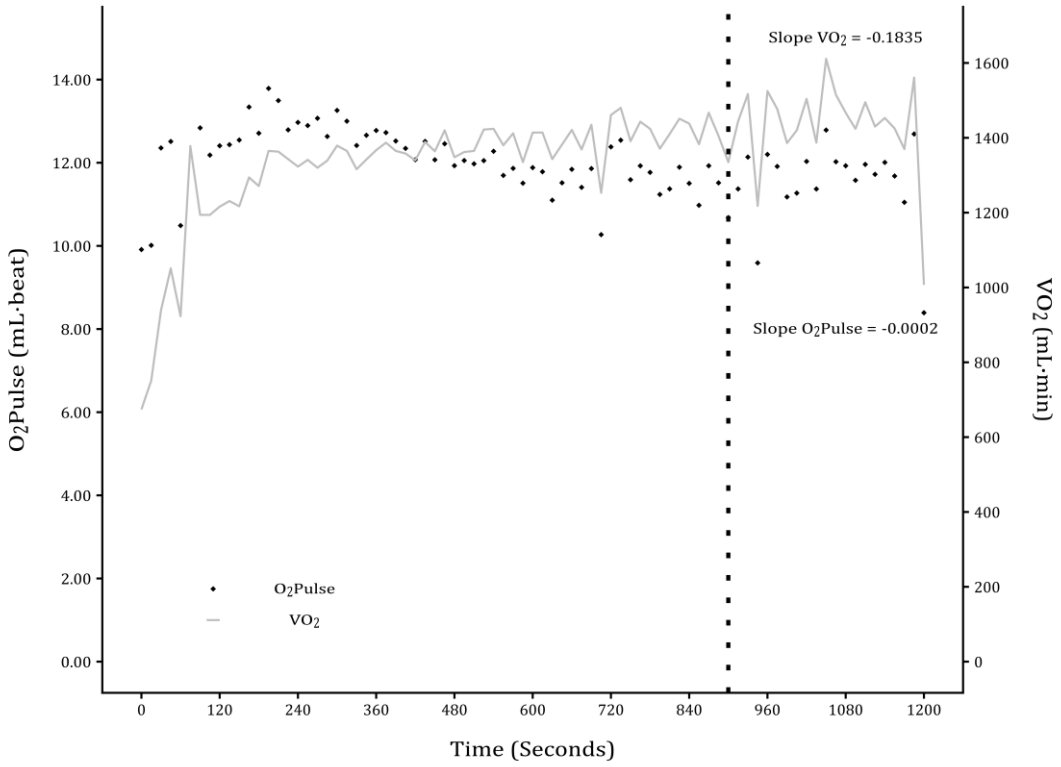

Figure 12. $\dot{V}O_2$ and O_2Pulse curves from Visit

The participant did not present with any symptoms of ischaemia or ST-segment depression during exercise. Occasional premature ventricular contractions were observed throughout the exercise period with no signs of serious arrhythmia. Furthermore, no inflections indicative of myocardial ischaemia were identifiable in O_2Pulse.

Immediately upon cessation of exercise the patient was assisted into a supine position and echocardiography was performed by an experienced operator. Despite acquiring clear images there were no signs of wall motion abnormalities consistent with myocardial ischaemia.

3.5 Discussion

The primary aim of this pilot feasibility study was to determine the rates of recruitment and adherence to the study protocol. Over the course of eighteen months this study attempted to recruit single vessel CTO patients from the local area (Humberside). In this period, nine patients agreed in principle to participate. However, due to the impact of COVID-19 and subsequent lock-down restrictions, it was not possible to test five

patients. If recruitment were to continue at this rate (absent of COVID-19) it would take approximately 24 months to achieve the pre-determined sample size of twelve. Therefore, this protocol is not feasible as a single centre study in this area. Retention amongst the four patients tested was 100%, however only one patient met the criteria to progress on to the second and third study visits. As only one patient completed the entire protocol it was not possible to use the planned frequentist statistical methods to determine reliability and agreement between inflection points as planned, and therefore there is not enough preliminary data with which to perform a power calculation for a larger and possibly multi-centre study in the future.

If inflections in $\Delta\dot{V}O_2/\Delta WR$ and O_2Pulse are to be used to prescribe exercise intensity for exCR, and guidelines recommend remaining below the ischaemic or anginal threshold (415), then the repeatability, of such inflections needs to be established. Previous studies using inflections in $\Delta\dot{V}O_2/\Delta WR$ and O_2Pulse have performed only one test (27,29,30) and therefore it was not known how repeatable these inflections could be. In the present study one of the four patients tested was found to have an inflection in the linear progression of O_2Pulse. The inflection was present in both CPETs with only minimal differences in the WR (10 W) and HR (5 beats) at which it occurred. Although this provides information from only a single patient, it does suggest that when present, infections could be used to accurately prescribe exCR intensity.

It is believed that the reductions in stroke volume caused by the onset of myocardial ischaemia are manifest by inflections in both O_2Pulse and $\Delta\dot{V}O_2/\Delta WR$. However, when O_2Pulse and HR are considered together over WR in the present study (Figure 10) the negative inflection in the former coincides with a positive inflection in the latter. It would appear therefore that a compensatory increase in HR occurring immediately after the onset of ischaemia can in some instances maintain cardiac output and masks the signs of ischaemia in the slope of $\Delta\dot{V}O_2/\Delta WR$.

Indeed, none of the four patients tested had identifiable inflections in the slope of $\Delta\dot{V}O_2/\Delta WR$. Although the present study has a highly restricted sample size these findings would seem to be in conflict with the evidence presented by Belardinelli and colleagues and others (29,30,274,302,401), who have demonstrated $\Delta\dot{V}O_2/\Delta WR$ inflections in diagnosed and suspected occlusive CAD patients during ramped CPET. Belardinelli and colleagues (30) report a 4% rate of false negative results when using inflections in $\Delta\dot{V}O_2/\Delta WR$ and O_2Pulse to diagnose obstructive CAD. The cohort in the present study all had angiographically documented CTO and only one from four had

clear inflections in O_2Pulse without any change in $\Delta\dot{V}O_2/\Delta WR$. These findings are surprising if the rate of false negative tests when using these inflections is 4%. However, there are methodological and cohort differences that could explain the divergent findings.

In both of the referenced studies by Belardinelli and colleagues patients stop cardiac medications such as oral nitrates, calcium-channel blockers, and beta-blockers prior to testing. In contrast I chose to allow patients to continue with their optimal medical therapy as prescribed as I believed this was in the patients' best interest. Furthermore, any inflections used to guide exCR intensity that were collected whilst not taking prescribed medications would likely cease being accurate when medications were reintroduced. Only one patient from the current cohort was not taking any medications associated with heart rate reduction or vasodilation. The pharmacotherapy of the remaining three patients could have impacted the results in two related but separate ways. Firstly, beta-blockers reduce heart rate and thus myocardial O_2 demand, which has been shown by Yoshida et al (292) to blunt the compensatory increase in HR above the ischaemic threshold, causing a greater reduction in $\Delta\dot{V}O_2/\Delta WR$. However, this is not something that was seen in the current study, even in light of a clear inflection in O_2Pulse. Secondly, ACE inhibitors, oral nitrates, and calcium channel blockers can induce arterial vasodilation, which in the context of this study could have increased the capacity of collateral arteries to perfuse otherwise ischaemic myocardium. Consequently, the patients enrolled in this study are perhaps exercising to their pharmacological rather than physiological limits.

In the present study, I prospectively recruited patients diagnosed as having single-vessel CTOs, whereas the cohorts recruited by Belardinelli and colleagues were heterogeneous in composition ranging from single- to triple-vessel disease. Belardinelli and colleagues (30) reported that only 9/64 CAD patients diagnosed through inflections in $\Delta\dot{V}O_2/\Delta WR$ and O_2Pulse had single vessel disease, with the remainder having double- (24) and triple-vessel disease (31). Multiple-vessel disease, even in the absence of CTOs may impact a greater volume of myocardium, which would have a more pronounced impact upon stroke volume and thus $\Delta\dot{V}O_2/\Delta WR$ and O_2Pulse. Furthermore, the authors make no specific mention of CTOs in the cohort. It is well established that the coronary collateral circulation is developed to a greater extent in the presence of CTO versus non-CTO CAD (420,421). Therefore, the lack of $\Delta\dot{V}O_2/\Delta WR$

inflections in the present study may be explained by a smaller ischaemic territory in combination with greater collateral development and effective pharmacotherapy.

Two of the patients recruited to the present study had $\Delta\dot{V}O_2/\Delta WR$ slopes below 8.5 $mL \cdot min^{-1} \cdot watt^{-1}$ which suggests poor cardiovascular efficiency. The same patients also exhibited low HR and $\dot{V}O_{2peak}$ when expressed as percent predicted. These low values are not likely to be caused by poor effort as both had peak RER >1.05. They may instead be caused by poor cardiovascular fitness, which perhaps stopped them from exercising to the point of ischaemia.

In the present study only one patient progressed on to perform 20 minutes of fixed workload exercise at an intensity corresponding to O_2Pulse inflections (minus 2/3 ramp rate). Therefore, generalisations as to the safety of prescribing this intensity of work in all CTO patients cannot be made. However, it should be noted that exercise was well tolerated in this patient and there were no adverse events either during or following the test session. The patient exhibited no signs or symptoms of myocardial ischaemia and presented only minor premature ventricular contractions throughout the session. Furthermore, the acquisition of clear echocardiographic images immediately following the cessation of exercise revealed no evidence of any wall motion abnormality associated with myocardial ischaemia. The exercise intensity was prescribed (inflection minus 2/3 ramp) to allow for some $\dot{V}O_2$ drift to occur without driving the intensity beyond the ischaemic threshold.

3.6 Conclusion

This study sought to determine the feasibility of recruiting and retaining a cohort of twelve CTO patents from the local area to undertake the study procedures. Recruitment was progressing slower than anticipated before it was ultimately halted by the government mandated COVID-19 lockdown. Prior to closing, the study was recruiting at a rate of one patient every two months and therefore it would not be feasible as a single centre study in this area. Although full recruitment was not achieved my preliminary findings conflict with what has previously been reported. The present cohort included angiographically documented CTOs, which theoretically should have resulted in individuals presenting with myocardial ischaemia during maximal exercise. However, hypothesised inflections in CPET variables previously reported to indicate myocardial ischaemia onset were observed in only one of the present cohort. The reasons for my anomalous findings when compared to previously reported data are not clear. Future research should aim to establish whether previously described

inflections are present in a larger cohort of CTO patients and determine whether inflections persist in non-CTO CAD patients who do not stop their prescribed pharmacotherapy.

3.7 Acknowledgements

We would like to thank the research nurses and patients at Castle Hill Hospital for participating in this research project.

Chapter 4 : Exercise Training as a Mediator for Enhancing Coronary Collateral Circulation: A Review of the Evidence

4.1 Abstract

Coronary collateral vessels supply blood to areas of myocardium at risk after arterial occlusion. Flow through these channels is driven by a pressure gradient between the donor and occluded artery. Concomitant with increased collateral flow is an increase in shear force, a potent stimulus for collateral development (arteriogenesis). Arteriogenesis is self-limiting, often ceasing prematurely when the pressure gradient is reduced by the expanding lumen of the collateral vessel. After the collateral has reached its self-limited maximal conductance, the only way to drive further increases is to re-establish the pressure gradient.

During exercise, the myocardial oxygen demand is increased, subsequently increasing coronary flow. Therefore, exercise may represent a means of augmenting arteriogenesis in patients with stable coronary artery disease. Studies investigating the ability of exercise to drive collateral development in humans are inconsistent. However, these inconsistencies may be due to the heterogeneity of assessment methods used to quantify change. This article summarises current evidence pertaining to the role of exercise in the development of coronary collaterals, highlighting areas of future research.

Keywords: chronic total occlusion, angiogenesis, arteriogenesis, shear force.

4.2 Introduction

Coronary collateral vessels are pre-existing anastomotic pathways interconnecting epicardial coronary arteries (190). The ability of these vessels to connect proximal and distal portions of the same artery (antegrade), or divergent adjacent vessels (retrograde) can provide an alternative blood supply to areas of the myocardium inadequately perfused by their native artery (Figure 13). Whilst these collaterals reduce the ischaemic burden, they are seldom sufficient to completely overcome ischaemia in patients with stable coronary artery disease (CAD), particularly during exercise (220). Furthermore, in the acute setting, the presence of collaterals is associated with an improved rate of survival following myocardial infarction (199). The development of collaterals is therefore an important protective process in patients with cardiovascular disease. However, the processes underpinning the development of coronary collaterals is complex, and the extent of development varies widely amongst individuals in clinical practice. In this review, I evaluate the current evidence regarding the development of coronary collaterals with a particular focus on the potential role of exercise.

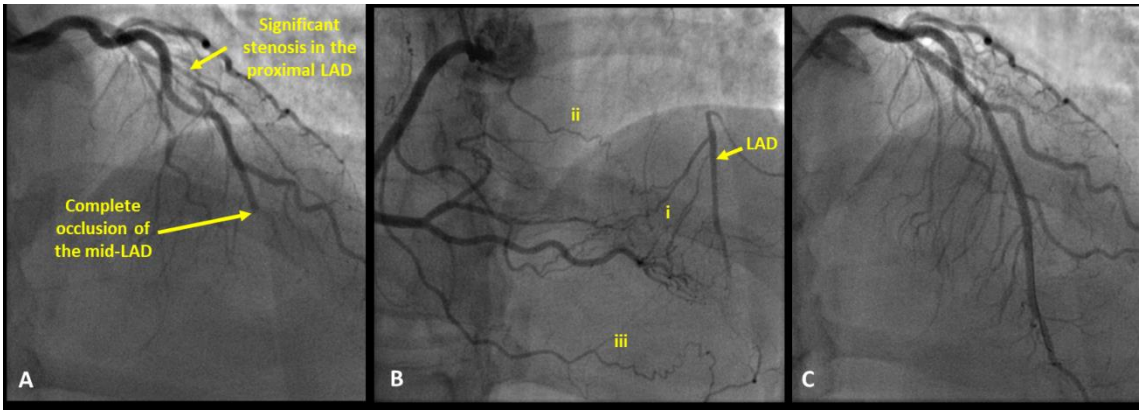

Figure 13. Angiography images of a patient with a chronic total occlusion (CTO) of the left anterior descending artery (LAD). A: contrast injected into the left coronary artery demonstrates a severe stenosis in the proximal part of the LAD, contrast flow stops abruptly at the point of complete occlusion in the mid-LAD. B: contrast injected into the right coronary demonstrating retrograde filling of the LAD via multiple collateral channels, both septal (i) as well as epicardial (ii, iii) channels can be identified. C: contrast injected into the left coronary artery after successful revascularisation of the LAD. Two stents have been implanted (one in the proximal LAD and a second at the site of the occlusion – Angiogram supplied by Dr Angela Hoye)

4.3 Review of Relevant Literature

4.3.1 Coronary collaterals

Post mortem studies have been used to demonstrate the presence of coronary collaterals even in individuals with healthy hearts (422), most likely related to remnants of the embryonic vascular network (190). In the presence of obstructive CAD, the extent of collateral development is related to both the severity and duration of obstruction. A more extensive network and larger calibre collateral vessels are evident in patients who have a longer history of angina. Interestingly, coronary collateral blood vessels are evident in 63% of hearts with significant CAD as opposed to 95% of hearts with a completely occluded coronary artery (423,424).

Human coronary arteries are not end arteries, they are instead interconnected by a network of pre-existing arteriolar anastomosis (198). Blood within this system, will flow from an area of high, to an area of low pressure, traveling across the path of least resistance. If the main coronary arteries are patent, then they indeed represent the most efficient path for coronary flow, and little flow will likely pass through the anastomosis. However, if the coronary arteries become stenotic and ultimately occluded, the pressure in the vessel distal to the occlusion will become significantly lower than that in the proximal portion. This pressure gradient will drive flow via the native collateral circuit (Ohm's Law).

$$\text{Flow} = \frac{\text{Proximal pressure} \; - \; \text{Distal pressure}}{\text{Collateral artery resistance}}$$

Increasing flow through these arterioles augments the physical forces acting upon the vessel wall (fluid shear stress (FSS)) (212,213). This enhanced physical stimuli causes the intimal endothelial layer of the collateral arteriole to becomes activated, initiating a process of gene expression that results in cellular proliferation and structural remodelling of the vessel (216,425). Once the endothelium is activated the vessel passes through four stages of vascular remodelling, including an increase in vascular permeability, digestion of extracellular scaffolding, reconstruction of the smooth muscle cell (SMC) coat along with production of a larger vascular scaffolding, and pruning of additional collateral vessels (205). Over the course of one week, arterioles of between 30–50 μm in diameter (207), ensheathed in one to two layers of SMC's (410) can develop into arterial structures up to 20-fold larger and more robust than their previous formation (217). These vessels become capable of supporting demonstrably greater levels of blood flow, with some researchers reporting a 25-fold increase above

baseline levels (207). This mechanism by which pre-existing collateral vessels mature into more substantial connections has been termed arteriogenesis (233).

Under pathologically occlusive conditions, coronary collateral vessels typically demonstrate compensatory maturation sufficient enough to provide only 30-40% of the flow supplied by the artery they bypass (205). This is due to the impact that arteriogenesis has on the collateral pressure gradient. As the collateral vessel matures, its luminal diameter increases, providing more flow to the distal portion of the occluded vessel. This reduces the pressure gradient, eventually reaching a nadir at which FSS no longer surpasses the threshold stimulation for collateral growth (219). At this point the collateral vessel will not continue to mature without increased provocation (205).

To test this assumption, Pipp and co-workers undertook a study using the swine hind limb model of occlusion in which the distal section of the ligated femoral artery was surgically grafted to the venous system (213). This graft acted as a pressure release valve, shunting blood from the distal portion of the occluded vessel. Consequently, the pressure in the vessel distal to the occlusion remained reduced, thereby maintaining the pressure gradient across the collateral. The arteriovenous shunt model produced a 2.3-fold increase in maximal collateral flow when compared to the standard ligature only model. A similar study by Eitenmüller and colleagues demonstrated consistent results in a rabbit model. After 4 weeks, the collateral vessels were sufficiently developed to provide 199±19% recovery of natural flow in animals with an arteriovenous shunt, in contrast to the non-shunted arteries which demonstrated no increase in flow beyond the initial 7 days (219).

4.3.2 Clinical studies

The aforementioned animal models are not suitable for transfer into human studies of coronary collateral development. However, an alternative mechanism could be to drive collateral development by increasing the arterial pressure proximal to the site of an occlusion. One method that has been evaluated is enhanced external counterpulsation (EECP). During EECP lower limb pressure cuffs are timed to synchronously inflate to an external hydraulic pressure of 300 mmHg during the diastolic phase of the cardiac cycle. This cuff inflation augments diastolic blood pressure and cardiac output, increasing pressure across all branches of the coronary tree (233). In principle, this transiently replicates the changes in physical forces (FSS) that are usually localised to collaterals terminating distal to an arterial stenosis. Clinical studies have demonstrated

that EECP does improve myocardial perfusion in CAD patients (234). Furthermore, results of a randomised controlled trial demonstrate that EECP increases the collateral flow index (CFI), indicating that clinical improvements are related to the development of coronary collateral vessels (236). Whilst it remains a promising avenue for clinical arteriogenesis, EECP procedures require expensive specialised equipment, trained staff, and numerous visits to medical facilities.

4.3.3 Exercise Training

An alternative means of transiently increasing a collateral vessel's FSS without specialist equipment, is physical exercise. During physical exercise training, heart rate and blood pressure are augmented in order to manage the increased cellular respiration (426). The peripheral increase in oxygen demand during exercise, is mirrored centrally by an increase in myocardial oxygen demand, subsequently driving an approximate 5-fold increase in coronary blood flow (426). This increase results in an amplification of the FSS disseminated across the endothelium of the coronary vasculature, and thus is hypothesised to augment arteriogenesis (Figure 14).

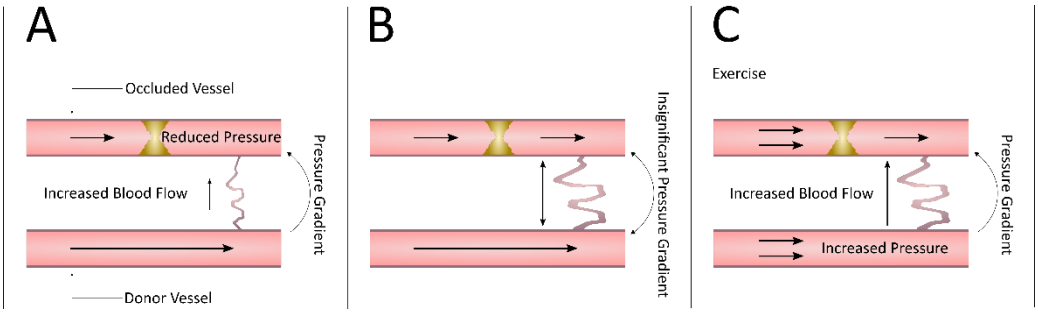

Figure 14. Pressure gradient of a developing collateral. Early after development of an arterial stenosis, low pressure distal to the stenosis draws flow through the collateral and increases shear stress on the endothelium (A). Collateral development reaches a plateau; collateral diameter increases, reducing collateral shear stress (B). An increase in donor artery pressure during exercise training reintroduces a pressure gradient across the collateral; fluid shear stress is again increased across the collateral endothelium (C)

Coronary perfusion pressure is the outcome of aortic diastolic pressure minus left ventricular end-diastolic pressure (427). The majority of coronary flow occurs during diastole, and any increase in heart rate negatively impacts diastole to a greater extent than systole (427). Regular exercise can reduce the resting heart rate, leading to an

increase in diastolic time and therefore an increase in shear stress. This hypothesis was evaluated in relation to arteriogenesis by using ivabradine medication which lowers the heart rate by blocking the If-channel of the sino-atrial node. Following positive data from animal studies (428), a randomised controlled trial of 46 patients with stable CAD was undertaken (429). At 6 months, patients who received ivabradine had a significant increase in CFI (p=0.05); those who received a placebo had a decrease in the CFI.

In 1957 Eckstein (430) reported that an exercise intervention successfully augmented collateral development in dogs with surgically occluded left circumflex coronary arteries. The researchers determined which animals developed ECG changes when the vessel was ligated, signifying a lack of collateral development at baseline. These animals had the ligation relaxed and, after recovering for one week, were randomised into exercising versus non-exercising groups. Exercise training was undertaken for 15-20 minutes, 4 times per day, 5 days per week for between 6 to 8 weeks. Subsequent assessment demonstrated that exercise trained animals had higher retrograde coronary flow, indicative of collateral development. In 1981 Scheel and colleagues (431) undertook a similar study in dogs with ligated circumflex arteries. They too found that 8 weeks of exercise training augmented collateral growth when compared to a group of sedentary animals. Although intriguing these results must be interpreted with caution before being extrapolated to human coronary pathophysiology, as there are substantial differences between species (410).

We have identified nine studies related to exercise-induced augmentation of coronary collateral flow that are included in this narrative review. Whilst my search strategy was not systematic, the apparent dearth of studies is indicative of the sparseness of evidence in this field. The nine studies I identified can be divided into two groups (Table 7 and Table 8) depending on their use of CFI. The Collateral flow index is now considered the 'gold standard' measurement of collateral flow and is much more sensitive than other modalities at detecting changes in collateral flow (432). Each of the five studies using CFI reported a relationship between CFI and exercise. In contrast, only two of the four studies not using CFI reported significant changes. Whist the heterogeneous methodology of these studies precludes meta-analysis, it is evident that introducing CFI into this field results in a more robust and accurate assessment of collateral channel conductance, compared to qualitative assessment alone.

Table 7. Summary of human studies examining exercise-induced changes in collateral flow, prior to the introduction of the coronary flow index measurement

Study	Population	Design	Duration	Intervention	Control	Outcomes	Results
Nolewajka et al., 1979	n = 20 men Mean age 48 years MI previous 3-6 months	RCT	7 months	Exercise = 60-70% max HR, 2x per week for 1 hour (Group session), supervised exercise session x2 per week, unsupervised home exercise x1 per week	x2 supervised sessions per week (Group) = Light calisthenics & volleyball.	Angiography, Scintigraphy, CPET with stress ECG	Exercise group significantly increased angina threshold and decreased HR at a set workload ($p<0.01$). No improvement in collateralization, perfusion or ventricular function.
Fujita et al., 1988	n =16 (4 men/2 women) Mean age 58 years ≥1 major coronary artery obstruction (16 CTO's)	RCT	22 days	Exercise (treadmill) 2x daily until angina pain was 60-80% max previously felt. Patients were pre-treated with 5000 IU intravenous heparin.	Exercise (treadmill) 2x daily until angina pain was 60-80% max previously felt.	ECG treadmill test (total exercise time, Rate pressure product (RPP) to time of angina), Radionuclide ventriculography, Angiography	Pre-exercise heparin group demonstrated significant increase ($p<0.001$) in exercise duration and RPP, as well as increase in RPP at angina onset & ST depression ($p<0.01$). None of the above were changed in the exercise only group. Angiography demonstrated improved collateralization (however this was only evaluated in the exercise & heparin group). No significant increase in ventricular function.
Niebauer et al., 1995	n = 113 men Mean age 53.5 years Documented coronary stenosis Left ventricular ejection fraction > 35%	RCT	1 year	Initial 3 weeks on a metabolic ward learning to reduce the fat content of their diet (<20% total energy). 30 min exercise daily on cycle ergometer at a target heart rate close to 75% max (achieved). ≥2 group training sessions per week (60min)	Initial week on metabolic ward receiving identical instructions on diet and the importance of regular physical exercise. Adherence to these instructions was left to their initiative (usual care given by physician)	Angiography, ventriculography, symptom limited exercise test with thallium-201 scintigraphy	Reduction in stenosis severity in the intervention group ($p<0.05$ versus control). No significant change in collateral formation for either group at 1 year. When both groups of patients were combined, there was a correlation between stenosis progression and in increase in collaterals ($p<0.00001$). No significant correlation between collateral formation and exercise performance. No significant difference between collateral formation and stress induced myocardial ischaemia on thallium-201 scintigraphy
Belardinelli et al., 1998	n = 46 (42 men / 4 women) Mean age 57 years Chronic coronary artery disease and impaired left ventricular function (ejection fraction < 40%)	RCT	8 weeks	Supervised exercise (cycle ergometer) at 60% of peak oxygen uptake for 60 min 3x per week for 8 weeks	Avoid regular exercise and activity with caloric expenditure over 80% peak oxygen consumption. Given a list of acceptable and unacceptable activities	CPET, Stress Echo, Scintigraphy, Angiography	VO_2 peak increased in exercise group versus control ($p<0.001$ versus control). Oxygen pulse for a set relative intensity was improved in exercise group ($p<0.01$). Collateral score significantly increased in the exercise group. Ejection fraction significantly improved in the exercise group ($p<0.001$ versus control). Thallium activity (scintigraphy) significantly improved in the exercise group ($p<0.001$ versus control). Mean collateral score significantly increased only in the exercise group ($p<0.001$ versus control).

Table 8. Summary of human studies examining exercise-induced changes in collateral flow through measurement of the collateral flow index

Study	Population	Design	Duration	Intervention	Control	Outcomes	Results
Zbinden et al., 2004	n =1 male Age 46 years Healthy amateur long distance runner	Case study	3 years	Angiography performed during 3 phases of endurance training: 1 = Baseline 2 = Intermediate 3 = High	N/A	Echocardiogram, angiography, CPET, CFR, CFI	Left ventricular ejection fraction increased from phase 1 to phase 2 but dropped below baseline levels during phase 3. Peak exercise capacity (W) increased during every subsequent phase. VO_2 (ml/min/kg) max increased during every subsequent phase. CFR increased during every subsequent phase. CFI increased from phase 2 to phase 3.
Zbinden et al., 2007	n = 40 (35 male / 5 female) Mean age 61 years Referred for coronary angiography	Retrospective cohort study	3 months	Cardiac Rehabilitation (jogging / cycling) 3x per week for >60 minutes at a target heart rate of 80% heart rate at VO_2 max.	Retrospective sedentary group who did not adhere to prescribed exercise programme.	Angiography, CFI, CPET	CFI in the occluded vessel significantly increased in the exercise group ($p<0.03$). CFI in the normal vessel significantly increased in the exercise group ($p<0.0002$). Significantly correlation between change in CFI and VO_2 max ($p<0.007$) in the exercise group.
Togni et al., 2010	n = 30 (28 men / 2 women) Mean age 59 years Chronic stable, non-occlusive CAD	Intra-individual comparison randomised crossover study	N/A	CFI comparatively measured during exercise and rest for each patient.	N/A	CFI, angiogram	CFI increased significantly from rest to peak exercise ($p<0.0002$).
Lin et al., 2012	n = 65 Mean age 60.2 years Single vessel CAD undergoing PCI	RCT	N/A	CFI during 1 minute of isometric hand grip exercise (50% maximal voluntary contraction)	CFI at rest.	CFI, angiogram	ΔCFI (CFI post occlusion – CFI pre occlusion) significantly increased in the exercising group ($p<0.01$).
Möbius-Winkler et al., 2016	n = 60 (45 men / 15 women) Median age 64 years Significant CAD (FFR≤ 0.75)	Open label RCT	4 weeks	High intensity versus moderate intensity training versus usual care	Usual care	CPET, CFI, angiogram	CFI increased significantly for both exercising groups when compared with usual care (high intensity $p=0.005$, moderate intensity $p=0.004$) VO_2 peak increased significantly for both exercising groups (high intensity $p=0.036$, moderate intensity $p=0.008$).

In 1979 Nolewajka and colleagues recruited 20 men with a mean age of 48 years, who had suffered a recent myocardial infarction (MI) (3-6 months) and randomly allocated them to an exercise training intervention (n=10) or control group (n=10) (433). Participants underwent a baseline angiogram, before those in the exercise group undertook an exercise training regimen. Exercise training consisting of one-hour, group-based exercise performed at 60-70% maximal achieved heart rate twice per week. Participants conducted a further two individual supervised sessions per week, and one day of unsupervised training at home. After 7 months, there was no difference between groups for collateral development (based on angiographic visualisation), myocardial perfusion or left ventricular function. However, the exercise-trained group experienced an increase in their angina threshold, indicating that some physiological adaptation had occurred. It is plausible however, that these adaptations took place in the peripheral musculoskeletal system, and not in the coronary vasculature. One limitation of the research was that controls also undertook group exercise sessions that included calisthenics and volleyball.

A lack of collateral development was also reported in a study of 133 patients with CAD randomised to a low-fat diet and exercise training, or control (434). Patients in the intervention group undertook ≥2 group training sessions (one hour each) per week, as well as 30 minutes of home-based exercise per day (target heart rate 'close' to 75% of max achieved). Unfortunately, this study is also confounded by the fact that the control group received the same educational sessions, focused on the benefits of healthy eating and exercise training, as the intervention group. Follow-up angiography was performed at 1 year in 92 patients (81%) which demonstrated no difference in collateralisation between the groups. Notably, adherence to the exercise training programme was only 68% (range 39-92%) for group sessions, and 60% self-reported participating in home-based training. It was also not possible to confirm whether the prescribed exercise intensity of group- or home-based exercise was maintained.

In contrast, a small study suggested that collaterals did increase if patients underwent treadmill exercise (435). However, the authors suggested that this effect was related to the use of IV heparin administered prior to each exercise session (based on results of animal experiments). A larger randomised study was subsequently undertaken by Belardinelli and colleagues (436), and demonstrated augmented collateral development in patients with CAD (n=50) who underwent an eight-week exercise training programme. Following baseline assessments, including maximal

cardiopulmonary exercise testing (CPET), and angiography, participants were randomised to either exercise training (n=26) or control (n=24). Contrary to the previous studies, control subjects were advised to avoid regular physical exercise, whilst those allocated to the intervention group performed approximately one hour of exercise training, 3 times per week, for 8 weeks using a cycle ergometer. The intensity of exercise was personalised to 60% of peak oxygen uptake ($\dot{V}O_{2peak}$) achieved during the CPET. After 8 weeks, 12 (46%) of the exercise-trained patients, and 11 (46%) controls underwent follow-up angiography. Collateral development was significantly augmented in the exercise-trained group, with no change in controls. Notably, the cohorts recruited in these studies are comparatively diverse. All patients recruited by Nolewajka et al (433) and Belardinelli et al(436) had a history of MI, compared to only 66% of patients recruited by Niebauer and colleagues(434). These differences could be indicative of a lower lesion severity in patients participating in the Niebauer et al study.

The aforementioned studies relied on visual assessment of coronary angiograms to measure collateral development. Unfortunately, the limited spatial resolution of angiography means that small diameter changes in collateral networks may have been overlooked (196). CFI is a more accurate direct measurement of collateral flow. Zbinden and colleagues (437) used CFI to evaluate collateral conductance in a healthy 46 year old male cardiologist with angiographically normal coronary arteries and no cardiovascular risk factors. The objective of the study was to invasively assess the non-pathological collateral flow response during three phases of exercise training. The participant had a 25-year history of amateur distance running and was performing 2 hours of endurance exercise training per week at the time of enrolment. He underwent coronary angiography during both intermediate (4 hours training per week for 4 months), and high phases of training (8-9 hours training per week for four months). Hyperaemic coronary flow reserve (CFR) was measured in the left anterior descending artery, as the maximum flow velocity after 18mg intra-coronary adenosine, divided by the baseline flow velocity. The CFI was determined by simultaneous measuring mean aortic pressure and mean distal coronary pressure at the end of a one-minute balloon occlusion.

$$\text{CFI} = \frac{\text{mean occlusive pressure} - \text{central venous pressure}}{\text{mean aortic pressure} - \text{central venous pressure}}$$

The CFI increased by more than 60% during the high training versus the intermediate training phase, and coincided with the eradication of symptoms felt during balloon occlusion. Given that the participant had normal coronary arteries, these changes were not driven by prolonged myocardial ischaemia.

More recently Zbinden and colleagues (438) recruited 40 patients undergoing percutaneous coronary intervention , measuring CFI in both the diseased and angiographically normal coronary artery at baseline. One day later, participants completed a CPET to establish their power to weight ratio ($W \cdot kg^{-1}$) and $\dot{V}O_{2max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$). For three months, the cohort exercised for at least 60 minutes, 3 times per week, by jogging or cycling at an intensity individualised to 80% of their heart rate at $\dot{V}O_{2max}$. After three months, patients were allocated to an exercise training group (n=24) or sedentary group (n=16), according to whether or not they adhered to the exercise programme. Repeated angiography and CFI was performed in 12 exercising (50%), and 10 sedentary patients (62%). Those in the exercise group were more resilient to ischaemia caused by balloon occlusion in the normal and previously stenotic vessels, whereas there was no significant improvement for either vessel in the sedentary group. CFI significantly increased in the exercise trained group for both the previously stenosed (0.155±0.081 to 0.204±0.056 (p=0.03)), and normal vessel (0.176±0.075 to 0.227±0.070 (p=0.0002)). By contrast, CFI did not change significantly in either vessel in the sedentary group. As expected, the exercise trained group showed significant improvements in $\dot{V}O_{2max}$ (p<0.0001) and power to weight ratio (p=0.001). Although this was not a randomised controlled trial, it does suggest that exercise training can augment collateral development, as evidenced by a "gold standard" method of quantification.

The largest and perhaps most notable human study into exercise induced collateral development is the EXCITE Trial (439). The trial recruited 60 stable angina patients with physiologically significant coronary stenosis (defined as a Fractional Flow Reserve (FFR) of ≤0.75 (440)). After baseline testing (spiroergometry, CFI, FFR) patients were randomly allocated to receive four weeks of high intensity training (group A), multimodal lifestyle intervention (group B), or usual care (group C) on a 1:1:1 basis. High intensity training consisted of 4 bouts of 30 minutes supervised exercise training at 70% angina free capacity, interspersed with 1 hour of recovery, 5 times per week for one month. In contrast, group B performed 6-8, 20 minute sessions at 60% of angina threshold per day, alongside lifestyle modification training. Usual care

participants were advised to perform physical activity 2-3 times per week, for 20-30 minutes, as per current recommendations. After 1 month, FFR did not significantly change in any group (p=0.148). However, CFI values did significantly increase post-training in both groups A and B (p=0.001), and this coincided with significant improvements in $\dot{V}O_{2peak}$ and an improved ischaemic threshold. The EXCITE Trial provides further evidence of improved collateral flow in response to exercise training, and the absence of a change in FFR indicates that this is not as a result of lesion regression.

Whilst the aforementioned studies all investigated medium to long term exercise training, two novel studies published in 2010 and 2012 examined the acute effects of exercise on collateral flow. Togni and colleagues recruited 30 patients with stable, non-occlusive CAD undergoing coronary angiography, and randomised them to either rest/exercise or exercise/rest groups (441). The rest/exercise group had baseline CFI measured during 1 minute balloon occlusion. Then, following 10 minutes of rest, they were asked to pedal a supine bike for 6 minutes, the intensity of which increased every 2 minutes (low/medium/high). Prior to the 6th minute the balloon catheter was again inflated and CFI was measured. To account for the possibility that repeated balloon occlusions may precondition the collaterals and confound the results, the exercise/rest group underwent the process in reverse. CFI increased significantly from 0.168±0.118 during resting conditions to 0.262±0.166 during exercise (p=0.0002). There was no statistical difference in this increase irrespective of group allocation.

Lin et al (247) recruited 65 single vessel CAD patients, randomly allocating them to either an isometric exercise training (n=33), or sedentary group (n=32). CFI was measured pre and post 1 minute balloon occlusion at the site of stenosis. During the occlusion the exercise group performed isometric hand grip exercise at 50% maximal voluntary contraction, whilst the sedentary group remained still. CFI post occlusion was significantly greater than pre-occlusion in the isometric exercise group, whilst there was no difference in the sedentary group (p<0.002).

4.4 Discussion and future research

Arteriogenesis is an important process to protect against the effects of ischaemia in both the stable and acute clinical settings. The current evidence-base indicates that collateral development through arteriogenesis is shear-force mediated. Shear stress is implicated in atherosclerotic development with areas of high shear stress being relatively protected from build-up of plaque. It is also transiently increased during

physical activity, and regular exercise is associated with a reduction in cardiovascular events, and is thus recommended in primary and secondary cardiovascular disease prevention.

The primary driver of shear stress in patients with a coronary lesion is the pressure gradient. Therefore, even if study participants exercise at the same intensity, the change in their individual pressure gradient will be diverse owing to heterogeneous lesion location and severity. In order to reduce these disparities, one strategy could be to evaluate a group of patients with a single vessel chronic total occlusion. By definition, the level of stenosis would be standardised, and each patient would potentially have a more comparable level of collateral development. Therefore, exercising these patients at or just below their individual ischemic threshold would ensure they were exercising at the same physiological limit. Additionally, research has linked transient and systemic increases in diastolic blood pressure to greater collateral development (442). A method for increasing diastolic pressure that has yet to be investigated in this regard is resistance training. Resistance training may be a potent arteriogenic trigger, as it has been shown to generate significantly larger increases in diastolic blood pressure compared to standard ergometer based training, which has little or very little impact on diastolic blood pressure (239). Furthermore, resistance exercise has been shown to result in a lower heart rate during training sessions, this may favourably increase coronary perfusion pressure and filling time (245). Therefore, future research should also seek to individualise exercise intensity, frequency, and modality in order to elicit enhanced collateral development.

4.5 Application to clinical practice

The development of coronary collaterals is a crucial mechanism to preserve the function of the myocardium and protect against ischaemia. This is particularly important in patients with severe occlusive coronary disease as well as those with diffuse disease that is not treatable by either PCI or coronary artery bypass graft surgery (CABG). Indeed, the current treatment options for patients with unrevascularizable coronary lesions are limited. Exercise may represent a cost effective and viable pro-arteriogenic treatment option in this patient group.

4.6 Summary

Coronary collateral vessels supply blood to ischaemic myocardium therefore protecting against damage. Exercise increases coronary flow and, since the introduction of CFI measurements, has consistently been shown to stimulate collateral development. However, fundamental questions relating to the aetiology of collateral development, such as identifying the inter-relationship between ischaemia, shear force, and the collateral network remain unresolved. Exercise training interventions represent a valid and viable means of furthering our current understanding of collateral development.

Chapter 5 : The Morphology and Stability of the Oxygen Pulse Curve During Cardiopulmonary Exercise Testing

5.1 Abstract

Cardiopulmonary exercise testing (CPET) is a valuable tool for assessing cardiopulmonary function and fitness. This study aimed to determine the reliability and agreement of multiple parameters derived from the oxygen pulse (V̇O2Pulse) curve during CPET. Twelve recreationally active male participants underwent two CPETs within a short test-retest interval (⩽72 hours). Various components of the V̇O2Pulse curve were analysed, including the area under the curve (AUC) and the slope in relation to work-rate. Statistical analysis revealed V̇O2Pulse curve parameters ranging from poor (ICC = 0.49) for slope values to excellent (ICC = 1.00) for the filtered V̇O2Pulse AUC. The mean percentage minimal detectable change (%MDC) for filtered AUC was 15 ± 0.8, indicating the boundary beyond which true change could be confidently determined. These findings suggest that the V̇O2Pulse curve is a robust and stable variable, providing important information about cardiovascular health. Understanding the reliability of V̇O2Pulse curve parameters has implications for exercise prescription, risk stratification, and rehabilitation in clinical populations. Future studies should adopt consistent reporting criteria, such as the %MDC, to facilitate comparisons across research and clinical settings.

5.2 Introduction

Cardiopulmonary exercise testing (CPET) allows clinicians to non-invasively interrogate the function and capacity of the cardiopulmonary system during maximal, or symptom limited graded exercise (263). CPET permits the simultaneous collection of multiple variables, ranging from minute ventilation ($\dot{V}E$), oxygen uptake ($\dot{V}O_2$) to carbon dioxide production ($\dot{V}CO_2$). CPET can be used for exercise prescription, and to guide initial exercise intensity (for example, percentage work-rate at first ventilatory threshold), or to assess alterations in cardiopulmonary fitness following intervention (443).

As with many physiological examinations, test-retest reliability is subject to a variety of intrinsic (related to the individual) and extrinsic factors (related to the experiment). The reliability of CPET can be investigated in relative terms, through measures such as intraclass correlation co-efficient (ICC) or coefficient of variation (CV), and absolute terms, via calculation of the standard error of measure (SEM) and minimal detectable change (MDC) (444). Previous research in this field indicates that commonly cited gas exchange variables such as $\dot{V}O_2$ and $\dot{V}CO_2$ exhibit excellent reliability across a spectrum of clinical cohorts, ranging from heart failure and valvular heart disease to pulmonary arterial hypertension (271,273,445–448).

A variable less commonly derived from CPET is the O_2Pulse, which is defined as the volume of oxygen utilised per heartbeat ($\dot{V}O_2$/heart rate (HR)) and is commonly expressed in mL·beat (290). O_2Pulse allows for the estimation of stroke volume (SV) during CPET through a simple modification of the Fick equation, in which $\dot{V}O_2$ is equal to the product of cardiac output ($\dot{Q}$) multiplied by the arteriovenous oxygen difference ($_{a\text{-}v}O_{2diff}$). Therefore, assuming equal or constant $_{a\text{-}v}O_{2diff}$:

$$O_2Pulse = \frac{VO_2}{HR}$$

O_2Pulse, its derivatives, and the morphology of its associated curve when plotted against work rate, have emerged as valuable but contentious tools in the assessment of patients with suspected or documented CAD (27–30,276,281–283,291,298,304,399,449–452). The shape of the O_2Pulse curve, provides important information about the health of the cardiovascular system and its ability to deliver oxygen to working muscles. The normal trajectory of this slope in healthy individuals is suggested to be a linear increase in y (O_2Pulse) in response to x (work-rate),

reflecting an incremental rise in Q̇ resulting from commensurate increases in both HR and SV (453). However, an early plateau or inflection in the slope of O_2Pulse (in those who do not reach ≥ 90% predicted $\dot{V}O_2$) is suggested to be evidence of a sudden reduction in the normal progression of SV (14,15,19). Reductions in SV during CPET are hypothesised to occur secondary to wall motion abnormalities caused by myocardial ischaemia (283).

Previous studies have established the reliability of peak O_2Pulse (O_2P_{peak}) and or O_2Pulse at first ventilatory threshold (VT_1O_2P) (271,447,454,455). In 1996, Lehman and Kölling recruited n=17 patients with valvular heart disease to complete two treadmill CPETs. The authors found that correlation coefficients for O_2P_{peak} and VT_1O_2P were r=0.980; p>0.001 and r = 0.991; p > 0.0001 respectively (447). Similarly, O_2P_{peak} reliability was reported by Barron et al in 2014 (CV of 8% and an ICC of 0.96 (95% CI = 0.94 - 0.97)) after recruiting 93 patients with either valvular heart disease (n=26), heart failure (n=43) or COPD (n=24).

Although O_2P_{peak} is a valid, and potentially clinically important variable of interest, quantifying reliability alone does not provide a complete assessment of all the characteristics of the O_2Pulse curve, including the inflection points. To date only two studies have attempted to investigate the stability of the curve, either in its entirety or at multiple intersects (454,455). Moreover, both studies utilised extended test-retest intervals to establish the long-term stability of the O_2Pulse curve. To the best of my knowledge no study to date has sought to establish the short-term reliability and agreement of multiple O_2Pulse curve parameters. Determining the within-subject variability of various components of the O_2Pulse curve has important implications for exercise prescription, risk stratification, and rehabilitation in a variety of clinical populations. Therefore, the aim of this research was to retrospectively examine repeated CPETs with a short test-retest interval (≤72 hours) to determine the reliability (ICC & CV), and absolute agreement (SEM & MDC) of multiple components of the O_2Pulse curve in healthy recreationally active participants.

5.3 **Methods**

This was a single site, retrospective reliability study. The original study recruited a convenience sample of healthy recreationally active participants. Participants who did not undertake regular structured exercise (>2 days per week) or who had diagnosed underlying health conditions were excluded. Twelve, apparently healthy, recreationally active male participants were recruited between March 2017 and June

2017. Prior to testing all participants completed a pre-exercise medical questionnaire and provided written informed consent. The study was granted institutional ethical approval from the University of Hull's Sport, Health and Exercise Science Ethics Committee (AN – 8765012), and conducted in accordance with the Declaration of Helsinki (456). The anonymised data for this retrospective analysis was accessed from 26 September 2022.

5.3.1 **Study Design**

Participants attended the laboratory on two occasions, the first of which included anthropometric data collection and a CPET taken to volitional exhaustion on a cycle ergometer. The second visit commenced ≤72 hours post, to ensure an adequate period of recovery between visits was observed. During the second visit the CPET was repeated under the same experimental conditions and with the same test administrator as visit one. Both tests were scheduled at the same time of day to account for diurnal variations.

5.3.2 **Cardiopulmonary Exercise Tests**

Breath by breath gas analysis was performed during both CPETs using a Jaegger OxyCon Pro metabolic cart (Hoechberg, Germany), synced with a Lode Excalibur (Groningen, Netherlands) cycle ergometer. Each participants CPET followed a standardised incremental ramp protocol, consisting of a 5-minute rest phase, 5-minute warm-up phase (50 watts), continuous test phase (50 watts; increasing by 20 watts per minute), and finishing with a 5-minute recovery phase. The test administrator instructed each participant to maintain a cadence of ≥60 revolutions per minute (RPM) for the duration of each test. Participants were asked to provide their rating of perceived exertion (RPE) every two minutes. Tests were considered to be maximal if there was an identifiable plateau in $\dot{V}O_2$, or if $\dot{V}O_2$ failed to increase by more than 150 $mL \cdot min^{-1}$ despite increasing workload. In the absence of these findings tests were still considered maximal providing ≥2 of the following was achieved;

- HR failed to increase despite increasing work.
- Respiratory Exchange Ratio (RER) ≥1.10.
- RPE at peak exercise ≥7.

5.3.3 **Data Processing**

Breath-by-breath data were filtered prior to export into Microsoft Excel using a 30 second segment mean average. O_2Pulse data was then further filtered to remove potential outlying values via a 9-point moving mean average. Both CPETs were assessed to determine the lowest peak workload (watts), each test was then analysed at 50, 60, 70, 80, 90, and 100% of this value. Variables calculated from the data were the area under the curve (AUC) and the slope of O_2Pulse in relation to work-rate (ΔO_2Pulse / ΔWR).

5.3.4 **Statistical analysis**

Statistical analysis was performed in RStudio version 4.2.2 (Integrated Development for R. PBC, Boston, MA, USA). Descriptive statistics are presented as mean ± standard deviation (SD) unless otherwise stated. Assumptions of normality and homogeneity were tested through Shapiro-Wilk and Levene's test respectively. Test-retest reliability was determined via a two-way random effects model ICC (2,1) for absolute agreement as recommended by Koo and Li (457) and expressed with 95% confidence intervals (CI). Absolute agreement was expressed as SEM and MDC and displayed where appropriate as a percentage of the grand mean (%SEM & %MDC).

5.4 **Results**

Eleven of the twelve males recruited to the study completed both CPETs within the designated window (27 ± 6 years, $\dot{V}O_{2max}$; 41.5 ± 9.9 mL·kg^{-1}·min^{-1}). One participant was removed from the analysis due to an equipment malfunction. The remaining cohort (n=11) completed testing without any adverse events. Maximal test criteria were achieved by ten participants for both CPETs. There was a 1.1 mL·kg^{-1}·min^{-1} increase in $\dot{V}O_2$ (41.5 ± 9.9 – 42.6 ± 8.6 mL·kg^{-1}·min^{-1}) and a 6 W increase in peak power (295 ± 55 – 301 ± 58 W) between visits one and two.

Results of the reliability and agreement analysis are presented in Table 1. The ICC values for filtered and unfiltered O_2P_{peak} and AUC across all percentages of peak work rate were statistically significant ($p \leq 0.05$). The 95% CI for O_2Pulse and O_2Pulse slope are inconsistent, ranging from poor to excellent. However, the 95% CI for O_2Pulse AUC values, both filtered and unfiltered never dropped below 0.96, indicating consistently excellent reliability. The mean difference in O_2P_{peak} between visits was 0.19 ± 0.94 and 0.21 ± 0.82 mL·beat for unfiltered and filtered data respectively. The SEM and MDC expressed as a percentage of the grand mean for all three variables are presented in Figure 15. Clearly, error as a percentage is more consistent in the filtered version of the

data. It also appears that the O_2Pulse slope has a greater degree of error when taken at the middle rather than the end of the test, which is perhaps to be expected, as the former presents less data points with which to formulate a precise slope than the latter.

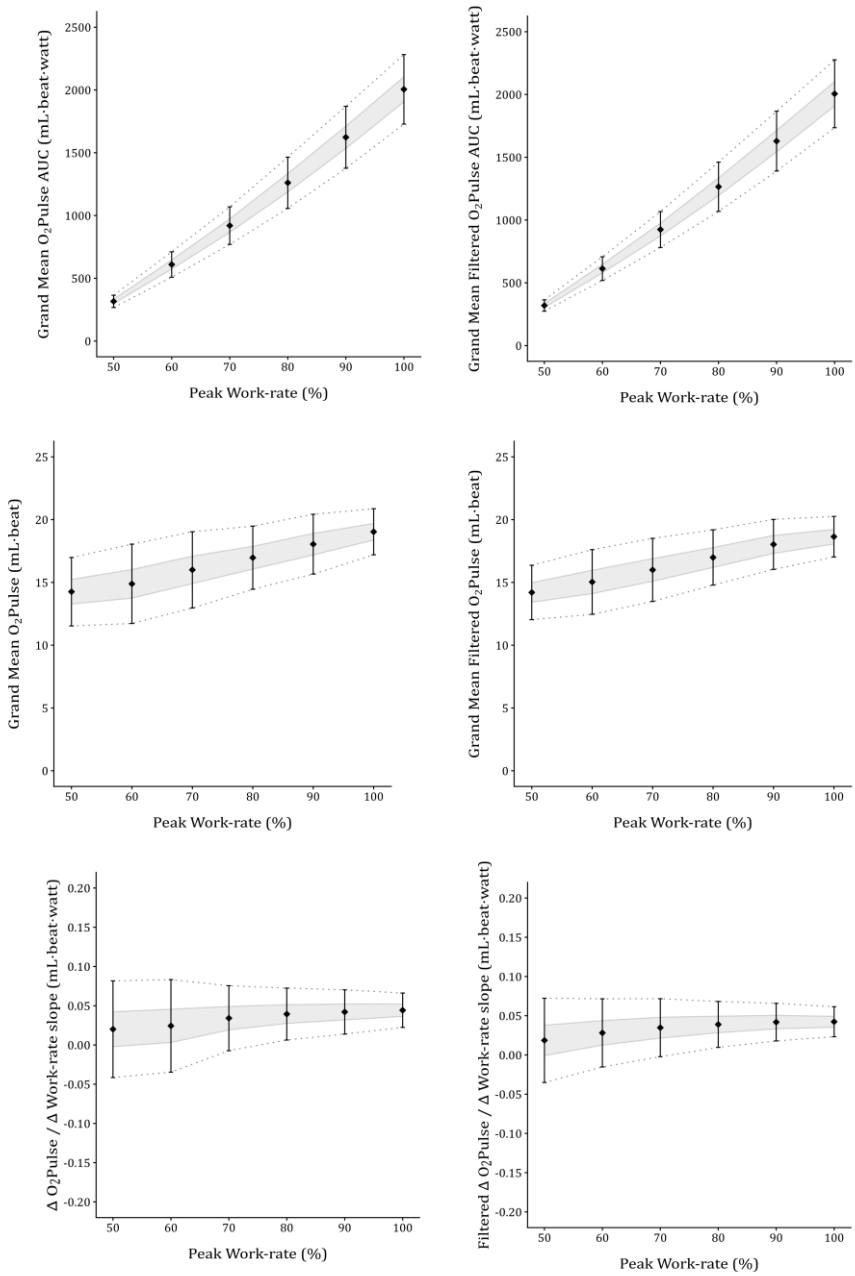

Figure 15. The SEM and MDC expressed as a percentage of the grand mean (grey = %SEM; error bars and dotted line = %MDC)

Table 9. Reliability and agreement tests at each percentage of peak work-rate

Variable	% of Peak work-rate	Mean ± SD	ICC	95% CI	*P*-Value	*F*	SEM	MDC
$\dot{V}O_2$Pulse	50%	14.259 ± 3.129	0.95	0.84 – 0.99	$P < 0.001$**	22	0.984	2.726
	60%	14.886 ± 3.386	0.95	0.81 – 0.99	$P < 0.001$**	18	1.139	3.158
	70%	16.000 ± 3.475	0.95	0.82 – 0.99	$P < 0.001$**	20	1.096	3.039
	80%	16.968 ± 3.507	0.97	0.89 – 0.99	$P < 0.001$**	33	0.907	2.515
	90%	18.045 ± 3.839	0.98	0.92 – 0.99	$P < 0.001$**	45	0.859	2.381
	100%	19.032 ± 4.044	0.99	0.96 – 1.00	$P < 0.001$**	81	0.662	1.835
Filtered $\dot{V}O_2$Pulse	50%	14.200 ± 3.955	0.97	0.89 - 0.99	$P < 0.001$**	31	0.650	2.166
	60%	15.036 ± 3.283	0.96	0.87 - 0.99	$P < 0.001$**	27	0.657	2.575
	70%	15.995 ± 3.324	0.96	0.88 - 0.99	$P < 0.001$**	28	0.595	2.510
	80%	16.986 ± 3.526	0.98	0.92 - 0.99	$P < 0.001$**	43	0.589	2.203
	90%	18.027 ± 3.722	0.98	0.94 – 1.00	$P < 0.001$**	60	0.652	1.990
	100%	18.641 ± 3.955	0.99	0.96 - 1.00	$P < 0.001$**	98	0.539	1.615
$\Delta\dot{V}O_2$Pulse / ΔWR slope	50%	0.020 ± 0.060	0.93	0.77 - 0.98	$P < 0.001$**	15	0.022	0.062
	60%	0.024 ± 0.030	0.72	-0.00 - 0.92	$P = 0.030$*	3.5	0.021	0.059
	70%	0.034 ± 0.020	0.67	-0.18 - 0.91	$P = 0.049$*	3	0.015	0.041
	80%	0.039 ± 0.017	0.73	0.04 - 0.93	$P = 0.025$*	3.7	0.012	0.033
	90%	0.042 ± 0.015	0.74	0.75 - 0.93	$P = 0.023$*	3.8	0.010	0.028
	100%	0.044 ± 0.014	0.84	0.42 - 0.96	$P = 0.004$*	6.1	0.008	0.022
Filtered $\Delta\dot{V}O_2$Pulse / ΔWR slope	50%	0.018 ± 0.022	0.49	-0.83 – 0.86	$P = 0.15$	2	0.019	0.054
	60%	0.028 ± 0.019	0.56	-0.55 – 0.88	$P = 0.026$*	2.3	0.016	0.043
	70%	0.034 ± 0.017	0.60	-0.41 – 0.89	$P = 0.080$	2.5	0.013	0.037
	80%	0.039 ± 0.015	0.72	0.00 – 0.92	$P = 0.029$*	3.6	0.011	0.029
	90%	0.042 ± 0.014	0.79	0.26 – 0.94	$P = 0.011$*	4.7	0.009	0.024
	100%	0.042 ± 0.014	0.87	0.54 – 0.96	$P = 0.002$*	7.7	0.007	0.019
$\dot{V}O_2$Pulse AUC	50%	316.280 ± 173.270	1.00	0.98 – 1.00	$P < 0.001$**	221	17.603	48.792
	60%	609.885 ± 274.781	0.99	0.97 – 1.00	$P < 0.001$**	129	36.543	101.292
	70%	919.700 ± 341.800	0.99	0.96 – 1.00	$P < 0.001$**	91	53.890	149.375
	80%	1261.073 ± 469.718	0.99	0.96 – 1.00	$P < 0.001$**	91	73.582	203.959
	90%	1623.182 ± 568.588	0.99	0.96 – 1.00	$P < 0.001$**	92	88.944	246.540
	100%	2005.305 ± 696.886	0.99	0.97 – 1.00	$P < 0.001$**	109	99.865	276.812
Filtered $\dot{V}O_2$Pulse AUC	50%	319.046 ± 176.296	1.00	0.99 – 1.00	$P < 0.001$**	272	16.218	44.953
	60%	612.997 ± 275.219	0.99	0.98 – 1.00	$P < 0.001$**	149	34.064	94.420
	70%	924.286 ± 342.603	0.99	0.96 – 1.00	$P < 0.001$**	100	51.568	142.927
	80%	1265.018 ± 469.447	0.99	0.96 – 1.00	$P < 0.001$**	99	70.760	196.136
	90%	1628.368 ± 568.862	0.99	0.96 – 1.00	$P < 0.001$**	98	85.951	238.243
	100%	2005.691 ± 697.074	0.99	0.97 – 1.00	$P < 0.001$**	114	97.568	270.445

Abbreviations: SD = standard deviation, ICC = intraclass correlation coefficient, CI = confidence interval. SEM = standard error of measure, MDC = minimal detectable change
* = $P \leq 0.05$; ** = $P \leq 0.001$

5.5 **Discussion**

The aim of the study was to determine the reliability and agreement of multiple parameters of the O_2Pulse curve for CPETs undertaken ≤72 hours apart. The data indicates that O_2Pulse, its slope and the AUC taken at 50 – 100% of peak workload are reliable in both their filtered and unfiltered forms. However, the most optimal parameter for reliability is the filtered O_2Pulse AUC. For all percentage ranges tested, the filtered O_2Pulse AUC returned statistically significant ($p \leq 0.05$) ICC values, which in accordance with the literature can be classified as excellent (95% CI = ≥0.95 – 1.00) (457).

The mean %MDC for filtered AUC was 15 ± 0.8 ranging from 14.1 at 100 to 13.5 at 50% peak work-rate. In contrast, the mean %MDC for filtered O_2Pulse and O_2Pulse slope were 13.5 ± 3.2 and 121.1 ± 90.9 respectively. It is perhaps not surprising that the error is greatest for the slope, especially at the lower percentages of work, whereby virtue of the test length there are less data points with which to formulate a replicable slope. The fact that the %MDC for both O_2Pulse and O_2Pulse AUC are so similar and consistent across percentages of work is not at all surprising, as the former is used to calculate the latter. The similarity between the percentage error in O_2Pulse and O_2Pulse AUC implies that the morphology of the slope itself is replicable.

The results of the present study are in accordance with previous findings, suggesting various parameters measured with metabolic gas carts during CPETs produce excellent reliability (ICC = ≥ 0.9) (271,273,445–448). Barron et al (271) reported an ICC value of 0.96 (95% CI = 0.94 - 0.97) for O_2P_{peak} with a CV of 8%. The authors recruited 93 patients with either valvular heart disease (n=26), heart failure (n=43) or COPD (n=24). In this instance, repeated CPET were performed on a cycle ergometer but were not identical. For the first test each patient generically undertook a 10 watt per minute ramp protocol, with the second test tailored to the individual based upon the results of the first (271). The authors concede that this is not ideal for reproducibility, however they contend it is more likely to occur in clinical settings. Whilst true this does impact the generalisability of the results and comparisons to my findings, as conditions, namely the work rate slope, were not held constant between visits.

As mentioned in the introduction, the reliability and agreements of additional components of the O_2Pulse slope, relating more to its morphology, maybe of greater clinical significance. To this end Perim and colleagues recruited n=49 professional footballers (18 – 31 years) from the 1st divisions of Brazil and Angola and conducted repeated CPETs (455). Each CPET was treadmill-based, utilising a ramp protocol starting at a velocity of 5.5 km/h for one minute, before increasing to 8 km/h, with 0.1km/h increases every 7.5 seconds thereafter. The tests themselves were separated by a mean of 12 months (range 2 – 24). O_2Pulse was compared every 10% of effective running time (≥ 8 km/h) for both tests and expressed normalised to body mass ($ml \cdot beat^{-1} \cdot kg^{-1}$). The authors used coefficients of determination (R^2) at each percentage point as a measure of reliability. They concluded that mean values of the coefficients were "*virtually identical*" for the first and second tests at 0.64 and 0.63 respectively (455). Clearly these values are exceptionally close to one another, but they only indicate that between 63 and 64% of the variation in the O_2Pulse curve during CPET can be explained by the treadmill velocity. Perhaps a more informative parameter for the reliability of the O_2Pulse curve explored by the authors was the slope and intercept. The study indicated no statistically significant differences between the slopes (p= 0.44) or intersects (p = 1.00), indicating that O_2Pulse at onset and increase throughout the CPET was indeed repeatable even when separated by 2 – 24 months. This paper is limited by the large variability in test-retest interval, and by the fact that the second CPET was taken to volitional exhaustion. As a result, participants achieved a significantly greater maximal velocity (p < 0.01) and exercise duration. This would have generated a rightward shift in the scale of effective running time and resulted in the comparison of O_2Pulse values elicited by different work-rates (WR). Furthermore, the authors used coefficients of determination and significance testing instead of absolute agreement metrics, such as SEM or MDC, which would have provided a quantitative parameter beyond which true change could be accepted.

The long-term stability of the O_2Pulse curve was also investigated by Olivera and colleagues in 2011. In this instance the authors retrospectively examined the O_2Pulse curve in 100 pairs of CPETs (80 male) (454). Participants (mean 59 years ± 12 years) were non-athletes for whom repeated test data was available with a minimum 3-month separation (median 15 months; range 5 – 62). Tests were completed either for clinical or

exercise prescription purposes. Both tests were performed on an electronically braked cycle ergometer using a personalised ramp protocol. The authors found that $\dot{V}O_{2peak}$ (11%) and O_2P_{peak} (10%) were significantly increased during the second CPET (p = 0.004 and p = 0.002), respectively. However, when separated into quintiles based upon O_2P_{peak} normalised to body mass, values achieved in the second CPET were not statistically significantly different in either their slope or intercept from the initial test, with the exception of the intercept in quintile 5 (p = 0.007). These findings were maintained in a subset analysis of slopes in patients with known CAD (p = 0.031). As with the findings of Perim and colleagues (455) there was no effort made to establish absolute agreement through SEM or MDC, which limits the utility of the results. Furthermore, 75% of the study cohort participated in a supervised exercise intervention three times per week, whilst the remaining 25% were supplied with exercise related advice (454), both of these interventions could have impacted upon the stability of the O_2Pulse curve.

Clearly caution should be taken when comparing these results with the present study, as I performed repeat tests over a period of days and compared only the responses to percentages of a fixed workload. However, these findings in combination do add to the existing literature around the reliability of O_2Pulse (454,455), suggesting it is a robust and stable variable, both in the longer and shorter term.

Establishing the reliability of measures during CPET is essential. Without knowledge and confidence in the degree of error it is impossible to individualise threshold-based exercise prescriptions or accurately establish improvement following intervention. Despite the clear requirement for studies of this nature there is no consensus reporting criteria. There are many statistical methods available to quantify test-retest reliability and agreement. However, when calculated as:

$$\Rightarrow \%MDC = \frac{1.96 * \sqrt{2} * SEM}{Grand\ Mean} * 100$$

The %MDC provides a boundary outside of which we can be confident true change will have occurred approximately 95% of the time. Furthermore, as this is expressed as a percentage of the sample mean (grand mean) it is consistent even with an increase in the unit measured and can be compared across studies and variables. It is my hope that

presenting the results in this fashion allows them to be adopted or used for direct comparison in future research.

Establishing the reliability of O_2Pulse curve parameters may be of particular importance to clinicians and clinical exercise physiologists. Previous research has established that O_2P_{peak} is a significant ($p \leq 0.05$) predictor of cardiovascular and all-cause mortality in people with and without cardiovascular disease (458,459). Furthermore, when normalised to body mass O_2P_{peak} exhibits an inverse linear relationship with cardiovascular and all-cause mortality in middle-aged men (450). A clear understanding of O_2P_{peak} reliability is essential if it is to be used in the early identification and modification of those at increased risk, here I provide evidence that the %SEM associated with O_2P_{peak} (O_2Pulse at 100%) is 3.48 with %MDC of 9.64.

Inflections or premature plateaus in the otherwise linear increase of O_2Pulse have been linked to the onset of myocardial ischaemia (27,29,30,399). One of the stated aims of exercise-based cardiac rehabilitation according to the Association of Chartered Physiotherapists in Cardiac Rehabilitation (ACPICR) standards (460) is to increase the ischaemic threshold. Additionally, existing training guidelines presented by the American College of Sports Medicine (ACSM), recommend outpatient training intensities for CR to be below the ischaemic threshold (<10 beats), or below a threshold that elicits the onset of angina symptoms (415). If practitioners are to accurately detect the ischaemic threshold, prescribe exercise training intensity based on the threshold, and then monitor changes in the threshold following a period of exercise training, it is first necessary to determine the SEM, and more importantly MDC at multiple points across the curve. This study demonstrates that in healthy male participants the mean %MDC of O_2Pulse from 50-100% of peak work-rate is 16 ± 4.34. This does not mean that once detected the ischaemic threshold holds the same level of consistency, it does however provide a boundary outside of which increases or decreases can confidently be determined.

5.6 Limitations

This study is not without its limitations, firstly, the small sample size is more prone to the influence of outliers, which could positively or negatively skew the differences between tests. The SD of the differences is used in the calculation of SEM and MDC and thus could

have artificially exaggerated the error in the sample versus the true error in the population. Secondly, the homogeneous nature of the sample, both in term of sex and age may further impact the transferability of these results. Finally, only two measures were taken for each participant, this introduces the possibility that the error observed may represent a learned effect resulting from familiarisation with the test procedure. Future research should perform a minimum of three tests, thus allowing for multiple pairwise comparisons to be made. It would then be possible to determine whether there exists a significant difference between minimal detectable changes, and ultimately whether a familiarisation visit is necessary.

5.7 Conclusion

In conclusion, this study demonstrates that when conducting a CPET, for points ranging from 50-100% of peak work-rate, the O_2Pulse has moderate to excellent reliability. Furthermore, when viewed with the AUC parameter, reliability increases to excellent (ICC ≥ 0.9). Previous guidelines indicate that the O_2Pulse curve should be assessed in clinical settings for the identification and assessment of CAD. These findings not only indicate that the O_2Pulse is reliable, but will also quantify the minimal value required to be confident of true change.

Chapter 6 : Inter- and Intra-Observer Reliability and Agreement of O_2Pulse Inflection during Cardiopulmonary Exercise Testing in Patients with Coronary Artery Disease: A Comparison of Subjective and Novel Objective Methodology

6.1 Abstract

Cardiopulmonary exercise testing (CPET) is the 'gold standard' method for evaluating functional capacity, with oxygen pulse (O_2Pulse) inflections serving as a potential indicator of myocardial ischaemia. However, the reliability and agreement of identifying these inflections have not been thoroughly investigated. This study aimed to assess the inter- and intra-observer reliability and agreement of a subjective quantification method for identifying O_2Pulse inflections during CPET, and to propose a more robust and objective novel algorithm as an alternative methodology.

A retrospective analysis was conducted using baseline data from the HIIT or MISS UK trial. The O_2Pulse curves (the progression of O_2Pulse over work rate) were visually inspected to identify the presence and consequent location of inflections by two independent examiners, and compared against an objective algorithm. Fleiss' Kappa was used to determine the agreement between the three groups of observations.

The results showed almost perfect agreement between the algorithm and both examiners, with a Fleiss' Kappa statistic of 0.89. The algorithm also demonstrated excellent inter-rater reliability (ICC) when compared to both examiners (0.92 – 0.98). However, a significant level ($P \leqslant 0.05$) of systematic bias was observed in Bland-Altman analysis for comparisons involving the novice examiner.

In conclusion, this study provides evidence for the reliability of both subjective and novel objective methods for identifying inflections in O_2Pulse during CPET. These findings suggest that further research into the clinical significance of O_2Pulse inflections is warranted, and that the adoption of a novel objective means of quantification may be preferable to ensure equality of outcome for patients.

6.2 Introduction

Cardiopulmonary exercise testing (CPET) allows for the non-invasive, objective quantification of cardiopulmonary fitness, and is thus held as the 'gold standard' methodology for evaluating functional capacity (22,23). In contrast to more traditional assessments, such as ECG stress testing and the 6-minute walk test, CPET makes it possible to determine the potential pathophysiological mechanisms underlying exercise intolerance, such as chronic heart failure and chronic obstructive pulmonary disease (23–25,290).

The utility of CPET as a diagnostic and prognostic tool in the evaluation of patients with coronary artery disease (CAD) and heart failure has received considerable attention (22–26). In particular, an early plateau or inflection in the normal linear progression of oxygen pulse (O_2Pulse) and oxygen consumption ($\dot{V}O_2$) despite an increasing work-rate (WR) are suggested to be indicative of inducible and reversable ischaemia (23,25,27–30). In principle, O_2Pulse reflects left ventricular stroke volume (SV) as is expressed in a modification of the Fick principle (461):

$$\frac{\dot{V}O_2}{HR} = SV \cdot a - \dot{V}O_{2diff}$$

(22,25). Consequently, a plateau or inflection in O_2Pulse, despite increasing WR suggests a pathological impairment of stroke volume, possibly caused by myocardial ischaemia (22,23,25).

To the best of my knowledge the reliability and agreement of O_2Pulse inflections have not been previously investigated. However, I have shown in a healthy cohort, the minimal detectable change (MDC) for 15-second time-averaged (mean) and filtered (9-point moving mean average) O_2Pulse, measured between 50 and 100% of peak work rate is 2.2 mL·beat, and 1.6 mL·beat respectively (see Chapter 5). If this level of agreement remains consistent for O_2Pulse at the point of inflection, and inflections truly are representative of ischaemic onset in CAD patients, it may be very useful to clinicians. For example, it could provide a marker with which to track the progression and severity of ischaemia, without the need for repeated exposure to radiation or invasive procedures. Moreover,

in rehabilitation settings it may provide a threshold value from which personalised exercise prescriptions could be developed.

However, to date the literature surrounding inflections in O_2Pulse typically classifies them categorically, as 'normal' (linear or curvilinear increase) or 'abnormal' (prolonged flattening or downloading). This system of classification does not quantify the position of inflection, for example the work rate or heart rate at which O_2Pulse deviates from normality (22,282,283,296,298,402,452). Categorisation of O_2Pulse morphology is usually performed in one of two ways, which I refer to as 'visual categorisation', and secondly, 'categorisation by regression'. In visual categorisation, one or more observers scrutinise the O_2Pulse curve to identify where the curve begins to deviate from a linear increase, usually referred to as a plateau or inflection. This point can sometimes be the sole focus of the investigation. However, in other instances, observers may be required to further categorise the curve as 'normal', 'probably normal', 'probably abnormal', or 'abnormal', depending on its characteristics (282). Alternatively, 'categorisation by regression' involves a quantified mathematical approach. Investigators select a specific point along the curve, such as two minutes before the cessation of exercise, and calculate the slope of the curve (slope A) from exercise beginning to this point using linear regression. This slope is then compared to the regression slope of the curve for the final two minutes (slope B) to quantify proportional change (304). Based on this comparison, the curve may be further categorised as 'normal augmentation', 'flat throughout', plateau in late exercise', and 'decline in late exercise' (inflection) (304).

The inter-rater agreement when categorising O_2Pulse curves as 'normal', 'probably normal', 'probably abnormal', ' definitely abnormal' has been reported by De Lorenzo and colleagues (282) to be $\kappa_C = 0.65$ (95% CI = 0.39 – 0.66). Efforts have been made by Chuang et al (402) to remove the subjectivity from categorisation by comparing an algorithmic approach to the consensus of two examiners. The resulting Kappa values were $\kappa_C = 0.86$ and 0.69 respectively for the conditions (normal) plateau and decrease.

To date there appears to have been no effort made to subjectively quantify the position of O_2Pulse inflections. This is perhaps due to their identification being influenced by a multitude of factors, such as the experience and opinion of the individual interpreting the

data, the method of data processing (mean time averaged versus data point mean averaging), and data presentation (axis size and aspect ratio). However, this form of data interpretation is not without precedent, the first ventilatory threshold (VT_1) during CPET is often identified in much the same way, through the modified V-slope method (462). Harwood et al (463) investigated the agreement of CPET parameters in patients with abdominal aortic aneurysms, utilising modified V-slope method to identify VT_1. The intraclass correlation coefficient (ICC) (two-way mixed) was used to measure reliability. For intra-rater reliability, the ICC was 0.834 (95% CI 0.215,0.975; p = 0.010) on the motorised treadmill and r=0.959 (95% CI 0.741,0.994; p = 0.000) on the cycle ergometer. For inter-rater reliability, the ICC was r=0.983 (95% CI 0.785,0.999; p =0.002) on the motorised treadmill and r=0.905 (95% CI 0.508,0.986; p=0.003) on the cycle ergometer.

O_2Pulse inflections may have the potential to be used to prescribe exercise intensity and monitor progression in much the same way VT_1 is currently used. Whilst VT_1 allows exercise prescriptions to be made around the individuals ventilatory anaerobic threshold, O_2Pulse inflections could allow training to be prescribed around the ischaemic threshold. However, we must first establish the inter- and intra-rater variability of identification, and suggest a suitable robust objective means of identification.

To the best of my knowledge there are no published data relating to the inter-, or intra-observer reliability and agreement of the subjective quantification of O_2Pulse inflections. Therefore, the primary aim of this research is to determine the inter- and intra-observer reliability and agreement of the subjective quantification method. The secondary aim is to establish a suitable objective alternative methodology that provides zero intra- and inter- observer variability.

6.3 Methods

This was a retrospective baseline analysis of the HIIT or MISS UK trial (18). The HIIT or MISS trial was a multicentre randomised controlled trial recruiting CAD patients referred for exercise-based cardiac rehabilitation (CR) in the UK. Detailed methodology of the trial procedures and primary outcomes have previously been reported (334), At baseline patients performed a baseline CPET on cycle ergometer following a standard ramp incremental protocol. For the purposes of my analysis, raw ventilatory gas exchange data

were exported as 15-second mean time averaged .csv files and used to generate O_2Pulse curves (x-axis = work rate; y-axis = O2Pulse).

Curves were then visually inspected by two independent examiners (TN & JM), each blinded to the interpretation of the other. Both examiners were clinical exercise physiologists with experience interpreting CPET. However, one examiner (TN) had substantially more experience interpreting O_2Pulse morphology (>6 years) and inflections. This examiner is subsequently referred to as 'experienced' whilst the other is termed 'novice' (<1 year). Each examiner viewed all available O_2Pulse curves, categorising each as 'yes', to indicate the perceived presence of inflection or plateau, or 'no' to indicate the normal linear progression of O_2Pulse. For each curve categorised as 'yes' the examiner would then quantify the threshold for inflection, identifying the exact point in the plot they believed represented a departure from normality. The 'experienced' examiner revisited the 'yes' curves at a later date (<2 weeks later) to re-quantify the inflection threshold. All subjective observations were then compared against an objective algorithm to compare categorisation and quantified threshold placement.

The algorithm was developed through an iterative process of trial and error, utilising a sub-sample of the first 20 participants from each of the three HIIT or MISS sites (Hull, Coventry and Cardiff). The filter (9-point) was chosen as it visually represented the best fit to the data trend (464). The algorithm was developed around the principle that a linear, or curvilinear increase in O_2Pulse was the expected normal response. The algorithm functions on 15-second mean time averaged data. To further reduce data noise without having to identify and correct for individual out-lying data points, I applied a 9-point moving mean average filter. This process involved replacing each data point with the mean average of the 9 data points centred around it, which included the 4 preceding points, the point itself, and the 4 subsequent points. From this processed data the algorithm simply identified the first occurrence of the series peak value using conditional formatting. If this peak value occurred ≥ 6 data points prior to the end of the test, the row was highlighted as a departure from normal linear or curvilinear increase, and the point was plotted on the embedded figure for visual inspection (Figure 16). Using the algorithm template, this requires the 15-second mean time averaged work rate and O_2Pulse data to be copied and pasted into columns A and B.

The additional criteria specified for accepting inflections in O_2Pulse, either via subjective observer or algorithm were as follows:

- The point of inflection should occur ≥ 6 data points (90 seconds) prior to the end of the test.
- The point of inflection in O_2Pulse should coincide with a reduction in the $\Delta\dot{V}O_2/\Delta WR$ slope of ≥ 10%.
- The patient must not have achieved ≥ 90% predicted $\dot{V}O_{2peak}$.

These criteria are derived from the original findings of Belardinelli and colleagues (7,8).

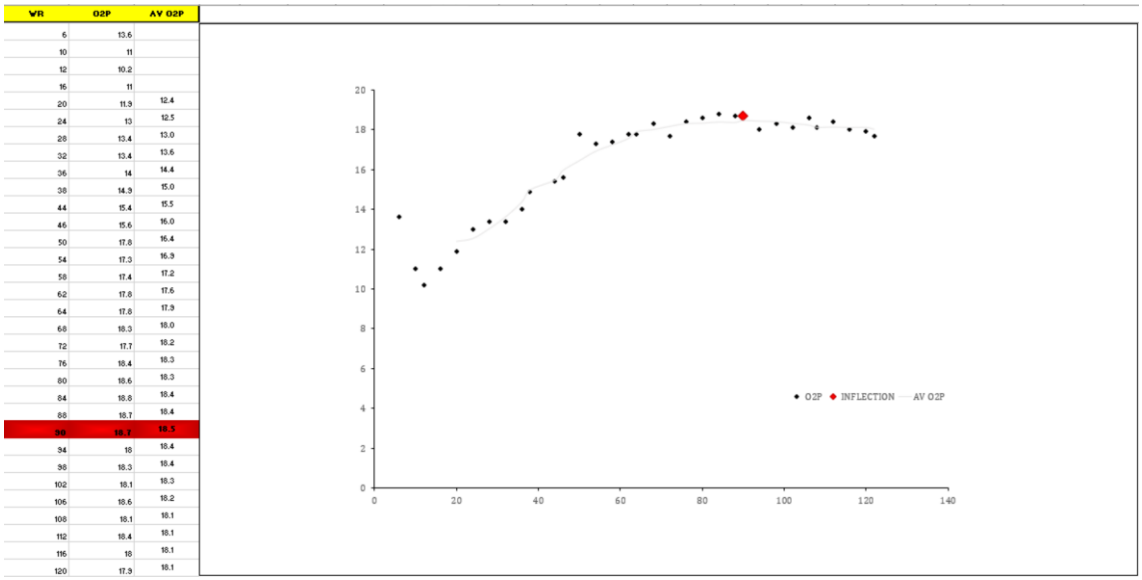

Figure 16. Example of the algorithm function as an Excel Template

6.3.1 Statistical analysis

Statistical analysis was performed in RStudio version 4.2.2 using the R programming language and packages “readxl”, “irr”, “epiR”, and “BlandAltmanLeh” (Integrated Development for R. PBC, Boston, MA, USA). The categorisations of each observer (coded as "Yes" or "No" to indicate the perceived presence or absence of an inflection or plateau) were compared against that of the objective algorithm to establish whether the algorithm could adequately categorise inflections. Fleiss’ Kappa (κ_F) was used to determine the reliability of agreement between the three groups of observations. Kappa statistics were

interpreted in accordance with the suggestions of Landis and Koch (465) with values <0.00, 0.00 – 0.20, 0.21 – 0.40. 0.41 – 0.60, 0.61 – 0.80 and 0.81 – 1.00 indicating poor, slight, fair, moderate, substantial and almost perfect respectively. In order to provide 95% confidence intervals around the Kappa value I performed 1000 bootstrap resamples with replacement from the original dataset. The algorithm was also compared against the consensus of both subjective examiners to determine its sensitivity and specificity as well as both positive and negative predictive values.

If all three observations were in agreement that an inflection had occurred, the threshold for inflection, expressed as heart rate and work rate were visually compared with Bland-Altman plots. In these instances, I compared experienced to novice, experienced to experienced (time), experienced to algorithm, and novice to algorithm. The intra-rater reliability was compared with a two-way random effects (2,1) ICC for absolute agreement and reported with standard error of measure (SEM) and minimal detectable change (MDC) values. The inter-rater reliability were compared using two-way mixed effects (3,1) model ICCs for absolute agreement (457). ICC outputs were interpreted based upon the recommendations of Koo and Li (457) with values <0.5, 0.5 – 0.75, 0.75 – 0.9 and >0.9 indicating poor, moderate, good and excellent reliability respectively. Statistical significance was accepted $p \leq 0.05$.

6.4 Results

In total 272 baseline CPET data in patients with CAD were analysed. The results of the analyses are presented in two parts: first, the inter-observer agreement of the subjective categorisation method versus the objective algorithm, and second, the evaluation of the proposed objective algorithms for quantifying thresholds in O_2Pulse.

6.4.1 Inter-Observer Agreement

The computed Fleiss' Kappa statistic for all raters was $\kappa_F = 0.89$ with a bootstrapped 95% confidence interval of 0.83 - 0.93. The corresponding z-score was 25.5 with a $p < 0.0001$. At least two raters were in agreement across all 272 files, with all three raters in agreement on 260 occasions (95.6%) The comparison of each interpreters' analysis is summarised in Table 10.

Table 10. Comparison of Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value Across Different Rater Comparisons

Comparison	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)
Algorithm Vs. Experienced	0.93 (0.82 – 0.99)	0.98 (0.96 – 1.00)	0.91 (0.79 – 0.98)	0.99 (0.96 – 1.00)
Algorithm Vs. Novice	0.89 (0.76 – 0.96)	0.99 (0.96 – 1.00)	0.93 (0.81 – 0.99)	0.98 (0.95 – 0.99)
Experienced Vs. Novice	0.93 (0.81 – 0.99)	0.97 (0.94 – 0.99)	0.87 (0.74 – 0.95)	0.99 (0.96 – 1.00)
Algorithm Vs. Consensus	0.82 (0.68 – 0.92)	0.99 (0.96 – 1.00)	0.92 (0.80 – 0.98)	0.97 (0.93 – 0.98)

95% CI = 95% Confidence Interval

6.4.2 Evaluation of the Objective Algorithm

In instances where all three observations agreed that an inflection had occurred (n=37; 13.6%), the threshold for inflection, expressed as heart rate and work rate, were compared using Bland Altman plots (Figure 17 & Figure 18). Values derived from or associated with Bland-Altman analysis, along with ICC values, are reported in Table 11.

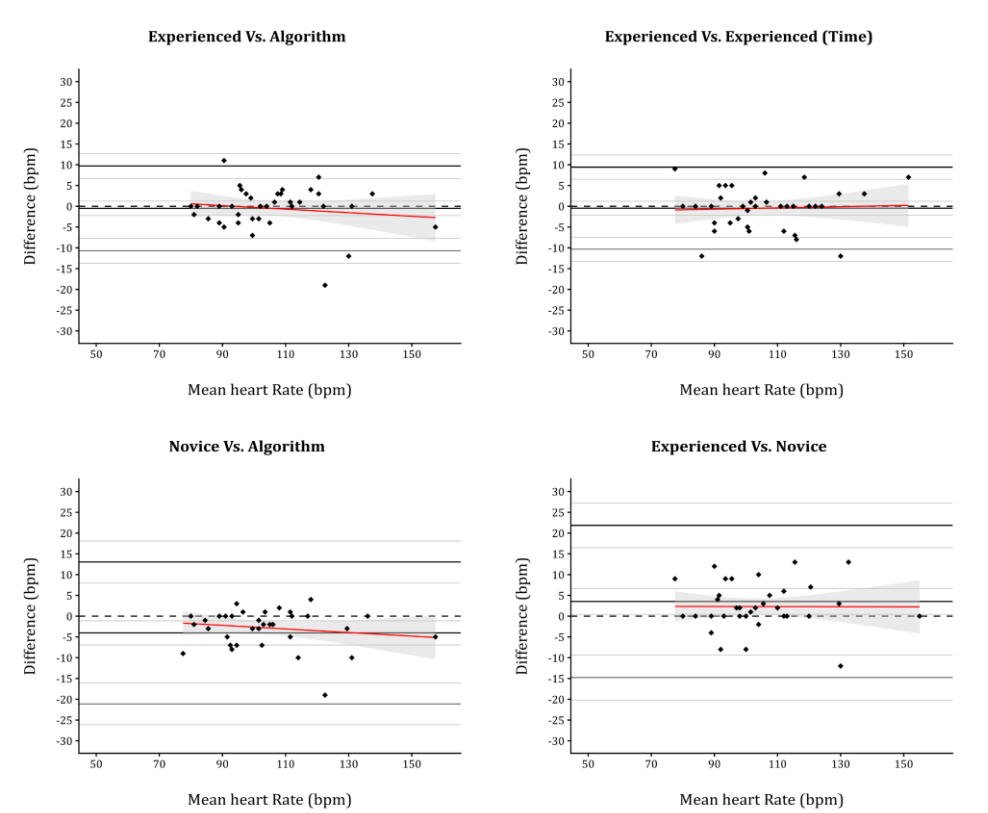

Figure 17. Bland-Altman Plots comparing agreement across subjective and objective inflection identification for heart rate

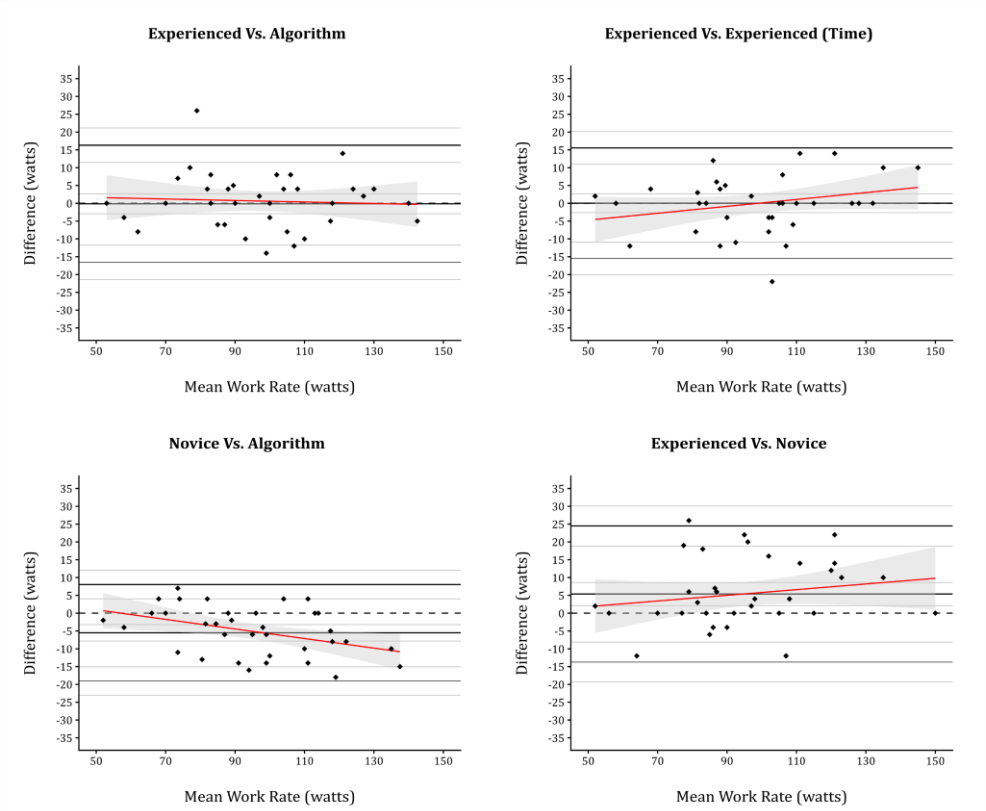

Figure 18. Bland-Altman Plots comparing agreement across subjective and objective inflection identification for work rate

Table 11. Reliability and Agreement Analysis for Inflection Thresholds in Heart Rate and Work Rate

Work Rate				
Statistic	**Algorithm Vs. Experienced**	**Algorithm Vs. Novice**	**Experienced Vs. Novice**	**Experienced Vs. Experienced (Time)**
SEM	11.86	9.77	13.8	11.2
%SEM	11.75	9.95	14.05	11.12
MDC	16.44	13.79	19.17	15.53
%MDC	16.29	13.79	19.47	15.39
ICC	0.97 (0.95 – 0.99)	0.97 (0.86 – 0.99)	0.95 (0.87 – 0.98)	0.95 (0.90 – 0.97)
Lower LOA (95% CI)	-16.57 (-21.42 - -11.73)	-19.06 (-23.05 - -15.07)	-13.74 (-19.37 - -8.11)	-15.49 (-20.07 - -10.92)
Upper LOA (95% CI)	16.30 (11.46 – 21.15)	8.03 (4.04 – 12.02)	24.50 (18.86 – 30.13)	15.55 (10.98 – 20.13)
Mean Bias (95% CI)	-0.14 (-2.93 – 2.66)	-5.51 (-7.82 - -3.21)	5.38 (2.13 – 8.63)	0.03 (-2.61 – 2.69)
Systematic bias	$P = 0.92$	$P < 0.0001$****	$P = 0.002$**	$P = 0.98$
Proportional bias	$P = 0.11$	$P = 0.002$**	$P = 0.48$	$P = 0.15$
Heart Rate				
Statistic	**Algorithm Vs. Experienced**	**Algorithm Vs. Novice**	**Experienced Vs. Novice**	**Experienced Vs. Experienced (Time)**
SEM	7.35	12.31	13.21	7.13
%SEM	7	11.9	12.78	6.77
MDC	10.19	17.07	18.31	9.88
%MDC	9.67	16.48	17.72	9.38
ICC	0.98 (0.96 – 0.99)	0.92 (0.82 – 0.96)	0.91 (0.81 – 0.95)	0.95 (0.91 – 0.98)
Lower LOA (95% CI)	-10.68 (-13.68 - -7.67)	-21.10 (-26.13 - -16.07)	-14.77 (-20.17 - -9.38)	-10.34 (-13.25 - -7.43)
Upper LOA (95% CI)	9.70 (6.70 – 12.71)	13.04 (8.01 – 18.07)	21.85 (16.46 – 27.25)	9.42 (6.51 – 12.33)
Mean Bias (95% CI)	-0.49 (-2.22 – 1.25)	-4.03 (-6.93 - -1.12)	3.54 (0.43 – 6.66)	0.46 (-2.14 – 1.22)
Systematic bias	$P = 0.57$	$P = 0.008$***	$P = 0.027$*	$P = 0.58$
Proportional bias	$P = 0.41$	$P = 0.83$	$P = 0.78$	$P = 0.77$

SEM = standard error of measure; MDC = minimal detectable change; LOA = limits of agreement; CI = confidence interval;
* = $P \leq 0.05$; ** = $P \leq 0.01$; *** = $P \leq 0.001$; **** = $P \leq 0.0001$

Excellent reliability was recorded for all ICC, with the highest heart rate values (0.97) occurring in both the experienced and novice versus algorithm comparisons. The highest heart rate ICC occurred in the algorithm versus experienced comparison (0.98). The intra-rater reliability for heart rate (0.95) was accompanied by SEM (%SEM) and MDC (%MDC) values of 7.13 (6.77%) and 9.88 (9.38%) respectively. Whilst the intra-rater work rate (0.95) SEM, and MDC values or 11.2 (11.12%) and 15.53 (15.39%).

Although ICC for comparisons involving the novice examiner were excellent, the 95% CI for all of these readings were consistently broader than those involving the experienced examiner. Furthermore, the mean bias when comparing the novice against the algorithm and experienced examiner was consistently different from zero. Indeed, in all comparisons involving the novice examiner there was a statistically significant level of systematic bias (Figure 17 & Figure 18). This systematic bias was compounded by significant proportional bias for comparisons versus the algorithm for work rate representing a statistically significant degree of both systematic and proportional bias. Indeed, all other comparison involving the novice examiner yielded statistically significant systematic bias.

6.5 Discussion

The primary aim of the study was to determine the inter- and intra-observer reliability and agreement of a subjective quantification method for identifying inflections in O_2Pulse during cardiopulmonary exercise testing (CPET). Secondly, I sought to evaluate a suitable objective algorithm as an alternative methodology.

Before attempting to quantify the threshold of inflection using the proposed algorithm it was necessary to determine whether it could differentiate between normal and abnormal data. The results of the present study indicate that the algorithm can differentiate between data, providing excellent agreement when compared with both experienced and novice examiners. Previous research by de Lorenzo et al and Chuang et al have reported levels of inter-rater reliability of between κ_C = 0.65 and κ_C = 0.69 (282,402) when categorising O2Pulse files, the value reported in the present study, however, are substantially higher at κ_F = 0.89 (0.83 - 0.93). There may be several reasons for this disparity. Firstly, the aforementioned studies applied Cohens' Kappa, as they were interested in the agreement of two examiners, whilst I applied Fleiss' Kappa to account for three 'examiners'. Although the additional 'examiner' in this analysis introduces the possibility of greater variability, examiners were only required to score across two categories, that is "Yes" or "No" to indicate the perceived presence or absence of an inflection or plateau. In contrast, the study by de Lorenzo and colleagues (282) required two experienced examiners to place files into one of four categories ('normal', 'probably normal', 'probably abnormal', ' definitely abnormal'), resulting in double the variation in

choice afforded in the present study. Similarly, Chuang and co-workers (452) placed an algorithm against the consensus of two human examiners, providing three choices for categorisation ('increasing', 'plateau', and 'decreasing').

The intra- and inter-observer reliability for subjective threshold quantification was assessed by two formats of ICC (2,1; 3,1). The analysis showed excellent reliability in both the intra- (r = 0.95) and inter-rater (r = 0.91 – 0.95) comparisons, irrespective of the unit of measurement (watts; bpm). As this is a novel methodology, there is no prior data with which to make comparison. However, the technique itself is reminiscent of the modified V-slope method (462), and thus comparisons with its reliability are perhaps justified. In this context, the subjective threshold quantification performs comparably well, as the modified V-slope reported intra-rater reliability of r = 0.83 when measured using treadmill, and r = 0.96 on cycle ergometry. Similarly, the inter-rater reliability is reported to be r = 0.98 (treadmill) and r = 0.91 (cycle ergometer). However, the mean bias for inter-rater comparisons of both work rate and heart rate was consistently different, as is evident from the significant levels of systematic bias (work rate p = 0.002; heart rate p = 0.027). This presents a substantial hurdle if inflection thresholds for O_2Pulse are to be used in a similar way to ventilatory thresholds, for example, to quantify health status and prescribe exercise. For example, the same participant, given the same CPET could be prescribed wholly different exercise intensities by two investigators. This difference appears to be mitigated somewhat if the same examiner were to receive the same CPET, as is reflected by the MDC (15 watts; 10 bpm) and consistent mean bias values (0.03 watts; 0.46 bpm) recorded for the experienced examiner.

The normal progression of O_2Pulse during CPET is linear or slightly curvilinear in nature, as stroke volume increase to peak exercise (453). In such cases, the filtered and smoothed O_2Pulse should peak in the latter stages of incremental exercise testing, especially when ≤90% predicted VO_{2peak} has been achieved. Based on these logical assumptions the proposed algorithm identifies when peak values occur ≥ 90 seconds prior to the end of exercise and labels them as points of inflection. The proposed algorithm would inherently have zero intra rater reliability and zero MDC, assuming it were executed as intended. The inter-rater reliability of the algorithm when compared to both experienced and

novice examiners was excellent (*r* = *0*.92 – 0.98). However, as was seen with the experienced and novice examiner comparison there was a significant level of systematic bias when the algorithm and novice operator was compared. As bias was not present in the experienced versus algorithm comparison, it is perhaps more suggestive of a difference in interpretation that stems from level of experience. Furthermore, the limits of agreement and mean bias for algorithm and experienced examiner comparisons were almost identical to those observed in intra-examiner comparisons. Thus, the algorithm could theoretically replace the experienced examiner and eradicate intra-observer variability.

In real-world applications, the experience of clinicians and rehabilitators is wide ranging, thus, the adoption of an objective means of quantification is likely preferable to ensure equality of outcome for patients. For example, guidelines presented by the American College of Sports Medicine (ACSM) (466) suggest exercise intensities for CR to be below the ischaemic threshold (<10 beats), or a threshold that elicits the onset of angina symptoms. When following this guidance it would be preferable to know that, given the same baseline CPET, patients would receive the same intensity recommendations irrespective of the site they test at or the examiner who reviews their results.

6.6 Limitations

The study is limited by both the small sample of examiners and the accompanying heterogeneous level of experience. Moreover, as there was no invasive ischaemic assessment, inflections in O_2Pulse are not guaranteed to align with the onset of myocardial ischaemia. There are two avenues of enquiry for future research to pursue, firstly the algorithm could be used in conjunction with myocardial scintigraphy in an effort to corroborate the ischaemic threshold. Secondly, a larger sample of examiners with diverse levels of training and experience could be used to further establish the agreement of subjective threshold quantification and algorithm performance.

In conclusion, this study provides evidence for the reliability of both subjective and novel objective methods for identifying inflections in O_2Pulse during CPET. These findings have important implications for the use of CPET in clinical populations, and suggest that further research into the clinical significance of O_2Pulse inflections is warranted.

Chapter 7 : Alterations in Oxygen Pulse Morphology Following HIIT or MISS Based Cardiac Rehabilitation: A Subset Analysis of the HIIT or MISS Trial

7.1 Abstract

Oxygen pulse (O_2Pulse) calculated during cardiopulmonary exercise testing (CPET) can be used as a surrogate for left ventricular stroke volume. In patients with coronary artery disease (CAD), O_2Pulse has been used as an indirect marker of myocardial ischemia, providing insights into the impact of CAD during exercise. This retrospective sub-group analysis primarily sought to establish the prevalence of O_2Pulse inflections patients with CAD before they begin exercise-based cardiac rehabilitation (exCR). A secondary aim was to ascertain the proportion of these patients for whom inflections occur within or below the recommended training intensity range of 40-70% heart rate reserve (HRR). Additionally, this study aimed to assess the adaptability of O_2Pulse morphology following an 8-week period of either high-intensity interval training (HIIT) or moderate-intensity steady-state training (MISS) exCR.

Baseline and 8-week post-intervention CPET data of CAD patients were examined. Among 272 patients at baseline, 16% exhibited O_2Pulse inflections, suggesting the presence of potential silent myocardial ischemia. Furthermore, 68% of patients with inflections had them manifest within or below the recommended 40-70% HRR range. Post-intervention results showed that O_2Pulse inflections were eliminated in 41% of the participants, with the majority (75%) of remaining inflections occurring within the 40-70% HRR range. There was no significant difference between the HIIT and MISS groups in terms of altering the work rate at which O_2Pulse inflections occurred.

The study highlights a notable presence of O_2Pulse inflections in CAD patients entering exCR, with both HIIT and MISS interventions effectively influencing these inflections. The findings demonstrate that an 8-week exCR program can potentially mitigate signs of silent myocardial ischemia, as indicated by changes in work-rate at inflection. These results reinforce the importance of structured exCR in the management of CAD and demonstrate a need for future research to explore optimal exercise prescriptions.

7.2 Introduction

Oxygen pulse (O_2Pulse) is calculated as the volume of oxygen utilised per heartbeat ($\dot{V}O_2$/heart rate (HR)) and is commonly expressed in millilitres per beat (mL·beat) (290). O_2Pulse recorded during graded symptom limited cardiopulmonary exercise testing (CPET) reflects the haemodynamic behaviour of the left ventricle and thus is taken as a surrogate marker for stroke volume (SV) (268,451). In healthy populations, O_2Pulse follows a linear or curvilinear increase during incremental exercise until reaching a peak around the limit of exercise capacity (27). However, in coronary artery disease (CAD) a spontaneous inflection in this response may be observed (29). Coronary stenosis may inhibit myocardial O_2 supply to the point where adenosine triphosphate re-synthesis is impaired and myocardial contractions become dyssynchronous. Subsequent myocardial wall motion abnormalities cause a reduction in SV, resulting in a compensatory HR increase to sustain cardiac output. As a consequence changes in O_2Pulse can be used to diagnose suspected exercise-induced myocardial ischaemia and flow limiting stenosis (27,29,467). Due to the ischaemic cascade wall motion abnormalities and reduced SV (O_2-Pulse inflections), are likely to occur prior to traditional ECG changes (ST-depression) or overt angina symptoms (31). Indeed, inflections have been reported to precede ST-depression by an 265 ± 33 seconds (29). Therefore, O_2Pulse inflections may be a useful marker of silent myocardial ischaemia.

Silent myocardial ischaemia (SMI) can be defined as quantifiable ischaemia in the absence of related symptoms (171–174). Treadmill stress testing with ECG or ambulatory monitoring with holter ECG are most commonly used to detect SMI. The prevalence of SMI varies depending upon the population under investigation. It has previously been estimated that SMI occurs in 2-4% of asymptomatic middle aged men, and in 18% of patients with known CAD (468,469). SMI is associated with poor clinical outcomes and reduced physical function (470). Consequently, any eradication or rightward shift in O_2Pulse inflection occurrence may be desirable as a marker of increased functional capacity.

Exercise-based cardiac rehabilitation (exCR) has become a cornerstone in the comprehensive care of patients with CAD (8). The benefits of exCR for CAD patients are well recognised, including but not limited to improved cardiorespiratory fitness (VO_{2peak}),

and enhanced quality of life (10,350,471). However, recent studies have questioned whether current exCR is being undertaken at an intensity sufficient to maximise improvements in cardiopulmonary function (10). Recent evidence from the HIIT or MISS UK trial indicates that low-volume high-intensity interval training (HIIT) may result in a more clinically meaningful increase in VO_{2peak} when compared to moderate-intensity steady-state training (MISS) in those with stable CAD (334). However, it remains to be determined whether exCR has a positive influence on the presentation of O_2Pulse inflections, irrespective of the level of training intensity.

The current exercise training guidelines recommended by the Association of Chartered Physiotherapists in Cardiac Rehabilitation (ACPICR) indicate training intensities of 40-70% heart rate reserve (HRR) for outpatient exCR (12). Moreover, the American College of Sports Medicine (ACSM) suggest the upper limit of exercise intensity for outpatient cardiac rehabilitation should be ≤10 beats per minute below the heart rate at ischaemic onset (466). However, as previously established, if the heart rate corresponding to ischaemia onset is dictated by ST-depression, it may overestimate the ischaemic threshold (≥265 seconds), resulting in people with CAD performing exercise close to, or beyond their ischaemic threshold. exercising whilst ischaemic.

The prevalence of patients entering outpatient exCR with identifiable O_2Pulse inflections suggestive of SMI has not yet been established. Therefore, the primary outcome of this retrospective sub-group analysis was to determine what percentage of the cohort were exhibiting O_2Pulse inflections prior to undertaking exCR. Secondary, I wanted to identify the proportion of CAD patients whose presented with O_2Pulse inflections within or below the recommended training intensity of 40-70% HRR. Finally, I wanted to determine the trainability of O_2Pulse morphology following 8-weeks of exCR, and distinguish whether training intensity (HIIT or MISS) impacted the outcome.

7.3 Methods

This retrospective sub-group analysis was derived from a larger pragmatic, parallel-group, single-blind randomised controlled trial (HIIT or MISS UK) conducted across six UK cardiac rehabilitation programmes from July 2016 to March 2020. Ethical approval for the HIIT or MISS UK trial was provided by the Health Research Authority (HRA) East

Midlands - Leicester South Research Ethics Committee on 4 March 2016 (16/EM/0079). The trial was prospectively registered with ClinicalTrials.gov: NCT02784873 and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The main trial compared the effectiveness of low-volume HIIT and MISS exercise training. The full details of the trial have been published elsewhere (334,472).

The HIIT or MISS UK trial enrolled patients recommended for exCR due to acute myocardial infarction (MI), coronary artery bypass graft (CABG) surgery, angiographically documented CAD, or elective percutaneous coronary intervention (PCI). Eligible participants, aged between 18 and 80 years, had successful revascularisation, a left ventricular ejection fraction >35%, and demonstrated clinical stability for over two weeks. Those with exercise-induced complications, severe NYHA symptoms, or other significant health issues preventing full participation were excluded.

For this retrospective sub-group analysis I focused on baseline and 8-week post-intervention CPET data, which consisted of a standard cycle ergometer ramp protocol (15 - 25 $W \cdot min^{-1}$) completed in accordance with established guidelines (461). Participants were verbally encouraged to maintain a 70-rpm cadence despite increasing workload until volitional exhaustion or symptom limitation.

Participants meeting inclusion criteria were randomly allocated to either the HIIT or MISS groups on a 1:1 basis via random number generator. Patients in the HIIT group performed low-volume high intensity aerobic interval training on an air-braked cycle ergometer, alternating between high intensity (85 – 90% peak power output [PPO]) and lower intensity (20 – 25% PPO) efforts. The intensity and volume increased from 5x30 second high intensity efforts interspersed with 5x60 second low intensity efforts during week 1, to 10x60 second high intensity efforts interspersed with 10x60 second low intensity efforts from weeks 4-8. Participants allocated to the MISS group performed moderate intensity interval training, which progressed between 20-40 minutes of steady-state training at an intensity between 40–70% HRR in accordance with UK guidelines (12).

Fifteen-second mean time averaged work rate and O_2P data were then imported into an algorithm to determine the points of inflection. The algorithm was designed to anticipate a linear or curvilinear increase in O_2P when plotted against work rate. To mitigate outlying data points after time averaging, a 9-point moving mean average filter was applied, averaging each data point with its surrounding eight points. The algorithm then highlighted the first peak value occurrence in the test. If this value appeared in at least 6 data points (90 seconds) before test termination, it was marked as the point of inflection.

Additional criteria for recognising O_2Pulse inflections included:

- The point of inflection in O_2Pulse should coincide with a reduction in the ΔVO2/ΔWR slope of ≥ 10%.

- Patients not reaching ≥90% of their predicted VO_{2peak}.

These standards were based on findings from Belardinelli and colleagues (29,30). A retrospective sub-group was then identified that encompassed all those with noted inflections during baseline CPET.

To determine %HRR at the point of inflection I followed the ACPICR recommendations for calculating training thresholds using the Inbar method (12,473), with recommended 30 beats per minute adjustment to account for beta-blocker use (12,474). The formula is as follows;

$$HRR = (205.8 – (0.685 * Age)) – resting\ HR$$

Thus, 40%HRR is calculated by multiplying the subsequent HRR by 0.4 and adding the resting HR. calculating 70%HRR is done in the same manner but is multiplied by 0.7 rather than 0.4.

7.3.1 Statistical analysis

Statistical analysis was performed in R studio version 4.2.2 (475) using the R programming language and packages "readxl", "dplyr", "tidyr", "ggplot2", "car", "ez", "nlme", "lme4", "cowplot", and "svglite". Descriptive statistics were used to characterise groups at baseline with continuous data displayed as mean ± standard deviation (SD) or

median and interquartile range (IQR) where applicable. Categorical data were reported as percentage and or frequency.

Within and between group differences from baseline to post-intervention for primary and secondary outcomes were assessed using mixed-model ANOVA with planned post-hoc pairwise comparison on statistically significant ($p \leq 0.05$) main interactions (arm*time). Where appropriate Bonferroni-Holm correction was planned to adjust for multiple pairwise comparisons. Assumptions of normality and homogeneity of variances for all primary and secondary outcome measures were assessed using Shapiro-Wilk and Levene's tests, respectively. The effect size for main interactions was reported as partial eta squared (η^2) whilst within-group comparisons was measured with Hedges' g and interpreted as small (0.01), moderate (0.06) and large (0.14), and trivial (<0.2), small (0.2 – 0.49), moderate (0.5 – 0.79) and large (≥0.8) respectively (476). Statistical significance for analysis was set to a two-sided $p < 0.05$.

7.4 Results

Participant progression for the main HIIT or MISS study has been reported extensively elsewhere (334,472). For the purpose of this subset analysis specifically, 272 baseline CPETs were available for initial analysis. From this number the algorithm detected the presence of inflections in 44 (16%) tests, 24 of which were attributable to the HIIT group.

During the course of the 8-week intervention five members of each group were lost to dropout (HIIT = 21%; MISS = 25%). Descriptive statistics for the resulting n=34 cohort are presented in Table 12. There were no statistically significant differences between groups for any variable at baseline and no statistical assumptions were violated.

Table 12. Demographics and baseline characteristics by group

	HIIT (n = 19)	MISS (n = 15)
Demographics		
Age (years), mean (SD)	60 (9)	63 (9)
Sex		
Male	18	13
Female	1	2
BMI (kg/m^2)	28.7 (5.0)	28.2 (4.0)
Ethnicity		
White	17	12
Black	0	1
Asian	1	1
Other	1	1
Smoking Status		
Never	7	9
Former	11	6
Current	1	0
Baseline CPET parameters		
VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$)	17 (4.5)	16.3 (3.5)
VT_1 ($mL \cdot kg^{-1} \cdot min^{-1}$)	11.2 (3.2)	11.5 (2.2)
WR_{peak} (watts)	147 (38)	132 (27)
O_2P_{peak} ($mL \cdot beat^{-1} \cdot min^{-1}$)	11.6 (2.4)	12.2 (2.4)
Medical		
Time Since Event (Days), median (IQR)	40 (38.5)	35 (28.5)

The change in CPET parameters from pre intervention to post for all outcome measures are presented in Table 13.

Table 13. Changes to primary and secondary outcome measures following the 8-week intervention period (n=11 HIIT; n=9 MISS)

Variable at inflection	Arm	Mean Change (SD)
WR (watts)	HIIT	9.25 (10.03)
	MISS	17.78 (21.88)
O_2P ($mL \cdot beat^{-1} \cdot min^{-1}$)	HIIT	1.47 (1.33)
	MISS	1.69 (1.73)
Heart rate (bpm)	HIIT	-5 (8)
	MISS	2 (13)
VO_2 ($mL \cdot kg^{-1} \cdot min^{-1}$)	HIIT	1.35 (1.36)
	MISS	2.29 (2.50)

Abbreviations: WR = work rate; O_2P = Oxygen Pulse; VO_2 = Oxygen Consumption

Post intervention CPETs revealed a lack of O_2Pulse inflections in 14 (41%) patients, 8 of which were from the HIIT group (42%) and 6 of which were from the MISS group (40%). From the initial cohort of 44 patients who displayed O_2Pulse inflections at baseline, 6.8% (3 patients) had their points of inflection manifest below the recommended 40-70% HRR range. Additionally, 61.4% (27 patients) showed inflection points within this recommended range, while 31.8% (14 patients), had inflections observed above the recommended range. Final analysis of the 20 patients who still exhibited O_2Pulse inflections during post-testing (Figure 19) revealed that n=15 had the inflection occur below (3 = 15%) or within (12 = 60%) the recommended training intensity band (40-70% HRR), with only n=5 (25%) experiencing inflections above 70% HRR.

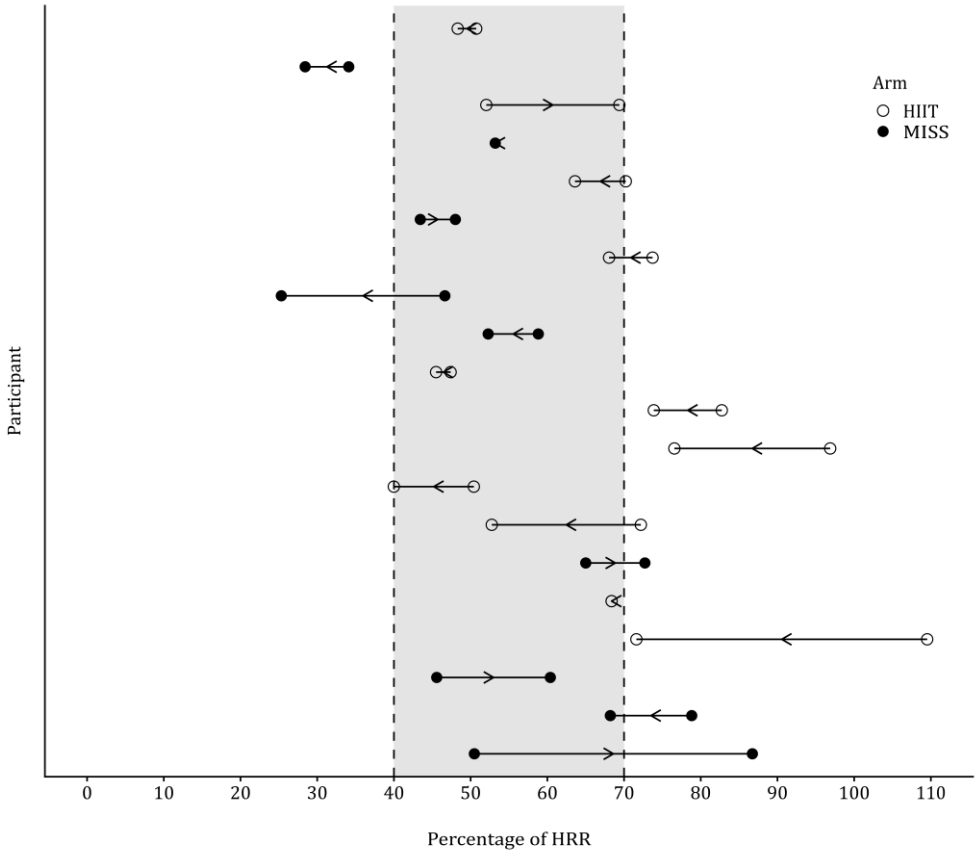

Figure 19. Change in percentage of heart rate reserve at inflection from baseline to post-testing (week 8). Arrows indicate either an increase or decrease after exCR; shaded area represents recommended training intensity for outpatient exCR

The mean change in inflection occurrence as a percentage of HRR was -8.8 ± 14 in the HIIT group and 2.1 ± 16.6 in the MISS group. A statistically significant main effect for time for WR at the point of inflection was noted in both groups (p<0.001; Figure 20), with no significant group-by-time interaction effect evident (The effect of time on WR at point of inflection was large (η^2 = 0.4), whilst the group effect, (HIIT or MISS) (η^2 = 0.01) and group by time (η^2 = 0.07) were small and moderate, respectively. For individuals who maintained O_2Pulse inflections following training (n=20), there was a significant increase in time effect (p<0.001) in all secondary outcomes with the exception of heart rate, for which group allocation was a significant (p = 0.05) mediator.

Table 14).

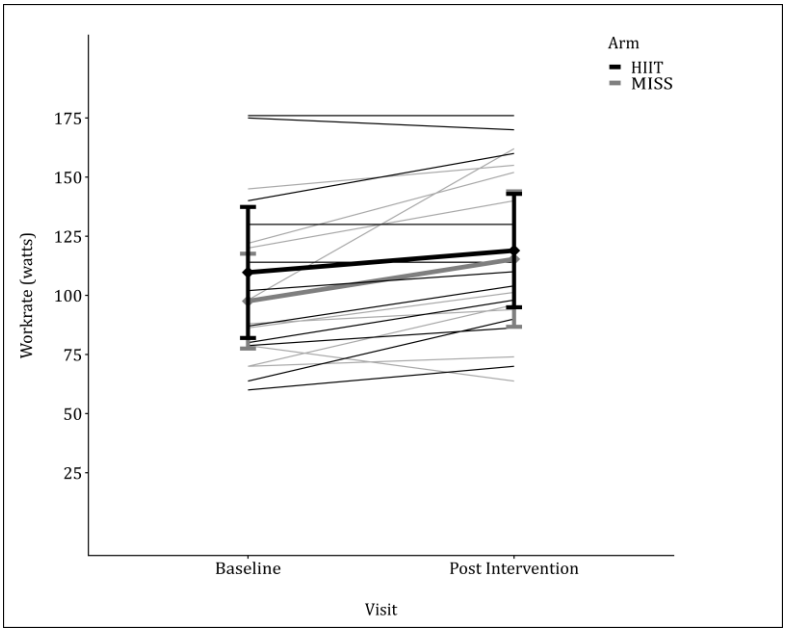

Figure 20. Change in workload at inflection following 8-weeks of intervention with HIIT or MISS

The effect of time on WR at point of inflection was large ($\eta^2 = 0.4$), whilst the group effect, (HIIT or MISS) ($\eta^2 = 0.01$) and group by time ($\eta^2 = 0.07$) were small and moderate, respectively. For individuals who maintained O_2Pulse inflections following training (n=20), there was a significant increase in time effect ($p<0.001$) in all secondary outcomes with the exception of heart rate, for which group allocation was a significant ($p = 0.05$) mediator.

Table 14. Mixed-model ANOVA results for the effects of 8 weeks of HIIT or MISS training on CPET parameters at O_2Pulse inflection

Variable at inflection	Arm	Mean square error	F-value	*p* - value	η^2
WR (watts)	Arm	2437.20	0.25	0.622	0.014
	Time	134.32	13.46	0.002**	0.428
	Arm*Time	134.32	1.34	0.262	0.069
O_2P (mL·beat^{-1}·min^{-1})	Arm	11.39	0.40	0.537	0.022
	Time	1.16	21.35	< 0.001***	0.543
	Arm*Time	1.16	0.11	0.746	0.006
Heart rate (bpm)	Arm	364.27	4.42	0.050*	0.197
	Time	53.23	0.37	0.550	0.020
	Arm*Time	53.23	2.77	0.113	0.133
VO_2 (mL·kg^{-1}·min^{-1})	Arm	22.23	0.02	0.888	0.001
	Time	1.90	17.28	< 0.001***	0.490
	Arm*Time	1.90	1.15	0.299	0.060

Abbreviations: WR = work rate; O_2P = Oxygen Pulse; VO_2 = Oxygen Consumption
* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$

7.5 Discussion

The primary objective of this retrospective sub-group analysis was to determine the prevalence of the population entering outpatient cardiac rehabilitation in the UK who exhibited O_2Pulse inflections during incremental exercise. I also sought to investigate whether current guideline exCR intensities of 40-70% HRR required patients to exercise at or above the point of inflection, and whether O_2Pulse inflections were trainable following moderate or high intensity exCR.

Our findings indicate O_2Pulse inflections were prevalent in 16% of people with CAD entering outpatient exCR. This value is difficult to contextualise as there have been no previously reported values with which to make comparisons. However, prevalence is comparable to the 18% of people with CAD who have documented SMI during ECG stress testing (469).

Guidelines from the ACSM indicate that patients with known CAD should not exercise within 10 beats of a heart rate that elicits myocardial ischaemia (466). However, in the

present cohort, >68% of patients exhibiting O_2Pulse inflections at baseline experienced inflections below the upper limit of exercise training guidance (<70% HRR) advocated in the UK. Following 8 weeks of exCR 8 patients from the HIIT group and 6 patients from the MISS group no longer had identifiable inflections in O_2Pulse, showing that presentation of inflections are trainable and respond to an exercise training stimulus, irrespective of intensity (moderate or high). Of the 20 patients who did still have inflections during post-testing 5% occurred below 40% HRR and 65% occurred below 70% HRR. The present study indicates that current guidance may not sufficiently account for CAD patients with O_2Pulse inflections, if, as indicated, O_2Pulse inflections represent the early onset of myocardial ischaemia before ECG change occurs (29). It should however be noted that there were no reported adverse events from any of the patients with O_2Pulse inflections, and the combined rate of dropout from HIIT and MISS was 23%, which, whilst in excess of the ≈15% reported for the whole HIIT or MISS trial, was within the withdrawal rate of 12-56% reported by other training interventions (477).

Our analysis reveals that exercise intensity does not discriminate between the manifestation of O_2Pulse inflections following 8 weeks of training. Training at moderate or high intensity reduces the manifestation of O_2P inflections, which may serve as a potential surrogate marker for myocardial ischaemia in people with CAD and provides further evidence regarding the benefits of exercise training in people with CAD.

Eight weeks of HIIT or MISS exCR (up to 16 individual training sessions) eliminated O_2P inflections in 41% of patients (8 = HIIT; 6 = MISS), whilst those with persistent inflections were able to achieve a greater amount of work prior to inflection occurrence. These findings highlight that either moderate or high intensity training have the potential to delay, or prevent myocardial ischaemia during exercise, ultimately enhancing functional capacity. Notably, group allocation was not a statistically significant factor in this improvement, indicating that exercise intensity during exCR may not be a pivotal component which influences O_2P inflections, particularly when viewed across an 8-week intervention period. The key recommendation for health professionals is to follow existing guidance and recommend a training stimulus of at least moderate intensity (40-70% HRR).

Our findings also indicate that moderate or high intensity exCR result in an increased O_2Pulse, and VO_2 at inflection. This rightward shift was significantly and largely ($\eta^2 > 0.4$) impacted by time ($P<0.001$) but not by group allocation. Interestingly heart rate at inflection was generally unaffected by time ($P= 0.5$; $\eta^2 = 0.02$) but was significantly and largely impacted by group allocation ($P= 0.05$; $\eta^2 = 0.2$), decreasing by 5 ± 8 bpm in the HIIT group and increasing by 2 ± 13 bpm in the MISS group.

It is hypothesised that O_2Pulse inflections during exercise reflect systolic dyskinesia secondary to myocardial ischaemia as a result of coronary stenosis (29,30,276,478). Studies have consistently highlighted the contribution heart rate makes to myocardial oxygen demand during exercise, with early indications of 30–40% contribution being revised to almost 70% (479), suggesting heart rate is perhaps the primary determinant of myocardial oxygen demand. Indeed, heart rate reduction is a primary target of modern pharmacotherapy in people with CAD, which is likely to leave limited scope for further improvement following exCR. If heart rate is a primary determinant of myocardial oxygen demand, and O_2Pulse inflections are the results of myocardial perfusion mismatching due to arterial stenosis, it is perhaps not surprising that heart rate at inflection is not altered after exCR. Absent of any change in coronary structure, either through percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) or arteriogenic collateral formation, inflection is likely to occur around the same threshold of myocardial oxygen demand. The underlying mechanism or mechanisms that allow patients to increase work-rate, O_2Pulse, and VO_2 before manifesting inflections, absent of any real change in heart rate following exCR are not immediately clear. However, these findings in combination are perhaps suggestive of an increase in stroke volume (SV), or arteriovenous oxygen difference (a-VO_{2diff}).

Previous work has indicated that MISS training in apparently healthy participants can increase left ventricular end-diastolic diameter and induce ventricular hypertrophy (480), both of which could lead to an increase in SV. Furthermore, SV increases of ≈10% have previously been reported following 8 weeks of HIIT training in moderately trained healthy individuals (481). Changes in SV following exCR in cardiac populations are rarely reported, although left ventricular ejection fraction (LVEF) is cited regularly. Evidence for an increase in LVEF following exCR is not compelling. A recent systematic review and

meta-analysis reported high levels of heterogeneity within the extant literature (I^2 = 95%; p < 00001). The review included 5 articles with a combined total of n=465 participants (n=236 intervention and n=229 control), with a reported mean difference of 2.5% (95%CI = -2.10 – 7.17; p = 0.28) (482).

Stroke volume and cardiac output (Q) were reportedly unchanged in both responders (VO_{2peak} ≥1 $mL \cdot kg^{-1} \cdot min^{-1}$) and non-responders to routine exCR across two centres in Poland (22). However, in responders the a-VO_{2diff} increased significantly at peak exercise (p = 0.009) rising from 13.9 ± 4.1 mL·dL to 17.0 ± 4.7 mL·dL (22). This is consistent with earlier evidence in which a-VO_{2diff} increased significantly (p < 0.001) at rest and during various stages of training following 12 weeks of exCR in 12 people with coronary heart disease (483).

Our findings align with previous research that have highlighted the benefits of exCR for improving multiple markers of exercise capacity. However, it is difficult to directly compare or contrast my findings with other research, as, to the best of my knowledge, no other efforts to directly quantify the change in O_2P inflections following exCR are in the public domain. Chaudhry and colleagues (28), published a case study based on three CPETs conducted on the same patient over 4.3 years. The patient was a 36-year-old male with a strong family history of premature CAD, usually occurring around the fourth or fifth decade. During his first CPET he achieved 91% age predicted HR and 70% predicted VO_{2peak}. However, he exhibited a clear inflection in O_2Pulse with concomitant decrease in the slope of $\Delta VO_2/\Delta WR$ shortly after passing the ventilatory anaerobic threshold VT_1 (100 watts). Upon further examination, the patient was found to have profound dyslipidaemia, which he attempted to rectify with a dietary intervention over the following 12 months. Another CPET was then performed in which the patient achieved 85% predicted HR and 66% predicted VO_{2peak}. As with the initial CPET, the O_2 kinetics became abnormal above VT_1, however, the inflection point had regressed to a workload of 75 Watts which equated to an ≈60 second reduction in exercise duration. At this point, the patient began aggressive pharmacotherapy, which he continued for 3.3 years. The patient undertook a final CPET 4.3 years after the initial test. He achieved 86% predicted HR and 80% predicted VO_{2peak}, and, on this occasion, the O_2 kinetics remained normal throughout the duration of the test. Whilst this does not align directly with my findings,

it does suggest that O_2Pulse inflections are amenable to change given appropriate intervention, either through exercise training, pharmacotherapy or both in combination.

Our findings hold considerable pragmatic implications for the clinical landscape of exCR. Specifically, my findings affirm the importance of engaging with structured exCR, demonstrating that it can have a tangible impact on O_2P inflections, which are potentially indicative of myocardial ischaemia at either moderate or high intensity (27–30). For clinicians and practitioners, this underscores the idea that exCR can be a powerful tool, not just for enhancing cardiorespiratory fitness but also potentially for removing or offsetting the manifestation of silent myocardial ischaemia.

Given the prevalence of CAD and its associated multimorbidity, I would strongly recommend either HIIT or MISS training as a primary and front-line therapy for reducing the prevalence of O_2Pulse inflections. The study's novel methodology offers a fresh lens through which the impact and efficacy of exCR can be evaluated.

7.6 Limitations

This study is not without limitations, firstly being a retrospective sub-group analysis, there was no a priori sample size calculation, and consequently the analysis may not be adequately powered to detect a true change in the primary outcome. Secondly, there is likely to be, as with other CPET parameters, inherent variability within the occurrence of O_2Pulse inflections. This may be in the form of natural fluctuations within an individual participants, or measurement error associated with the identification of the inflection. I aimed to mitigate some of this human error by employing an objective algorithm to detect points of inflection. Whilst this algorithm has been validated internally, these findings have yet to be published or replicated externally. It should also be noted that the intervention period was 8 weeks (up to 16 training sessions). Whilst standard Phase III CR is not of a fixed duration, and alters between centres, it typically varies between 6 to 12 weeks (484). It remains to be seen if a dose-response relationship exists between the manifestation of points of oxygen pulse inflection during exercise testing and exercise training dose. Finally, participants were primarily middle-aged white males and I was unable to generalise my findings to females or individuals from ethnic communities.

7.7 Future directions

Future studies should assess the impact the dose-response relationship between exercise training duration and manifestation of oxygen pulse inflections to observe whether a further rightward shift is noted and determine any association with exCR adherence. The effect seen here following HIIT and MISS training could be combined to a group performing HIIT and MISS in combination (separate sessions). Furthermore, the addition of an alternate exercise modality, such as resistance training could be employed to determine any impact on the point of O_2P inflection. Any future research that assess the change in O_2P inflection as a primary outcome should aim to use a gold-standard measure of myocardial perfusion alongside CPET to validate inflection detection.

7.8 Conclusion

In conclusion, my study indicates that an 8-week exCR programme, either completely abolishes, or offsets the potential early signs of myocardial ischaemia (based on the detection of O_2Pulse inflections), irrespective of training intensity (HIIT or MISS) in people with CAD. This has potential implications for the treatment, management, and prognosis of people with CAD, especially those with SMI. Further research is needed to determine the mechanisms underlying these observations and to optimise exCR programmes for maximum benefit.

Chapter 8 : General Discussion

8.1 Overview and Main Findings

The main aim of this thesis was to explore the potential use of CPET in interpreting cardiovascular function and adaptation in patients with CAD, especially those with CTO. The research sought to investigate how analysing abnormalities in important CPET derived parameters like O_2Pulse and $\Delta\dot{V}O_2/\Delta WR$, can indicate changes in cardiac function that may be related to myocardial ischemia. The overall objective was to improve the application of CPET in clinical practice, focusing on its ability to provide better patient care through individualised exCR prescriptions. These aims and objectives were pursued through a series of specific chapter aims addressing various aspects of CPET's role in CAD assessment and management.

8.1.1 Chapter 3

The aims of Chapter 3 was a pilot study with the aim of establish the feasibility of recruiting and maintaining adherence for repeated CPETs among CTO patients within the local area (Humberside), targeting enrolment completion within 18 months. Additional aims of this chapter were to investigate whether CTO patients exhibit O_2Pulse and/or $\Delta\dot{V}O2/\Delta WR$ inflections indicative of myocardial ischemia during CPET, to assess the reliability and agreement of inflections if preset, and finally to evaluate the safety of 20-minute fixed workload exercise at intensities associated with these inflections.

Recruitment prior to COVID-19 had been unanticipatedly slow, with only four patients passing through the study. The clinical opinion prior to undertaking the study was that 12 patients in 18-months was a very realistic target. However, in reality over half of those invited to partake in the study declined. Recruitment was ongoing when COVID-19 began to emerge, and at the time of the first lockdown I did have five patients willing to join. However, as a result of the pandemic and subsequent lockdowns and restrictions these patients were never tested. This challenge extended the projected timeline for achieving the desired sample size, thereby rendering the protocol infeasible as a single-centre study in the Humberside area. Despite a 100% retention rate among the four patients who were tested, only one patient completed the entire study protocol. Consequently, the statistical plan to assess reliability and agreement between inflection points was not possible.

Furthermore, the ability to perform a power calculation for future, potentially larger or multi-centre studies.

Data collected from the four participants who did undertake testing in Chapter 3 still provides some valuable insights. Only one of the four patients demonstrated an inflection in the O_2Pulse curve during CPET. Such inflections are purported to be indicative of the onset of myocardial ischaemia (22,27–30,265–275,275–287). The lack of O_2Pulse inflections in three patients with angiographically documented CTO is thus surprising, as, by definition, these patients are likely to experience myocardial perfusion mismatching when physical activity is increased. However, this studies recruitment of patients with single-vessel CTO, is not something that has been done before, previous cohorts have been comprised of patients with heterogeneous CAD diagnosis. The seminal work of Belardinelli and colleagues (30) reported that only 16% CAD patients diagnosed through inflections in $\Delta\dot{V}O_2/\Delta WR$ and O_2Pulse had single vessel disease, with the remainder having double- and triple-vessel disease. Although chronically occluded in a single vessel, it is possible that my cohort had a small ischaemic territory, especially considering collateral development is greater in the presence of a CTO (423,424).

This study's observations further challenge the earlier findings by Belardinelli and colleagues, as no identifiable inflections in $\Delta\dot{V}O_2/\Delta WR$ were observed in any of the tested patients, even when O_2Pulse inflections were present. This discrepancy could be attributed to methodological differences, such as the continuation of cardiac medications affecting heart rate and arterial vasodilation in my study. Interestingly, despite the continued use of a beta-blocker, calcium channel blocker, and ACE inhibitor, the patient who did exhibit O_2Pulse inflections also displayed concomitant increases in heart rate at the point of inflection. This is aligned with the work of Chaudhry et al (277,485) and Yoshida et al (292), both of whom have reported a compensatory increase in heart rate to account for reduced SV at the ischaemic threshold. However, Yoshida and colleagues (292) reported that beta-blocker use amplified $\Delta\dot{V}O_2/\Delta WR$ inflections, something that I did not observe in the current study. This perhaps highlights a disparity in beta-blocker optimisation between studies.

In the lone case where a 20-minute fixed workload exercise was performed, no adverse events or signs of myocardial ischemia were observed, indicating potential safety in prescribing exercise at such intensity.

8.1.2 Chapter 4

The aim of Chapter 4 was to collate and evaluate the existing literature on exercise induced collateral development. This aim wsa addressed by way of a published narrative review. The chapter highlights the intricate network of coronary collateral vessels, their development, function, and possible therapeutic application through physical exercise. Whilst it is believed that coronary collateral vessels are present in all hearts as remnant of the embryonic vascular network (190,422), they are developed to a greater degree in the presence of obstructive CAD (423,424). The process by which these vessels remodel into a more robust vessel capable providing 30-40% of the fluid carrying capacity of the native artery is termed arteriogenesis (205).

The chapter emphasizes the shear stress mediated nature of arteriogenesis. It underscores the dual role of shear stress, which is associated with both the development and prevention of atherosclerosis. Particularly notable is the increase in shear stress during physical activity, aligning with the reduction in cardiovascular events and its recommendation in both primary and secondary prevention of CAD. The evidence presented, drawing from post-mortem studies, animal models, and clinical observations, indicates that physical exercise may have a positive role in promoting collateral development. Myocardial O_2 demand is increased during physical exercise, which is results in a ≈5-fold increase in coronary blood flow (426). The increase in coronary flow is coupled with an increase in fluid sheer stress, which is the proposed mechanism of arteriogneic collateral development. Collateral development is best assessed through the collateral flow index, which is an invasive measure taken during coronary angiography. Indeed, all of the studies in this chapter that measured the collateral flow index pre and post exercise intervention found statistically significant increases (437–439,441). Mechanistically the arteriogenic process is exploited during enhanced external counterpulsation, during which pneumatic cuffs are placed around the lower limbs before being sequentially inflated to an external hydraulic pressure of 300 mmHg during diastole (gated by ECG), then rapidly deflated prior to systole (232). This process

generates an increase in coronary blood flow and thus fluid sheers stress. Intriguingly, resistance training may present an alternative method to stimulate collateral development, given its significant impact on diastolic blood pressure compared to standard aerobic HIIT or MISS training. This chapter thus provides a comprehensive overview of the current state of knowledge regarding coronary collateral vessels, their significance in cardiovascular health, and the potential of exercise in their development, paving the way for future research in this vital area of cardiovascular physiology.

8.1.3 Chapter 5

The aim of Chapter 5 was to evaluate the short-term stability of the O_2Pulse curve in healthy, recreationally active participants. To achieve this, the chapter conducted a retrospective analysis focused on assessing the reliability and agreement of O_2Pulse curve parameters from CPETs performed within a 72-hour interval. The chapter demonstrates that both raw and filtered 15 second mean time averaged O_2Pulse, and the area under the curve taken at 10% increments from 50 to 100% of peak workload are reliable, with ICC values not dropping below .095 for any of the 24 variables. This finding aligns with previous research by Barron et al (271), who reported similarly high reliability (ICC = 0.96) for O_2P_{peak} in a diverse patient population. Similarly Perim and colleagues (455) reported coefficients of determination (R^2) as a measure of long-term (12-month) reliability for O_2Pulse in professional footballers, concluding that the mean values were virtually identical across tests (0.64 and 0.63). In combination these findings support the concept of a stable and reliable O_2Pulse curve. However, reliability does not necessarily necessitate agreement, which is necessary to establish if O_2Pulse is be used in a prescriptive manner. To this end Chapter 5 reports the SEM and MDC for all 36 variables, with the mean to allow determination of %SEM and %MDC.

When considering agreement for the 15 second mean time averaged (raw) O_2Pulse data, which is what the majority of interpreters will initially evaluate, the mean MDC across all six percentages of workload is 2.6 ± 0.5 mL·beat^{-1}. This is reduced to 2.2 ± 0.4 mL·beat^{-1} when data is filtered with a 9-point moving mean average filter. As a percentage of the sample mean averaged across all six percentages of workload this is 16 ± 4% for raw and 13 ± 3% for filtered data. These findings indicate that if O_2Pulse (taken across the second half of a CPET) were to be used to monitor change following an exercise intervention,

perhaps such as exCR, it would need to increase or decrease by 2.6 ± 0.5 mL·beat^{-1} to be confident true change had occurred. However, when compared against the only available data on the short-term repeatability of O_2Pulse inflection in patients with CAD from the patient in Chapter 3, this MDC appears conservative. The patient in Chapter 3 for example had only a 0.5 mL·beat^{-1} difference in the occurrence of O_2Pulse inflections, well within the MDC boundary established here. This perhaps indicates that my modelling of MDC from a healthy cohort does not apply to those with CAD, and that the pathological limitation believed to induced O_2Pulse inflections in patients with CAD imposes a tighter, less varied threshold. Indeed, the MDC at a specific threshold (100%) in Chapter 3 was tighter at 1.8 mL·beat^{-1} raw and 1.6 mL·beat^{-1} filtered.

Given the established significance of O_2P_{peak} as a predictor of cardiovascular and all-cause mortality (450), understanding its reliability is essential for risk assessment in cardiovascular disease. Additionally, inflections in the O_2Pulse curve, indicative of myocardial ischemia onset, as highlighted in studies by researchers (27,29,30,399), may be of benefit for setting exCR thresholds.

8.1.4 Chapter 6

Whilst Chapter 5 demonstrated the short-term reliability and agreement of the O_2Pulse curve in a small, healthy, recreationally active cohort, it did not address the reliability and agreement introduced with the subjective identification of points of abnormality in the usual progression of O_2Pulse. Chapter 6 therefore builds on the findings of Chapter 5, addresses this gap in the literature by retrospectively analysing data from the HIIT or MISS UK trial. The aim of Chapter 6 was to determine the inter- and intra-rater reliability and agreement associated with the subjective identification of O_2Pulse inflections in patients with CAD, and to compare these to an objective algorithmic means of identification.

The reliability of agreement for categorising normal and abnormal O_2Pulse responses between a novice, experienced, and algorithmic rater were compared via Fleiss' Kappa. After reviewing 272 CPETs the Kappa statistic for all raters was $\kappa F = 0.89$ with a bootstrapped 95% confidence interval of 0.83 - 0.93. This compares favourably with previously reported values of between $\kappa C = 0.65$ and $\kappa C = 0.69$ (282,402). The higher

kappa value in the current study may be attributed to the use of Fleiss' Kappa for three raters, as opposed to Cohen's Kappa (κC) used in the previous studies for two raters. Despite the potential for increased variability with more raters, the task required only binary "Yes" or "No" decisions about the presence of inflections or plateaus, which might have contributed to the higher agreement level.

For O_2Pulse inflections to be used as a threshold from which exCR intensity is prescribed and cardiopulmonary fitness is monitored, the intra-individual variability in its appearance needs to be low, which Chapter 3 suggests it is, and the method of identification needs to be both reliable and precise. There were 37 cases in which agreement was reached between all three raters, in these instances the intra-rater MDC for the experienced rater was 15.5 W for work rate and 8.6 beats for heart rate. If I relate this to the findings of Chapter 3, in which short-term repeated CPETs elicited O_2Pulse inflections that were separated by 10 W and 5 beats, it is evident that, at least in the one patient observed in Chapter 3, that the inter-individual variation in inflection occurrence is within the intra-rater MDC.

In clinical practice it unlikely that the same rater will always be interpreting results, and large differences between raters would translate to large differences in prescribed intensities. The inter-rater MDC between the novice and experienced rater was 52.7 W for work rate and 17.5 beats for heart rate, both of which are accompanied by significant levels of systematic bias (p<0.05). This perhaps underscores the need for an objective means of identification, which, given the same data on repeated occasions would produce the same outcome. The algorithm proposed in Chapter 6 had excellent reliability for heart rate and work rate across comparison with experienced and novice raters (ICC = 0.92 – 0.98). However, in comparisons with the novice rater there was a significant degree of systematic bias for both (p<0.05). Despite this bias the agreement between the algorithm and novice rater for work rate at inflection was better than for the algorithm and experienced rater (MDC = 13.8 W versus 16.3 W). However, the Bland-Altman plot demonstrates that this discrepancy is due to the small but consistent overestimation by the novice rater.

8.1.5 Chapter 7

The primary aim of Chapter 7 was to determine what percentage of the cohort were exhibiting O_2Pulse inflections prior to undertaking exCR. Secondary, I wanted to identify the proportion of CAD patients whose presented with O_2Pulse inflections within or below the recommended training intensity of 40-70% HRR. Finally, I wanted to determine the trainability of O_2Pulse morphology following 8-weeks of exCR and distinguish whether training intensity (HIIT or MISS) impacted the outcome.

The results showed that 16% of patients entering outpatient exCR had identifiable inflections in O_2Pulse, with 68% of patients displaying inflections within or below the recommended training intensities for UK exCR. Both HIIT and MISS interventions effectively influenced O_2Pulse inflections, eliminating these inflections in a significant proportion of patients (41%). Importantly, the remaining patients with inflections demonstrated a significantly (p<0.05) increased capacity to perform more work before reaching the inflection point. These results suggests that both exercise modalities could potentially delay or even prevent myocardial ischemia during exercise, enhancing exercise capacity in CHD patients. This finding is critical, as it aligns with previous research underscoring the benefits of exCR in improving exercise capacity and cardiovascular fitness. However, data from Chapter 3 indicates that whilst statistically significant, this increase in workload at point of inflection may not be sufficient in magnitude to confidently identify change.

The study found a statistically significant (p<0.05) increase in O_2Pulse and $\dot{V}O_2$ at the inflection point post-intervention, suggesting improvements in cardiovascular function. Whilst in Chapter 3 I demonstrated that the intra-patient agreement for O_2Pulse at inflection in one CTO patient was 0.5 mL·beat^{-1}, in Chapter 5 I demonstrated that the mean MDC for the O_2Pulse curve in recreationally active healthy participants was 2.6 ± 0.5 mL·beat^{-1}. Taken in totality these findings make it difficult to be confident that the observed significant change in O_2Pulse at inflection is representative of a true adaptation to the intervention.

If inflections in O_2Pulse are apparent in CPET due to myocardial ischaemia resulting from occlusive CAD, then their eradication or rightward shift following 8 weeks of exCR (HIIT

or MISS) may also be explained by an increase in collateral supply or arterial vasodilation. Mechanistically the atherosclerotic lesion causing the occlusion cannot reduce in size. However, the myocardial supply could be augmented by a dynamic increase in diameter of the occluded vessel (vasodilation), or an increase in the fluid carrying capacity of the collateral network bypassing the occlusion. However, both HIIT and MISS groups displayed only minor, non-statistically significant changes in heart rate at the point of inflection. This is consistent with the findings observed in Chapter 3, in which the sole patient tested had only a 5-beat difference at point of inflection. If, as has been reported, heart rate is the primary determinant of myocardial O_2 demand (479), then an increase in supply through collateralisation or vasodilation would perhaps be reflected by an increase in the heart rate at inflection. As O_2Pulse and $\dot{V}O_2$ at inflection increased without increases in heart rate this may suggest a possible increase in SV or a-vO_{2diff}, contributing to the enhanced exercise performance.

These findings have profound implications for the management of CHD patients. They suggest that both HIIT and MISS training modalities in exCR can have a tangible impact on O_2Pulse inflections, potentially indicative of myocardial ischemia. This reinforces the concept that exCR, beyond enhancing cardiovascular fitness, might also play a role in mitigating the effects of silent myocardial ischemia, a common manifestation in CHD.

8.2 Strengths and Limitations

As with any thesis there are strengths and limitations to the work that is presented here. Chapter 3 was limited in the most part by poor recruitment and the outbreak of COVID-19 in 2019. Whilst the global pandemic is something that could not be foreseen or planned for, the issues in recruitment may have been avoided by a slightly more relaxed inclusion criteria. The planned statistical analysis of Chapter 3 was also made impossible by the sole progression of one participant through all phases of testing. At first this appears to be unavoidable and due solely to the physiological response inherent to each participant. However, in retrospect my decision to run the experiment without requiring that cardiac medications were ceased prior to testing may have had a considerable impact upon the results. Still, the decision was not made without consideration, and I do not believe ceasing medications would have been in the best interest of the patients or the study, as any findings would relate only to a status quo that is not applicable to the reality

of usual care. The strength of Chapter 3 would have been its novelty and rigor. As mentioned previously there is currently no data pertaining to the reliability, and perhaps more importantly agreement of inflections in O_2Pulse. The matter of agreement is one that is recurring throughout this PhD, and for good reason. If a variable or tool is to be used to measure progress, guide prescription, or avoid ischaemia, then clinicians and academics must first know its MDC. Unfortunately, I was not able to suggest an MDC for O_2Pulse inflections in Chapter 3 due to the mentioned issues with recruitment and patients progression, this is something that is paramount for research in this field moving forward.

Chapters 5, 6 and 7 were all limited by the retrospective nature of their design. Whilst this retrospective analysis was necessary due to the finite PhD timeframe and the COVID-19 pandemic, it did not allow the studies to be powered or optimised. Chapter 5 for example permitted the calculation of an MDC for the second half of the O_2Pulse curve in recreationally active participants, but this was accomplished with data from only 11 participants for only two visits. The small sample and limited data from which this has been calculated could have inflated the MDC due to the standard deviation of the sample used in the SEM calculation. Furthermore, the use of a healthy population free from inflections dramatically reduces the generalisability of the findings.

The use of only two human raters in Chapter 6 is a limitation that somewhat reduces the transferability of the findings. The time investment from raters for this study was large, with the requirement to review 272 CPET files in detail. In retrospect I could perhaps have invited multiple raters, for example ten, to each review a random sample of 50 CPETs. This would have allowed 500 points of comparison against the algorithm and introduced a greater degree of experience across human raters. Moreover, the algorithm has only been tested against the abnormalities on CPET believed to be associated with myocardial ischaemia. Assessing the true utility of the algorithm would require it to be validated against stress myocardial perfusion imaging. In such a case the graded exercise could be performed on a supine bike with simultaneous breath-by-breath gas analysis and time synched imaging, thus allowing inflections identified with the algorithm to be compared with the occurrence of perfusion abnormalities. Still, Chapter 6 is not without strengths, it provides a novel contribution to the discussion of inflection identification

and suggests a structured algorithmic approach, which, if widely adopted would eliminate the chance that the same CPET results could be interpreted differently across facilities or clinicians.

The main limitation of Chapter 7 is the lack of any invasive confirmation of ischaemia or measure of collateral flow. However, as mentioned above the retrospective nature of the analysis was born of necessity due to the finite PhD timeframe and COVID-19. The main strengths of Chapter 7 were its large, multi-centre randomised control design, and the routine delivery of interventions (non-research staff). The cohort was comparable to the general population enrolled in UK exCR despite consisting of almost entirely white male patients aged 50-70 years. Consequently, the percentage of patients with O_2Pulse inflections entering exCR, and the percentage of patients potentially exercising with myocardial ischaemia may very well be representative of the UK exCR population at large.

8.3 Future Directions

This thesis merely scratches the surface of this field of study and perhaps provides more questions than answers. Some key areas for future to work address are as follows:

1. Validate an objective means of identifying myocardial ischaemia through non-invasive CPET derived variables, such as O_2Pulse, $\Delta\dot{V}O2/\Delta WR$, and heart rate against myocardial perfusion imaging in a cohort of patients with CAD who are still receiving OMT.
2. Establish the short-term reliability and agreement of the above-mentioned method of objective identification in a cohort of patients with CAD who are still receiving OMT.
3. Determine whether it is safe or effective to prescribe exCR intensity below, at, and above the individual ischaemic threshold in a cohort of patients with CAD who are still receiving OMT.
4. Use CFI to determine whether routine exCR or resistance training have a greater impact upon the collateral flow, and if this impact is visible as a rightward shift in the above-mentioned method of objective identification in a cohort of patients with CAD who are still receiving OMT.

Chapter 9 : General Conclusions

The outcomes of this thesis highlight the potential utility of CPET in monitoring and prescribing exCR intensity for patients with CAD, particularly through identification of abnormalities in the usual progression of O_2Pulse and $\Delta\dot{V}O_2/\Delta WR$. The findings offer valuable insights into the reliability and clinical implications of CPET abnormalities.

The challenges faced in Chapter 3, particularly in recruiting CTO patients, highlight the complexities of researching this niche patient group and underscore the need for larger, potentially multi-centre studies to gain a comprehensive understanding of the interplay between physical activity and myocardial ischemia during CPET. Despite these challenges, the study provides some preliminary evidence that CPET variables traditionally linked to myocardial ischemia may not be as prevalent in patients with CTO as previously thought, perhaps due to the continuation of OMT. However, when present these variables appear to be stable in the short term.

In Chapters 5 and 6, the reliability of various O_2Pulse parameters was shown to be moderate to excellent, with agreement in the form of %MDC for O_2Pulse recorded at 13.5 ± 3.2. The introduction of an objective algorithm for identifying inflections in O_2Pulse offers a promising tool for standardising interpretation and ensuring consistent outcomes across different sites and clinicians.

Finally, Chapter 7 presents compelling evidence that 16% of patients entering exCR have possible silent myocardial ischaemia during exercise, and that the recommended exCR of 40-70% HRR is not enough to avoid the possible threshold for ischaemia in 68% of cases. Furthermore, an 8-week exCR program, regardless of whether it is based around the principles of HIIT or MISS training, can positively influence O_2Pulse inflections in patients with CAD. This finding is particularly relevant for the monitoring and prescription of exercise in patients with CAD, especially those with silent myocardial ischemia. It also opens avenues for optimising exCR programs to maximise their benefits.

In summary, this thesis contributes significantly to the understanding of CPET in the context of CAD, particularly in the assessment of potential myocardial ischemia through

O_2Pulse inflections. The findings underscore the potential of CPET as a valuable tool in clinical practice, while also highlighting areas where further research is needed.

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Chapter 11 : Appendices

11.1 Appendix A - EChO

11.1.1 EChO - HRH Ethics Approval Letter

Dr Angela Hoye
Academic Cardiology
1st Floor Daisy Building
Castle Hill Cottingham
HU16 5JQ

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

28 January 2019

Dear Dr Hoye

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Exercise in patients with a total Coronary Occlusion (EChO)**
IRAS project ID:	**247135**
Protocol number:	**N/A**
REC reference:	**18/YH/0360**
Sponsor	**Hull University**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

This is a single site study sponsored by the site. The sponsor R&D office will confirm to you when the study can start following issue of HRA and HCRW Approval.

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this

IRAS project ID	247135

letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?
The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?
You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: Tom Nickolay
Email: hytn5@hyms.ac.uk

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **247135**. Please quote this on all correspondence.

Yours sincerely,

Natalie Wilson
Assessor

Email: hra.approval@nhs.net

Copy to: *Dr Andrew Taylor, University of Hull, Sponsor contact*
Mr James Illingworth, Hull and East Yorkshire Hospitals NHS Trust, Lead NHS R&D contact

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List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Covering letter on headed paper [Cover Letter]	2	18 January 2019
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance Document]	1	07 March 2018
GP/consultant information sheets or letters [Doctors Letter]	3	14 November 2018
IRAS Application Form [IRAS_Form_17012019]		17 January 2019
IRAS Checklist XML [Checklist_22012019]		22 January 2019
Participant consent form [Informed Consent to Participate in Research]	4	22 January 2019
Participant information sheet (PIS) [Patient Information Leaflet]	5	22 January 2019
Research protocol or project proposal [Protocol]	9	14 November 2018
Summary CV for Chief Investigator (CI) [Summary CV]		05 June 2018
Summary CV for student [Summary CV Student]		27 July 2018
Summary CV for supervisor (student research) [Simon Nichols CV]		15 August 2018
Summary CV for supervisor (student research) [Lee Ingle CV]		15 August 2018

IRAS project ID	247135

Summary of assessment

The following information provides assurance to you, the sponsor and the NHS in England and Wales that the study, as assessed for HRA and HCRW Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England and Wales to assist in assessing, arranging and confirming capacity and capability.

Assessment criteria

Section	Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	No comments
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	This is a non-commercial, single site study taking place in the NHS where the single participating NHS organisation is also part of a joint research office with sponsor. Therefore, no study agreements are expected.
4.2	Insurance/indemnity arrangements assessed	Yes	The applicant has confirmed that the University of Hull possesses public liability insurance. In addition, Hull and East Yorkshire Hospitals NHS Trust is part of the NHS risk pooling scheme to provide insurance for clinical trials. The applicant should provide an updated insurance certificate to participating NHS organisations as soon as possible.
4.3	Financial arrangements assessed	Yes	No comments
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments

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Section	Assessment Criteria	Compliant with Standards	Comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	No comments
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	
6.3	Devices – MHRA notice of no objection received	Not Applicable	
6.4	Other regulatory approvals and authorisations received	Not Applicable	

Participating NHS Organisations in England and Wales

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
This is a non-commercial, single site study. There is one site-type involved in the research. Activities and procedures as detailed in the protocol will take place at participating NHS organisations. If this study is subsequently extended to other NHS organisation(s) in England or Wales, an amendment should be submitted, with a Statement of Activities and Schedule of Events for the newly participating NHS organisation(s) in England or Wales. The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England and Wales in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. Where applicable, the local LCRN contact should also be copied into this correspondence. If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England and Wales which are not provided in IRAS, the HRA or HCRW websites, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net or HCRW at Research-permissions@wales.nhs.uk. We will work with these organisations to achieve a consistent approach to information provision.

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Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and Wales, and the minimum expectations for education, training and experience that PIs should meet (where applicable).
A Principal Investigator (PI) is expected at participating NHS organisations. Sponsor will confirm any training requirements with research staff directly. GCP training is not a generic training expectation, in line with the HRA/HCRW/MHRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
No Honorary Research Contracts, Letters of Access or pre-engagement checks are expected for local staff employed by the participating NHS organisations. Where arrangements are not already in place, research staff not employed by the NHS host organisation undertaking any of the research activities listed in the research application would be expected to obtain an honorary research contract. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm enhanced DBS checks, including appropriate barred list checks, and occupational health clearance.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales to aid study set-up.
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

11.2 Appendix B - The Morphology and Stability of the Oxygen Pulse Curve During Cardiopulmonary Exercise Testing

11.2.1 Morphology and Stability of the Oxygen Pulse Curve Ethics Approval letter

V1 Independent Reviewer's Report EC6

This form is periodically updated so please download the latest version from ebridge before completing

Department of Sport, Health & Exercise Science

UNIVERSITY OF Hull
Faculty of Science

Ethics Independent Reviewer's Report

This form should be completed by a member of the Department of Sport, Health and Exercise Science Ethics Committee who has been assigned to review a particular ethics application by the chair of the committee. The front section of the Independent's Reviewer's Report should be printed, signed and dated, and attached to the back of the reviewed ethics application. The reviewed ethics application should be given to the Ethics Committee chair once all reviews have been completed. The checklist provided at this end of this form is to help the reviewer complete the review and guide the content of his or her written report, which should be typed into the relevant boxes that are given before the checklist. Any checkbox highlighted red that has been checked requires attention.

Please note that the checklist is for guidance only and reviewers should be aware of other ethical considerations relevant to the ethics application being reviewed.

An electronic copy of the completed report should be stored on the reviewer's computer.

Independent reviewer's name	Dr Mark Fogarty
Application number	8765012
Principal investigator's name	Dr Andrew Garrett
Student investigator's name (if applicable)	Damien Gleadhall-Siddall

Reviewer's recommended outcome			
Approve ☒	Revise ☐	Reject ☐	Refer ☐

Reviewers comments	
Section	**Comment**
Click here to enter text.	This application is suitable for approval
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Name of independent reviewer **Date** **Signature**

V1 Independent Reviewer's Report EC6

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Please note that this section of the form should NOT be printed out and attached to the ethics application.

Independent Reviewer's Checklist				
Section	**Question**	**Yes**	**No**	**N/A**
1,2,3,4,5	Have all details been provided in full?	☒	■	☐
6	If there are collaborators, has the name, affiliation, email address, and telephone number for each collaborator been provided?	☐	■	☒
7	Is the location of the project a safe place to undertake the project for both the participants and investigators?	☒	■	☐
7	If equipment or facilities are been used other than in SHES, has a letter of support from an appropriately authorised person been included?	☐	■	☒
8	Have realistic dates been provided?	☒	■	☐
9	If the project has been funded, could there be any conflicts of interest between the investigators and the funding they have received?	■	☐	☒
10	Has the purpose and benefit of the project being clearly identified?	☒	■	☐
11.1	Is the sample size adequate?	☒	■	☐
11.2	If not an undergraduate project, has the sample size been sufficiently rationalised (this will typically be the results of a power analysis)?	☒	■	☐
11.3	Does the research involve people with any of the following: aged less than 18 years, suffering from acute or chronic health conditions, communication or learning difficulties, in police custody or with Her Majesty's Prison Service, engaged in illegal activities?	■	☒	☐
11.3	Are the inclusion/exclusion criteria sufficiently detailed that it is clear who will be recruited into the project?			
11.4	Are the screening procedures appropriate for ensuring only those people that satisfy the inclusion and exclusion criteria are included in the project?	☒	■	☐
11.5	Are recruitment strategies such that they might unduly influence someone to participate in the project that would not otherwise do so?	■	☒	☐
11.6	Are the incentives to participate such that they might unduly influence someone to participate in the project that would not otherwise do so?	■	☒	☐
12	Is the experimental design and methodology sufficiently comprehensive that someone could conduct the study by reading the information provided?	☒	■	☐
12	Is deception involved?	■	☒	☐
13	If substances are to be administered is the following information provided for each substance? The specific substance to be administered, the dosage, the timing of administration, and who will administer the substance.	☐	■	☒
13	Are there any concerns regarding the health and safety of any substances to be administered?	■	☐	☒
14	Are participants or investigators exposed to unacceptable risks,	■	☒	☐

V1 Independent Reviewer's Report EC6

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	discomforts, or burdens?	
12,13,14	Have all relevant risk assessments been included?	☒ ■ ☐
15	Are the investigators sufficiently competent to undertake each of the procedures involved in the project, or are otherwise being adequately supervised by a competent person?	☒ ■ ☐
15	If an undergraduate student is testing in one of the laboratories is there a statement that a SHES member of staff will be present at all times?	☒ ■ ☐
16	Is the participant debriefing sheet adequate?	☒ ■ ☐
17.1	Will the confidentiality and anonymity of participants be preserved?	☒ ■ ☐
17.2	If the principal investigator is not responsible, has the name, affiliation, email address, and telephone number of the person responsible been provided?	☒ ■ ☐
17.3	Has anyone got named access to the data that is unnecessary?	■ ☒ ☐
17.4	Have issues of data storage been adequately considered, particularly relating to security of the stored data?	☒ ■ ☐
Informed consent	Is the informed consent written so that a lay person could clearly understand what is expected of them in relation to potential risks, discomforts, time commitments, and other burdens?	☒ ■ ☐
Other forms	Have all other relevant documents been submitted and completed properly?	☒ ■ ☐

11.3 Appendix C - HIIT or MISS UK

11.3.1 HIIT or MISS UK HRA Ethics Approval letter

NHS
Health Research Authority
East Midlands - Leicester South Research Ethics Committee
Royal Standard Place
Nottingham
NG1 6FS

04 March 2016

Dr Gordon McGregor
Clinical Exercise Physiologist, Research Fellow
UHCW NHS Trust
Centre for Exercise & Health
Atrium Health
Watch Close, Coventry
CV1 3LN

Dear Dr McGregor,

Study title:	**High intensity interval training (HIIT)versus moderate intensity steady state training (MISS) in UK Cardiac Rehabilitation programmes: a multi-centre randomised control trial.**
REC reference:	**16/EM/0079**
IRAS project ID:	**187642**

Thank you for your letter of 03 March 2016, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Rebecca Morledge, NRESCommittee.EastMidlands-LeicesterSouth@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

I am pleased to confirm that the favourable opinion applies to the following research site(s), subject to site management permission being obtained prior to the start of the study at the site (see under 'Conditions of the favourable opinion below').

Research site	*Principal Investigator / Local Collaborator*
City Health Care Partnership CIC	Mr Simon Nichols

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper [cover letter 3.3.16 version 1.0]	1.0	03 March 2016
GP/consultant information sheets or letters [GP letter]	2.0	03 March 2016
IRAS Checklist XML [Checklist_03032016]		03 March 2016
Letter from sponsor [Letter from sponsor]	1.0	01 February 2016
Other [appointment letter]	1.0	01 February 2016
Participant consent form [Consent form]	2.0	03 March 2016
Participant information sheet (PIS) [PIS]	2.0	03 March 2016
Participant information sheet (PIS) [Pilot Study Participant Information Sheet - version 1.0 - 3.3.16]	1.0	03 March 2016
Participant information sheet (PIS) [non-NHS Participant Information Sheet HIIT - version 2.0 - 3.3.16]	2.0	03 March 2016
REC Application Form [REC_Form_03022016]		03 February 2016
Research protocol or project proposal [Research protocol]	1.0	01 February 2016
Summary CV for Chief Investigator (CI) [CV for CI]	1.0	01 February 2016
Validated questionnaire [EQ-5D]	1.0	01 February 2016
Validated questionnaire [MSEES]	1.0	01 February 2016
Validated questionnaire [service utilisation]	1.0	01 February 2016
Validated questionnaire [pnses]	1.0	01 February 2016
Validated questionnaire [C&B]	1.0	01 February 2016
Validated questionnaire [breq-2]	1.0	01 February 2016

Statement of compliance

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

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

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

16/EM/0079	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely,

Mr John Aldridge
Chair

Email:NRESCommittee.EastMidlands-LeicesterSouth@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Mrs Ceri Jones, University Hospitals Coventry & Warwickshire NHS Trust*

11.4 Appendix D - The intra-participant/intra-observer repeatability of Electromyography during the barbell and belt squat

11.4.1 EMG Study Ethics Approval letter

UNIVERSITY OF HULL

University of Hull
Hull, HU6 7RX
United Kingdom
T: +44 (0)1482 463336 | **E:** e.walker@hull.ac.uk
w: www.hull.ac.uk

PRIVATE AND CONFIDENTIAL
Thomas Nickolay
Faculty of Health Sciences
University of Hull
Via email

17th July 2019

Dear Thomas

REF: FHS153 - The intra-participant / intra-observer repeatability of Electromyography during the barbell and belt squat.

Thank you for your responses to the points raised by the Faculty of Health Sciences Research Ethics Committee.

Given the information you have provided I confirm approval by Chair's action.

Please refer to the Research Ethics Committee web page for reporting requirements in the event of any amendments to your study.

I wish you every success with your study.

Yours sincerely

Professor Liz Walker
Chair, FHS Research Ethics Committee

UNIVERSITY OF HULL

Liz Walker | Professor of Health and Social Work Research | Faculty of Health Sciences
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11.4.2 EMG Study Manuscript

Reliability and Agreement of Non-normalised Electromyography During the Barbell and Belt Squat

1Thomas J Nickolay

2Lee Ingle

3Simon Nichols

1Angela Hoye

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Abstract

EMG signals are sensitive to the influence of extrinsic factors, such as skin preparation and electrode placement. Normalisation to maximal contractions prior to analysis has become commonplace. In some populations and/or research questions this is not possible. In such cases raw EMG comparison would be invaluable. This study investigated the repeatability of raw EMG of the rectus femoris during the back squat and the belt squat. Eleven, healthy volunteers (30.27±7.39 years) participated. EMG was captured during 10 repetitions at 70% of an individualised 10 repetition maximum for each squat variation on two separate days. Signals were filtered, and full wave rectified prior to calculation of mean and area under the curve (AUC). Intra-class correlation coefficients (alpha <0.05) were greatest for the back squat AUC (0.960; 95%CI 0.860 - 0.989) and lowest for belt squat mean (0.523; 95%CI -0.025 - 0.840). Repeatability was reported as standard error of measure (SEM%) and minimal detectable change (MDC%). Agreement was greater for both measures of the back squat compared to the belt squat. The highest level of agreement for the belt squat was seen in AUC (SEM% 22.18). Raw EMG provided comparable repeatability to the standard method of normalisation during a familiar movement pattern.

Keywords (EMG, Normalisation, Repeatability)

Introduction

Electromyography (EMG) signals can be measured invasively via fine wire electrodes or non-invasively via surface electrodes (EMG) (Konrad, 2006). EMG readings are sensitive, and as such are susceptible to many intrinsic and extrinsic influences (De Luca, 1997). Whilst intrinsic factors, such as; skeletal muscle morphology, composition, and location are not subject to investigator influence, extrinsic factors like electrode shape, orientation, and location are (Burden & Bartlett, 1999). It is widely recommended that investigators 'normalise' data prior to making comparisons between participants, tests, or anatomical sites (Halaki & Gi, 2012). Normalisation effectively allows investigators to represent the signal as a percentage of a standardised reference value (Burden & Bartlett, 1999; Mathiassen et al., 1995) . The "gold standard" method of normalisation is the maximal voluntary contraction (MVC) (often isometric - MVIC) (Tabard-Fougère et al., 2018).

Normalised EMG has proven to have good relative reliability when applied to resistance training exercises. Intra-class correlation coefficients (ICC) for 'within-session' trial-to-trial EMG during ballistic style movements have been reported to be >0.80, with the majority of values exceeding 0.90 (Fauth et al., 2010). Similarly, Bamman et al (1997) found comparable ICC values when repeating maximal voluntary isometric knee extension tests after a minimum of five days (ICC 0.93). Likewise high levels of between day reliability (ICC 0.81- 0.95) were reported by Claiborne and colleagues (2009) when assessing isokinetic hip flexion, extension and internal, external rotation. However, ICC is affected not only by intra-participant inter-session variability but also inter-participant variability. As a result, it is possible for a measure to record high relative reliability (ICC) and low agreement. Agreement is often expressed as standard error of measure (SEM) or minimal detectable change (MDC).

The absolute inter-day agreement of normalised EMG has been investigated in numerous studies, table 1 summarises some of their findings.

Table 1. Summary of research investigating the absolute inter-test reliability of normalised EMG.

Author (year)	Normalisation method	Days between tests	Muscle(s)	Agreement
Larsson et al (2003)	Mean of three initial contractions (from 100 dynamic maximum consentric)	7-8	Rectus femoris, vastus medialis, Vastus lateralis, Biceps femoris.	9-69 (SEM)
Dankaerts et al (2004)	Maximal and sub-maximal isometric voluntary contractions	≤7	Rectus abdominis, internal oblique, external oblique, lumbar multifidus, iliocostalis lumborum, thoracis erector spinae	3-36 (SEM%)
Seitz & Uhl, (2012)	Maximal voluntary isometric contraction	7	Anterior deltoid, upper trapezius, lower trapezius, serratus anterior	2.3-8.3 (SEM) 3.2-11.7 (MDC)
Hashemi Oskouei et al (2013)	Maximal voluntary contraction	2 days – 1 month	Flexor carpi ulnaris, flexor carpi radialis, flexor digitorum superficialis, flexor pollicis longus, flexor palmaris longus	13.5-35 (SEM%)
Rota et al (2013)	Maximal voluntary contraction	2-15	Latissimus dorsi, pectoralis major, posterior deltoid, medial deltoid, anterior deltoid, biceps brachii, triceps	14.1-27.7 (SEM%)
	Dynamic strength exercise			12.4-37.5 (SEM%)

			brachii, flexor carpi radialis, extensor carpi radialis	
Gaudet et al (2016)	Single maximal voluntary isometric contraction	1	Triceps brachii, biceps brachii, pronator teres, pronator quadratus, brachialis, brachioradialis	19.5-48.6 (SEM%)
	Mean maximal voluntary isometric contraction			14.7-48.1 (SEM%)
Brandt et al (2017)	Maximal voluntary contraction	13.8±1.1	Erector spinae, trapezius	10.2-70.4 (SEM%)
				28.3-195.2 (MDC%)
Kukic et al (2017)	Maximal voluntary isometric contraction	7-8	Vastus lateralis, vastus medialis, rectus femoris	7.14-43.63 (SEM)
Bussey et al (2018)	Maximal voluntary contraction	≈7	Biceps femoris, gluteus maximus	3.69-6.84 (SEM%)
	Submaximal voluntary contraction			8.39-13.76 (SEM%)
Chaikumarn et al (2018)	Maximal voluntary isometric contraction (peak and median)	3-7	Upper trapezius, lower trapezius, anterior deltoid, cervical erector spinae	7.72-12.56 (SEM%)
				2.65-5.82 (SEM%)

Cid et al (2018)	Maximal voluntary isometric contraction	≤7	Trapezius	11.54-45.17 (SEM%)
	Sub-maximal isometric contraction			5.09-54.16 (SEM%)
Singla et al (2018)	Maximal voluntary isometric contraction	7	Biceps brachii, triceps brachii	0.018-0.052 (mV) (SEM)
				0.144-0.051 (mV) (MDC)
Tabard-Fougère et al., (2018)	Maximal voluntary isometric contraction (mean of three)	7	Gluteus medius, rectus femoris, semitendinosus, tibialis anterior	16.1-24 (SEM)
				23.1-28.9 (SEM%)

Making direct comparisons of SEM across studies is not possible, as the raw value does not account for the mean magnitude in activation, which is influenced by the muscle under investigation. Comparisons can however be made for research in which SEM has been normalised to the grand mean (SEM%).

Notwithstanding its utility when comparing EMG data between participants, and within or between session intra-patient variability, normalisation of this kind does have its limitations. Take for example the research question; "Does eight weeks of resistance training change the neuromuscular response to a pre-determined load?" In this instance, it can be assumed that following the training intervention a participant would have increased their maximal strength (and thus MVC). If the investigators perform a pre and post intervention MVC, they can only assess the neuromuscular change in response to percentage old and new maximal contractions. Whilst this would provide valid physiological insights into the effects of the intervention, it cannot definitively answer the question posed. In this instance the 'old' (pre intervention – relatively weaker) EMG response to the set load must be directly compared to the 'new' (post intervention – relatively stronger) response. Unfortunately, due to the extrinsic factors described it is widely considered that EMG may not be conducive to this manner of direct comparison. However, if the researcher were to establish a SEM and MDC for non-normalised repeated intra participant EMG, then any deviation exceeding this measure following an intervention may be attributed to a training adaption.

Furthermore, the requirement to undertake MVCs in some clinical populations would preclude the use of standard normalisation (cardiac, cerebrovascular, abdominal aortic aneurysm etc). In these groups, identification of altered neuromuscular response to pre-determined loads following exercise interventions, may be permissible through the generation of a SEM and MDC, thus allowing the EMG activation change to be detected in response to submaximal exercise.

At the time of writing there are no studies comparing the inter-session reliability and agreement of non-normalised EMG data during performance of the belt squat (Figure 1).

Figure 1. Example of the top (left) and bottom (right) position in the belt squat when performed using a modified cable pulley system.

Experimental approach to the problem

The primary aim of this study was to quantify the inter-test, intra-rater reliability and agreement of non-normalised EMG activity taken from the rectus femoris (RF) during the belt squat when electrodes were placed according to the surface EMG for non-invasive assessment of muscles (SENIAM) guidelines. The secondary aim was to compare reliability and agreement measures taken during the belt squat with those taken during the more traditional back squat. Finally, I sought to compare the reliability and agreement of total activation, defined as the area under the curve (AUC), with mean activation for both the belt squat and back squat. I hypothesised that AUC would provide levels of between day reliability comparable to standard normalisation for the belt squat.

Methods

Ethical approval for this research was provided by the University of Hull institutional ethics committee (FHS153). Prior to testing all participants were required to provide written informed consent. This study complied with the deceleration of Helsinki.

Subjects

Eleven healthy, recreationally active participants were recruited to the study. Participants were eligible to join the study if they were aged 18-50, able to provide informed consent, and functionally capable of performing the movements as described. Criteria for exclusion were known cardiovascular/respiratory pathology or orthopaedic injury and or impairment.

Procedures

Visit 1

Participants attended the laboratory for three experimental sessions, on three separate occasions. Movement specific screening for each participant was completed by the research team to ensure participant safety and data accuracy. All participants who volunteered for the study were deemed capable of performing the movements to the requisite standard.

Participants completed an initial warm-up consisting of five minutes aerobic exercise (cycle ergometer) followed by three rounds of movement specific body weight exercises (Table 2).

Table 2. Warm-up protocol.

Movement	Sets	Repetitions
Cycle ergometer	1	N/A
Body weight squat	3	10
Body weight reverse lunge	3	10
Standing tuck jumps	3	5
Broad jumps	3	5

After the warm-up participants performed self-prescribed stretching of the hips, hamstrings, quadriceps, and calves. To determine each participants ten repetition maximum (10RM) in each squat variation, multiple repetitions of the belt squat or back squat were performed with incrementally increasing load until either participant or researcher deemed maximal load had been attained (American College of Sports Medicine, 2018). The cadence of each repetition was standardised using an online metronome (60 bpm), with the participant required to perform a two second eccentric (descent), one second isometric (bottom of the lift), and one to three second concentric contraction (rise). The range of motion of each squat variation was standardised, requiring the hip crease to be parallel with the top of the knee at the bottom position of each repetition. Participants were required to maintain correct technique and proper form throughout testing. The heaviest set fulfilling these criteria was recorded as the individualised 10RM load. The order in which each squat variation was performed was alternated, so that in total five participants performed 10RM belt squat prior to back squat and six participants established 10RM back squat prior to belt squat. Following on from setting a 10RM load in the first squat variation participants were permitted ad libitum rest before attempting to establish a 10RM for the remaining movement.

Visits 2 & 3

Participants attended the laboratory for visits two and three wearing clothing that enabled the researcher to identify the sites for surface electrode placement. Excess hair and oil were removed from the skin by shaving, abrading and swabbing (alcohol swab) prior to the placement of surface electrodes. Following this preparation disposable, self-adhesive, pre-gelled electrodes with a 1cm internal diameter (Ambu blue, Denmark) were aligned and applied parallel to the fibres of the RF. Electrodes were located in conjunction with the SENIAM guidelines (Frericks et al., 1999). The electrodes were placed precisely, either side of the pre-defined marker at 50% of the distance from the anterior superior iliac spine and the superior margin of the patella (Figure 2). For each participant, the dominant leg was used for testing. After the electrodes were placed the participants were asked to contract the muscle to ensure signal quality. The same researcher measured and applied the electrodes to each participant throughout the study.

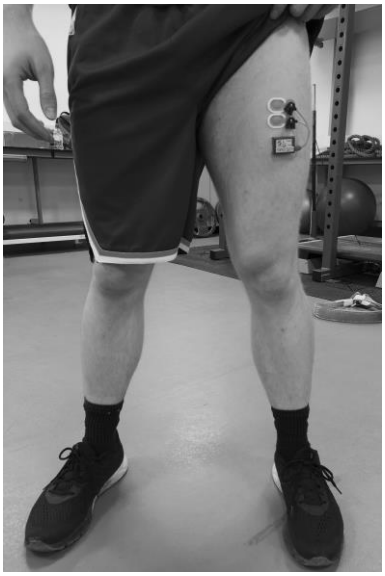

Figure 2. Representative electrode placement for the Rectus Femoris.

Participants were then asked to complete the warm-up and stretching protocol described for visit 1 (Table 1). After completing the warm-up participants performed 3-4 sets with incrementally heavier weights, before completing two sets of ten repetitions using 70% of their individualised 10RM. The order in which each participant performed the squat variations did not deviate from baseline testing, for example; if at baseline the participant

performed the back squat first, they did the same during visits two and three, completing all sets of the back squat before progressing on to the belt squat. Participants had a minimum of three days and a maximum of three weeks between visits.

Data analyses

Raw EMG data was sampled at 1500 Hz using Noraxon TeleMyo desktop receiver and MR3 software (Noraxon, USA) before being exported to MATLAB 2020a (The MathWorks Inc, USA) for processing. Data were filtered using a 4th order bi-directional Butterworth (500 Hz – low pass; 10 Hz – high pass) and linear envelope filters (2Hz cut off). Onset-offset and peak detection was undertaken in order to delineate each repetition of the set, allowing mean integrated area under the curve (iAUC) and peak activation to be calculated.

Statistical analyses

Statistical analysis was performed using SPSS software version 26 (IBM, New York, NY, USA). The between session reproducibility of using non-normalised EMG data was separated into reliability and agreement (de Vet et al., 2006). Reliability was calculated and reported as intra-class correlation coefficients (ICC) using a two-way mixed effects model for absolute agreement (single measure) with 95% confidence intervals (CI). Statistical significance was accepted at P=<0.05. The interpretation of ICC was based on the recommendations of Koo and Li (2016), with ⩽0.5, 0.5-0.75, 0.75-0.9, and ⩾0.9 representing “poor”, “moderate”, “good”, and “excellent” reliability, respectively. Agreement was reported through SEM, SEM% MDC, and MDC% expressed where appropriate in either micro- (μV) or millivolt (mV). The SEM was calculated as the square root of the mean square error following repeated measures ANOVA, with SEM% calculated as a percentage of the grand mean (Weir, 2005). Minimal detectable change was calculated as (SEM.1.96). √ ((2)) (Weir, 2005).

Results

Eleven healthy, recreationally active participants (n=10 male; age = 30.27 ± 7.39; height = 176 ± 5.33cm; body mass = 78.65 ± 10.47 kg) volunteered for this study. Resistance training experience amongst the cohort ranged from 2 – 29 years (11.5 ± 8.61). All participants had previous experience of performing the barbell back squat prior to testing. In contrast, no participant had previously been exposed to the belt squat before baseline testing.

Reliability

ICC values and agreement parameters for test retest non-normalised EMG data are presented in Table 3. All participants completed the study requirements. The ICC between visits was statistically significant for mean and AUC in both squat modalities. The intra-rater reliability of non-normalised EMG in the belt squat was moderate – good for mean (0.523; 95% CI: -0.025 to 0.840) and AUC (0.834; 95% CI: 0.505 to 0.952), with large 95% CI for each. In contrast, measures for the back squat were good to excellent for both mean activation (ICC: 0.925; 95% CI: 0.752 – 0.975) and AUC (ICC: 0.960; 95% CI: 0.860 – 0.989).

Agreement

Repeated measures ANOVA demonstrated no significant systemic bias for any of the four measured variables (Figure 3). Mean values for each variable were consistently higher in the belt squat versus the back squat, although the coefficient of variation was comparable across measures. Standard error of measurement for mean activation when expressed as a percentage of the grand mean (SEM%) was 32% lower for the back squat versus the belt squat. Moreover, the back squat presented with a 55% lower SEM% when total activation was measured via AUC. The MDC for mean activation and AUC in the belt squat were more than double that of the back squat. When viewed in relation to the grand mean the MDC for mean activation in the belt squat was approximately 40% greater than that of the back squat.

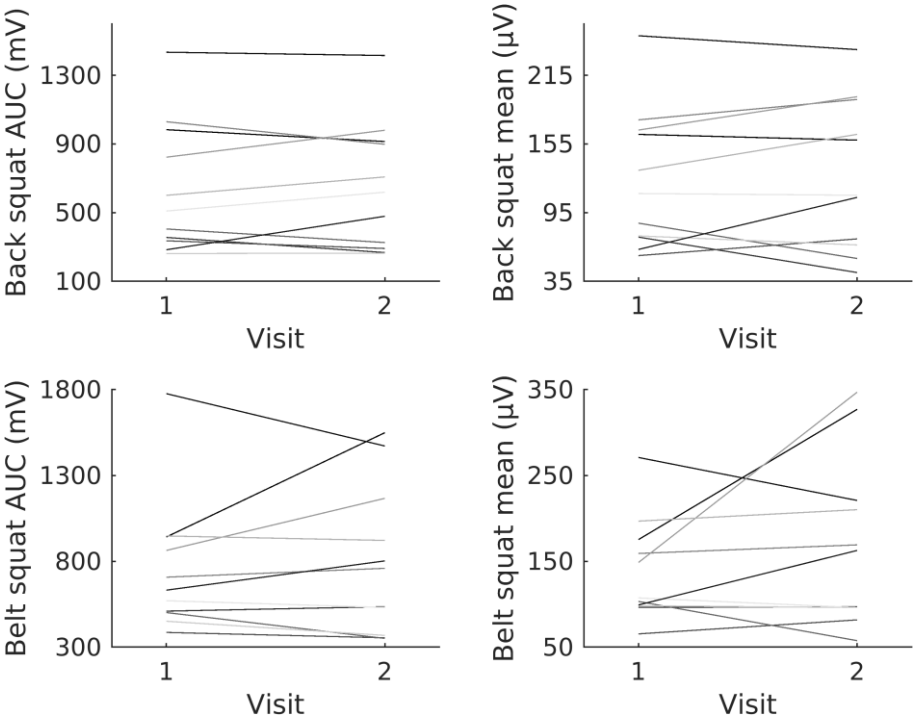

Figure 3. Baseline and Follow-up measures for all (n=11) participants.

Table 3. Measures of reliability and agreement for non-normalised EMG data

	Mean activation (μV)						Total activation (AUC – mV)					
	Barbell squat		*P*	Belt squat		*P*	Barbell squat		*P*	Belt squat		*P*
Visit	One	Two		One	Two		One	Two		One	Two	
Mean (SD)	123.09 (60.56)	127.65 (65.84)		138.22 (59.42)	169.56 (98.45)		638.3 (381.02)	651.02 (372.60)		753.24 (391.32)	800.90 (434.90)	
CV	49.20	51.58		42.99	58.06		59.69	57.23		51.59	54.30	
Grand mean (SD)	125.37 (61.77)		-	153.89 (80.96)		-	644.66 (367.76)		-	777.07 (404.45)		-
CV	49.27		-	52.61		-	57.05		-	52.05		-
ANOVA	-		0.562	-		0.212	-		0.711	-		0.531
ICC (95% CI)	0.925 (0.752 to 0.979)		0.000*	0.523 (-0.025 to 0.840)		0.035*	0.960 (0.860 to 0.989)		0.000*	0.834 (0.505 to 0.952)		0.000*
SEM (95% CI)	17.82 (-17.11 to 52.75)		-	55.17 (-52.96 to 163.30)		-	78.34 (-75.21 to 231.89)		-	172.33 (-165.44 to 510.10)		-
SEM%	14.21		-	35.85		-	12.15		-	22.18		-
MDC	49.39		-	152.92		-	217.15		-	477.67		-
MDC%	39.4			99.37			33.68			61.47		

CV = coefficient of variation; ICC = intra-class correlation coefficient; CI = confidence interval; SEM = standard error of measure; SEM% = standard error of measure as a percentage of the grand mean; MDC = minimal detectable change; MDC% = minimal detectable change as a percentage of the grand mean; * = Statistically significant (*P*=<0.05)

Discussion and Implications

The primary purpose of this study was to establish the intra-test, inter-observer reliability and agreement of non-normalised EMG activity from the RF during the belt squat. The initial hypothesis was that the between day reliability and agreement of the belt squat would be comparable to standard measures of normalisation when presented as total activation (AUC). When interpreted with their respective 95% CI the ICC results for belt squat varied substantially, ranging from poor to excellent. By comparison, the more traditional back squat consistently presented good to excellent reliability. These values are analogous to those previously reported for between session MVIC (Bamman et al., 1997; Claiborne et al., 2009). However, the use of intra-class correlation coefficient to determine reliability has received criticism as it is influenced by the magnitude of between-subject variance, with greater variance resulting in high reliability (Larsson et al., 2003). As a result it is advisable to evaluate ICC in conjunction with group heterogeneity and markers of agreement (Weir, 2005). The within group heterogeneity for each movement and each visit was large, as is evident from the CV. This variance could have contributed to the high relative reliability observed.

Reliability, as measured through ICC is affected by the heterogeneity of the sample. Agreement is based on measurement error, such as SEM, which is better suited to assess repeatability, i.e. the use of the same measurement tool for repeated measures (de Vet et al., 2006).

Table 1 contains 9 studies in which SEM% has been reported, the mean SEM% across all muscles and all normalisation methods is 17.54%±4.06, this is greater than the non-normalised SEM% I found for both the back squat mean activation (14.21%) and AUC (12.15%). These results suggest that using non-normalised RF activation during the back squat, either as mean or total activation, may be preferable to using MVIC normalisation in the assessment of changes following an intervention.

In contrast, the absolute reliability of non-normalised EMG for the belt squat, reported as SEM%, was 35.85% and 22.18% for mean and total activation respectively, making it less reliable then MVIC. However, when the studies from Table 1 are condensed down to contain only peak MVIC and SEM% the mean value is 23.5%±12.9, making it comparable to the non-normalised AUC values identified in the current study for the belt squat (22.18%).

The only study from Table 1 to report SEM% for the RF was by Tabard-Fougère and colleagues (2018). In this investigation the researchers normalised by calculating the mean of three MVIC for the RF. After one week the healthy participants (n=9) were invited back to repeat the testing procedures. Analysis revealed that the absolute between day reliability of RF MVIC expressed as SEM% was 23.1%. When viewed in relation to my non-normalised findings this is superior to the belt squat mean, comparable to belt squat AUC, and inferior to back squat mean and AUC.

The MDC is a measure of variability associated with the SEM, calculating the MDC using the formula described (SEM.1.96). √ ((2)) provides a value above or below which activation can be considered to have truly changed with 95% confidence (Rai et al., 2015).

When expressed as MDC%, an increase or decrease of RF activation during the belt squat would need to exceed 99.37% (mean), or 61.47% (AUC) to be accepted (with 95% confidence) that the difference was the result of the intervention. By comparison activation changes of only 39.4% (mean) and 33.68% (AUC) would be required when performing the back squat. Returning to the example research question proposed in the introduction, using non-normalised EMG from the RF during the back squat could provide a viable means of assessing change in activation following intervention, with activation expressed as AUC the most sensible option.

There are no studies in Table 1 that directly report MDC% for the RF. However, Larsson and colleagues (2003) did report the SEM (17) and the mean normalised value for visit

1 (104) and 2 (103). If I were to use these values to generate a grand mean (103.5) I can calculate the MDC (17*1.96* √(2) = 47.12) and subsequent MDC% (47.12 ÷ 103.5*100=45.53). The resulting value of 45.53 for normalised RF activation is similar to the MDC% I found for non-normalised mean (39.4%) and AUC (33.68%) activation during the back squat. This provides more evidence to suggest inter-day non-normalised EMG from the RF during performance of the back squat may reliably be compared.

The AUC proved to have higher reliability and agreement for the belt squat and back squat. It may be that averaging data across a set number of repetitions is more prone to the influence of outlying values. Whereas calculating the AUC yields minimal data loss and thus provides greater consistency across the set.

It can be seen from Figure 3 that the lower absolute reliability for belt squat mean and total activation is largely the result of three participants having greater than average (mean) intra-visit variability. If this variability were the result of extrinsic factors (namely electrode placement) the increase or decrease in activation would be expected to occur not only in the belt squat but the back squat, as during each visit both movements were performed without removing or replacing electrodes. However, as can be seen from the figure this is not the case and the three participants who exhibited a variation in activation during the belt squat had no corresponding change during the back squat. This anomaly may be explained by a difference in experience and proficiency between the back squat and belt squat across the cohort. In the present study resistance training experience ranged from 2-29 years (11.5±8.61), with all participants having previous experience of the back squat but not the belt squat. It is perhaps reasonable to assume that due to a lack of experience with the belt squat equipment and movement pattern, some participants may have altered their weight distribution and joint angles during the second visit compared with the first. Research suggests that increasing the hip angle (upright torso) during loaded squatting generates a greater RF activation (Yavuz et al., 2015), if there were variations in joint

angle between visits this could have confounded the results. Furthermore, recent research by Joseph and colleagues (2020) suggests that the belt squat elicits a lower amount of activation from gluteus and hamstring musculature when compared to the back squat. This may indicate a greater reliance on the quadriceps during the belt squat. If the quadriceps are relied upon more during the belt squat any misalignment or balance issues during repetitions would likely be counteracted by large perturbations in RF activation. The authors found no difference in quadriceps activation between the back squat and belt squat. However, their findings must be interpreted with caution as they failed to standardise the load used in each modality, using 100% bodyweight for each.

These findings suggest that non-normalised EMG from the RF during the back squat, either as mean or total activation, may provide similar inter-day reliability as traditional normalisation procedures. Whilst data for the back squat proved superior to the belt squat, the fact that both squats were performed each visit without removing the electrodes suggests that the difference in reliability was purely down to participants' inexperience with the movement and not the electrode placement.

In populations for which MVC (MVIC) are contraindicated, non-normalised EMG taken from the RF during performance of the barbell back squat and processed as either mean or AUC may provide a viable alternative to gold standard normalisation. Equally, non-normalised RF mean or AUC during the barbell back squat could be used to assess the absolute change in activation following intervention with superior measurement error to MVC normalisation.

The primary limitation of this study is its homogeneous sample, future research should aim to confirm these findings in a larger heterogeneous population. Additionally, data were only recorded from a single muscle during two similar movements, consequently the agreement cannot be generalised to additional muscles or alternative movements.

Future research should aim to determine the absolute agreement of non-normalised EMG mean and AUC in larger populations, during more diverse movements and repetition ranges, using different investigators, and in multiple muscles.

Conclusion

In conclusion, the absolute agreement of non-normalised EMG, reported as mean or total activation, is superior when participants perform the traditional back squat as opposed to the novel belt squat. Values of SEM% and MDC% appear comparable, if not preferable for both mean and total activation in the back squat when compared to standard MVIC normalisation procedures.

Acknowledgements

The authors would like to thank the participants who freely gave their time to this study.

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11.5 Appendix E - REACTOr Study

11.5.1 REACTOr HRA Ethics Approval Letter

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Angela Hoye
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Castle Hill Cottingham
HU16 5JQ

Email: hra.approval@nhs.net

10 December 2019

Dear Dr Hoye

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Resistance training in cardiac patients with a Chronic Total Occlusion (REACTOr)**
IRAS project ID:	**259510**
Protocol number:	**N/A**
REC reference:	**19/YH/0405**
Sponsor	**Hull University**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **259510**. Please quote this on all correspondence.

Yours sincerely,
Rebecca Evans
Approval Specialist

Email: hra.approval@nhs.net

Copy to: *Dr Danielle Smith,*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
GP/consultant information sheets or letters [Dr Letter]	2	10 July 2019
IRAS Application Form [IRAS_Form_01112019]		01 November 2019
IRAS Application Form XML file [IRAS_Form_01112019]		01 November 2019
IRAS Checklist XML [Checklist_01112019]		01 November 2019
Letter from sponsor [Sponsorship letter]		09 July 2019
Non-validated questionnaire [Study Participation Questionnaire (SPQ)]	2	17 May 2019
Organisation Information Document [OID]	1	
Other [Insurance Certificate]		10 December 2019
Participant consent form [Informed consent]	2	10 July 2019
Participant information sheet (PIS) [PIS]	v3	10 December 2019
Referee's report or other scientific critique report [Support letter from patient group meeting]	1	22 July 2019
Research protocol or project proposal [REACTOr Protocol]	11	10 October 2019
Schedule of Events or SoECAT	1	
Validated questionnaire [The Seattle Angina Questionnaire-7]	1	

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
There is only one participating NHS organisation therefore there is only one site type.	Research activities should not commence at participating NHS organisations in England or Wales prior to their formal confirmation of capacity and capability to deliver the study.	An Organisation Information Document has been submitted and the sponsor is not requesting and does not expect any other site agreement to be used.	No external study funding has been sought.	The Sponsor has confirmed that a Principal Investigator is required at site.	No Honorary Research Contracts, Letters of Access or pre-engagement checks are expected for local staff employed by the participating NHS organisations. Where arrangements are not already in place, research staff not employed by the NHS host organisation undertaking any of the research activities listed in the research application would be expected to obtain a Letter of Access based on standard DBS checks and occupational health clearance.

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Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated they do not intend to apply for inclusion on the NIHR CRN Portfolio.

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11.5.2 REACTOr Protocol

Resistance training in cardiac patients with a Chronic Total Occlusion

REACTOr - 259510 – Version 11 –10/10/2019

Research Team

Dr Angela Hoye (Clinical Lead / Principal Investigator / Chief Investigator)

Dr Simon Nichols (Investigator)

Prof Lee Ingle (Investigator)

Thomas Nickolay BSc (Hons) (Investigator)

Title - Resistance Versus traditional Aerobic training in Chronic Total Occlusion patients

Version number – 11

Date – 10/10/2019

Name of Sponsor – University of Hull

Address – Cottingham Road, Hull HU6 7RX

Investigators - Dr Angela Hoye (Clinical Lead / Principle Investigator)

Tom Nickolay BSc (Hons) (Investigator)

Prof Lee Ingle (Investigator)

Dr Simon Nichols (Investigator)

Name and Address of research site – Daisy Building Castle Hill Hospital, Castle Road, Cottingham HU16 5JQ.

Telephone number of research site – 01482 461909

Name and Address of other institutions – University of Hull, Cottingham Road, Hull HU6 7RX.

Rationale and Background Information

Cardiovascular Diseases (CVD) as a whole are the leading causes of death globally (Townsend, Nichols, Scarborough, & Rayner, 2015). Within this cluster of diseases, ischaemic heart disease (IHD) or coronary heart disease (CHD) accounts for the largest percentage of deaths each year ('The top 10 causes of death', n.d.). According to the British Heart Foundation 66,076 deaths in the United Kingdom (UK) were attributable to CHD in 2016, this represented 14% and 9% of male and female deaths respectively ('Heart and Circulatory Diseases Statistics 2018', n.d.). One common finding amongst patients referred for coronary angiogram is the presence of a Chronic Total Occlusion (CTO) (≈18%) (Elkassas, Faisal, & Salah, 2018). A CTO is defined as complete (100%) coronary occlusion with a Thrombolysis in Myocardial Infarction (TIMI) flow score of 0, believed to be present for at least 3 months (Tajti Peter & Brilakis Emmanouil S., 2018).

In patients with a CTO the lumen distal to the occluded segment is perfused via pre-existing collateral arteries (Seiler, 2003). In some individuals the collateral circulation is sufficient to prevent signs of myocardial ischemia during brief coronary occlusion (Seiler, 2003), and perhaps limit the area at risk after myocardial infarction (MI) (Meier et al., 2012). However, it is not likely to prevent symptomatic ischemia during physical activity (Meier et al., 2013).

CTO are treated most frequently via Percutaneous Coronary Intervention (PCI) (Bardají, Rodriguez-López, & Torres-Sánchez, 2014). However, CTO have historically proved difficult to treat percutaneously, and the decision to do so has been shown to vary significantly depending on the patients location (Bardají et al., 2014). In recent years CTO PCI success rates have increased owing to the introduction of innovative technologies, novel techniques, and the growing expertise of practitioners (Choi et al., 2017; Tajti Peter & Brilakis Emmanouil S., 2018). Despite an increase in its procedural success, PCI is not always possible and cannot always return patency to the occluded vessel. A meta-analysis published in 2013 reported the angiographic success rate across 65 studies to be just 77% (Patel et al., 2013). If these figures are truly representative of CTO PCI as a whole, then approximately 23% of CTO patients require an alternative treatment strategy. The only treatment option commonly made available to these patients is long term pharmacological management with optimal medical therapy (OMT) (Fefer et al., 2012; Guo, Zhong, Chen, Wu, & Huang, 2018).

In a retrospective analysis CTO PCI patients had lower incidence of death and MI (propensity score matched) after a mean follow up of 4 years when compared to those receiving OMT alone (Choi et al., 2017). Similar results had previously been demonstrated by Ladwiniec and colleagues in 2015). In a cohort of 294 propensity score matched pairs of CTO patients all-cause mortality at 5 years was 5.1% greater when treated with OMT alone versus PCI. Furthermore, a large European randomised control trial that compared OMT with PCI + OMT combined determined that combined treatment yielded a significantly greater improvement in self-reported quality of life, and reductions in physical limitations and angina frequency (G. S. Werner et al., 2018). Whilst PCI would appear to be a more efficacious treatment then OMT, Hambrecht and colleagues (2004) demonstrated that 12 months of exercise in selected patients with stable coronary artery disease (CAD) yielded a significantly superior event free survival and exercise capacity when compared to PCI.

A large percentage of patients with advanced and/or unrevascularisable CAD (such a CTO) are left with refractory angina (RA) (Henry, Satran, & Jolicoeur, 2014). In recent

years research has begun to focus on the development of novel interventions to treat these patients, many centred around augmenting the collateral network (Heil, Eitenmüller, Schmitz-Rixen, & Schaper, 2006). The ability to increase the diameter and fluid carrying capacity of the collateral arteries may not only increase the patients ischemic threshold (Möbius-Winkler et al., 2016), but also facilitate the traversal of these channels during retrograde PCI (Touma, Ramsay, & Weaver, 2015).

Physiological Principles

Under non-pathological conditions collateral arteries are typically 30–50μm in diameter (I. Buschmann & Schaper, 1999; Scholz et al., 2001). Upon arterial occlusion a pressure gradient forms between the donor artery (origin of the collateral vessel) and recipient artery (distal portion of the occluded vessel) (Pipp et al., 2004). This pressure gradient in conjunction with the collateral artery resistance dictates the amount of flow (Goodwill, Dick, Kiel, & Tune, 2017), and thus fluid shear stress (FSS) across the collateral vessel (Prior, Yang, & Terjung, 2004). The increased blood flow and FSS causes the collateral endothelium to undergo a process of cellular proliferation and structural remodelling, termed arteriogenesis (Figure 1, A-B) (Buschmann & Schaper, 1999; Schaper & Scholz, 2003; van Royen, Piek, Schaper, Bode, & Buschmann, 2001). This remodelling yields vessels capable of supporting demonstrably greater levels of blood flow, with some researchers reporting a 25-fold increase above baseline levels (Scholz et al., 2001). However, as the vessel remodels and its diameter expands the increase in FSS quickly subsides (Pipp et al., 2004). Once this occurs the collateral will not, without increased provocation, induce additional development (Schaper, 2009). Consequently, the developed collateral is typically only capable of replacing 30-40% of the patent flow supplied by the artery it bypasses (Schaper, 2009) (Figure 1).

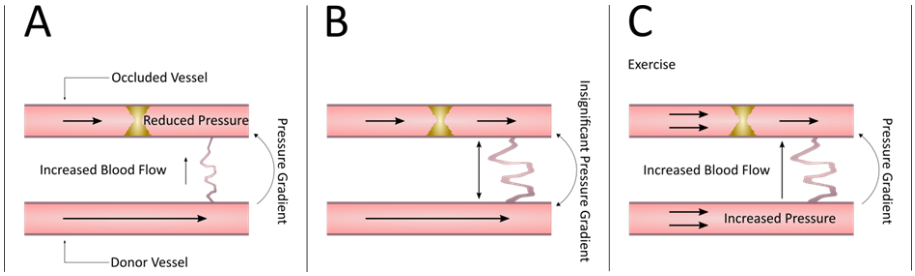

Figure 1. Pressure gradient of a developing collateral. Early after arterial occlusion; low pressure distal to the occlusion draws flow through the collateral and increases shear stress on the endothelium (A). Collateral development reaches plateau; collateral diameter increases, reducing collateral shear stress (B). An increase in donor artery pressure during exercise training reintroduces a pressure gradient across the collateral; fluid shear stress is again increased across the collateral endothelium (C).

Pipp and colleagues (2004) demonstrated that collateral vessels in rabbits and pigs are capable of progressing well beyond their usual pathological capacity, almost replacing unobstructed flow when FSS is not prematurely relieved. Therefore, re-introducing the collateral pressure gradient in CTO patients could theoretically increase arteriogenesis. Once the collateral lumen has expanded enough to relieve the increased FSS the only way to non-invasively increase the pressure gradient would be to increase coronary flow / pressure in the donor artery (Figure 1, B-C).

Coronary flow is modulated via multiple mechanisms, one of which is perfusion pressure (Goodwill et al., 2017). Coronary perfusion pressure is equal to aortic diastolic pressure, minus left ventricular end-diastolic pressure (Ramanathan & Skinner, 2005). The majority of coronary flow occurs during diastole, and any increase in heart rate negatively impacts diastole to a greater extent than systole (Ramanathan & Skinner, 2005). Therefore activities that increase heart rate will impede perfusion time (Figure 2).

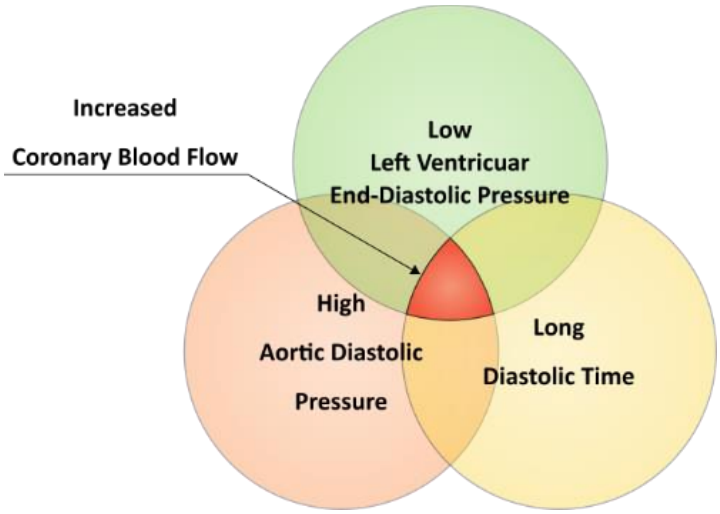

Figure 2. Venn Diagram of factors positively influencing coronary blood flow.

One non-invasive treatment option known to increase diastolic blood pressure without generating an increase in heart rate or systolic blood pressure is enhanced external counterpulsation (EECP) (D. Werner, Marthol, Brown, Daniel, & Hilz, 2003; Zhang et al., 2007).

Enhanced External Counterpulsation (EECP) is a non-invasive procedure used in the treatment of refractory angina (Sharma, Ramsey, & Tak, 2013). During EECP 3 sets of inflatable pneumatic cuffs are placed around the lower limbs before being sequentially inflated during diastole, and rapidly deflated prior to systole (Braith, Casey, & Beck, 2012). In a cohort of 10 Patients referred for diagnostic coronary angiography, intra-arterial diastolic blood pressure was monitored during EECP cuff inflation, and was found to increase by 92% from baseline (71±10 mmHg to 136±22 mmHg / $p<0.0001$) (Michaels, Accad, Ports, & Grossman, 2002) This increase in pressure resulted in a 150% increase in peak intracoronary diastolic blood velocity (18±7 cm/s to 45±14cm/s, $p=0.0004$) (Michaels et al., 2002). In a randomised controlled trial EECP significantly increased collateral flow, as measured by the gold standard collateral flow index (CFI) in a group of CAD patients ($p=0.006$), this improvement was not observed in a group receiving sham EECP treatment ($p=0.14$) (Gloekler et al., 2010). Although EECP has shown promise in treating CAD it is not suitable for every patient. EECP is

contraindicated in the presence of congestive heart failure, peripheral arterial disease, atrial fibrillation, and frequent ventricular ectopic heart beats (Fujita & Sasayama, 2010). Other factors limiting the utility of EECP are the bruising and discomfort caused by the high pressure cuff inflations (Fujita & Sasayama, 2010), the amount of time needed to undergo treatment (one hour attendance at the clinic five days a week for 7 weeks), and the per patient cost, estimated to be £4347.0 per standard 35 hour treatment block (McKenna et al., 2010).

One possible means of transiently increasing coronary flow / FSS is physical exercise (Al-Mamari, 2009). Traditional aerobic exercise can drive an approximate 5-fold increase in coronary blood flow (Duncker & Bache, 2008). Concomitant with an increase in blood flow is an increase in FSS that is directly related to blood velocity and viscosity (Pyke & Tschakovsky, 2005). Research by Möbius-Winkler and colleagues (2016) demonstrated that both high and moderate intensity aerobic exercise increased collateral flow in patients with CAD, as measured by CFI. However, during aerobic exercise heart rate and systolic blood pressure are augmented, whilst diastolic blood pressure remains relatively unaffected (Karlsdottir, Foster, Porcari, Palmer-McLean, et al., 2002). Consequently, although some collateral augmentation does occur coronary perfusion pressure and perfusion time are not optimised for arteriogenesis (Figure 2).

In contrast, resistance exercises have been shown to transiently and significantly increase diastolic blood pressure (Fleck & Dean, 1987; Gotshall et al., n.d.; MacDougall, Tuxen, Sale, Moroz, & Sutton, 1985). Resistance exercise has also been shown to result in a lower heart rate than traditional aerobic exercise (McCartney, 1999). When viewed in combination, these two factors could indicate that resistance exercise more favourably influences perfusion pressure and time (Figure 2). In research by Featherstone and colleagues (1993) 12 men with stable CAD performed resistance exercises (bench press, shoulder press, biceps curl, quadriceps extension) for maximal repetitions using 40, 60, 80 and 100% of their one repetition maximum weight. The researchers non-invasively observed diastolic blood pressures as high as 138 mmHg, however values were predominantly below 126 mmHg (Featherstone et al., 1993). In

contrast to the indirect measure of diastolic blood pressure by Featherstone et al (1993), research using intra-arterial pressure measures after cannulation in healthy cohorts report figures as high as 156 mmHg during resistance exercise (Fleck & Dean, 1987). These values are comparable to the increases observed during EECP (136±22 mmHg) and are likely to provide similar increases in FSS. It is therefore theorised that resistance training has the potential to replicate the therapeutic arteriogenic effects of EECP.

Resistance exercise training could be beneficial for patients with CAD even in the absence of significant coronary collateral development. In a cross-sectional study of 31,108 asymptomatic participants, skeletal muscle mass was negatively associated with coronary artery calcification (Ko et al., 2016). Furthermore, low muscular strength is associated with an increased oxygen requirement for a given workload (low mechanical efficiency) (Helgerud et al., 2011). CAD patients have been shown to walk with "mechanical inefficiency" when compared with a healthy age matched reference group (Høydal et al., 2007). Increasing muscular strength in these patients restores the mechanical efficiency of walking to a level matching that of healthy age matched controls even in the absence of increases in VO2peak.

Resistance training in healthy young cohorts yields little if any improvement in aerobic fitness (Tanaka & Swensen, 1998). However, recent evidence in patients with CAD has shown that skeletal muscle mass is positively associated with VO2peak, oxygen pulse (VO2/heart rate), the ventilator anaerobic threshold (VAT), and negatively associated with cardiac stress markers (NT-proBNP) (Nichols et al., 2019). Three recent reviews also found that resistance exercise training may engender increases in VO2peak comparable to aerobic training in those with CAD (Hollings, Mavros, Freeston, & Fiatarone Singh, 2017; Xanthos, Gordon, & Kingsley, 2017; Yamamoto, Hotta, Ota, Mori, & Matsunaga, 2016).

One reason for this seeming disparity between the responses to resistance training in health and disease is the relative quality of peripheral skeletal muscle. For example,

there is a reduction in skeletal muscle mitochondrial volume density and oxidative enzyme activity in patients with heart failure (HF) (Poole, Hirari, Copp, & Musch, 2011), as a result peripheral oxygen extraction in this cohort may limit VO2peak (Nichols et al., 2019). There is some evidence to suggest that resistance training could increase the mitochondrial density of skeletal muscle (Jubrias, Esselman, Price, Cress, & Conley, 2001) thus restoring its capacity to utilise the oxygen delivered. The mitochondria present in skeletal muscle are capable of operating at low partial pressures of oxygen, as a result they likely provide a buffer, allowing skeletal muscle to maintain perfusion in the presence of reduced flow (Joyner & Casey, 2015). This buffer is likely depleted in HF patients due to the overall reduction in mitochondrial volume density. Therefore, the reason that augmenting mitochondrial volume density contributes to increased VO2peak in diseased and not healthy participant is perhaps linked to the restoration of this buffer. This is also likely to be applicable to CAD patients, as research has strongly implicated CAD in the aetiology of HF (Velagaleti & Vasan, 2007).

Research has shown that increasing musculoskeletal strength through resistance training can lessen the heart rate and blood pressure response to a given absolute load (McCartney, McKelvie, Martin, Sale, & MacDougall, 1993). It has been proposed that since activities of daily living (such as walking up a flight of stairs) require a minimum threshold of muscular strength (Helgerud et al., 2011), increasing absolute strength could potentially make problematic activities of daily living more tolerable (Karlsen, Helgerud, Støylen, Lauritsen, & Hoff, 2009).

Research suggests that if appropriately supervised, resistance exercise in CAD patients could be a safe mode of rehabilitation (Crozier Ghilarducci, Holly, & Amsterdam, 1989; Featherstone et al., 1993; Haslam, McCartney, McKelvie, & MacDougall, 1988), however it should be noted that these studies are often underpowered and contain relatively low risk stable CAD patients (Featherstone et al., 1993).

Summary of the Background to the proposed Study

Exercise is now widely regarded as a staple component of cardiac rehabilitation (CR) (Anderson et al., 2016). Traditionally exercise-based CR has consisted of more aerobically biased training modalities, namely walking and cycling (Ades, 2001). However, undertaking tasks associated with daily living likely stresses the musculoskeletal system to a greater extent than the cardiovascular system (Adams et al., 2006), therefore training to increase skeletal muscle strength is an important component of CR.

Despite fears to the contrary maximal strength testing in cardiac patients has repeatedly proven to elicit no adverse hemodynamic responses (Vescovi & Fernhall, 2000). When aerobic and resistance training were haemodynamically compared, aerobic training (treadmill test) produced a greater intra-patient heart rate response, a comparable systolic blood pressure response (168±31 [aerobic] versus 174±19 mmHg [resistance]), and a lower diastolic blood pressure response in 12 stable CAD patients (Featherstone et al., 1993).

Research has demonstrated that EECP has the capacity to reduce exercise induced myocardial ischaemia (Arora et al., 1999; Urano et al., 2001). The mechanism of action believed to confer this clinical improvement is an increase in diastolic blood pressure, and thus FSS across the coronary collateral network (Michaels et al., 2002; Urano et al., 2001). Considering the existing evidence of similar diastolic blood pressure increases during resistance training (Featherstone et al., 1993; Michaels et al., 2002), this modality may represent a cheaper, more readily accessible means of generating an increase in FSS across the coronary vasculature, and thus provide the stimulus for clinical arteriogenesis and enhance endothelium mediated vasodilation. Furthermore, increasing musculoskeletal strength in coronary patients could reduce the metabolic requirement to lift a given load, making strenuous or challenging daily activities more manageable.

The proposed study will therefore evaluate the efficacy and feasibility of prescribing resistance-based exercise in patients with a coronary CTO.

Aims

- Determine the feasibility of conducting a randomised controlled trial (RCT). As the intervention described has not previously been investigated in this patient population there is uncertainty as to the number patients that would be willing to participate in a RCT. Information on study adherence to the protocol is also required prior to initiation of a RCT. Therefore, I will first ascertain the number of consecutive CTO patients willing to consent to the protocol and, the rate of adherence over the full 8-week intervention.
- Explore potential primary outcome measures for a future RCT. To my knowledge there has been no resistance-based exercise intervention in CTO patients. However, similar interventions have successfully been prescribed in general CAD cohorts. These interventions have successfully increased skeletal muscle strength, and VO2peak, therefore potential primary outcome measures will include the individual ischemic threshold, skeletal muscle strength, aerobic capacity, and EMG. Potential secondary outcomes will include self-reported quality of life, body composition, and haemodynamic changes during exercise sessions.
- The novel nature of the intervention and the group involved means safety information must be collected to determine patient tolerability prior to initiation of a future RCT.
- Calculate the effect size for potential outcome measures (positive signal) prior to a definitive RCT. Effect size will be used to explore treatment efficacy and inform the choice of primary outcomes for a future RCT.

Objectives

- To assess the rate of recruitment and adherence to a resistance-based exercise intervention in CTO patients.
- To assess the ease of data collection for potential outcome measures.
- To determine a suitable primary outcome measure for future a randomised controlled trial (RCT).

- To examine the safety of resistance-based exercise in CTO patients.
- To explore patients' experiences of the study protocol and how this may influence future recruitment to a definitive RCT.

Success criteria

- Identification of appropriate primary outcome measures.
- Satisfactory recruitment and timely programme completion.
- Intervention adherence (<87.5% of prescribed sessions completed by each participant)

Study Design

The study protocol is outlined in Figure 1. This will be a single centre, feasibility study recruiting patients with ≥1 CTO's. Consecutive patients will either be identified at the time of diagnostic coronary angiography, or retrospectively from a dedicated departmental database containing information on every patient who undergoes angiography / angioplasty by their usual clinical care team. Patients will be eligible for inclusion if they are;

1. awaiting attempted angioplasty, or

2. being managed with medical therapy.

The department performs approximately 100 CTO procedures per year. I will recruit 15 consecutive patients who have ≥1 CTO. All patients will have good resting left ventricular function as evidenced by either echocardiography or left ventriculography. Wherever possible, patients will be stabilised on optimal medical therapy so that adjustments to this therapy can be avoided during the study period.

Fifteen consecutive patients fitting the inclusion criteria will be approached at the time of coronary angiography or will receive a telephone call from a member of their usual clinical care team inviting them to take part in the study. A patient information leaflet

(PIL) will be provided or sent through the post if the patient expresses interest in participating. Approximately one week later, after the patient has had time to consider their involvement (>24 hours later) they will be followed up by their usual clinical care team to ask if they would like to proceed with study participation, and whether they would consent to be contacted by the research team. Once agreed, a patient will be contacted by the research team to answer any questions they may have about the protocol and be invited for a baseline assessment (visit 1) where informed consent will be obtained.

Visit one will be a baseline assessment consisting of a brief medical evaluation involving the collection of resting pulse rate, blood pressure, height, weight, waist / hip circumference, resting 12 lead ECG, resting echocardiogram, and spirometry. Patients will also complete a disease specific quality of life questionnaire (short form Seattle angina questionnaire – SAQ-7 (Chan, Jones, Arnold, & Spertus, 2014)). Following these measures, the patient will complete a symptom limited maximal cardiopulmonary exercise test (CPET).

Following visit one the cohort will attend a familiarisation / baseline strength assessment (Visit 2). During the session the patient will be introduced to the equipment that will be utilised during their training intervention. The patient will then be instructed on how to perform each exercise with proper technique to reduce the risk of injury during the study period. Following this familiarisation, patients will establish a 5 repetition maximum (5 RM) lift on each exercise. Each repetition will be standardised as described in more detail below. Prior to the session patients will complete a 10 minute warm up on the cycle ergometer in which expired gas will be collected for analyses. During the session patients will have electromyography (EMG) recorded from the rectus femoris / biceps femoris during lower body exercises and biceps brachii / triceps brachii (lateral head) during upper body exercises.

The resistance-based exercise intervention will consist of 8 weeks of an individualised exercise program. Following this training period, all 12 patients will attend the

laboratory on two separate occasions to complete follow-up assessments identical to those undertaken during visit 1 (visit 3) and visit 2 (visit 4).

Study flow chart

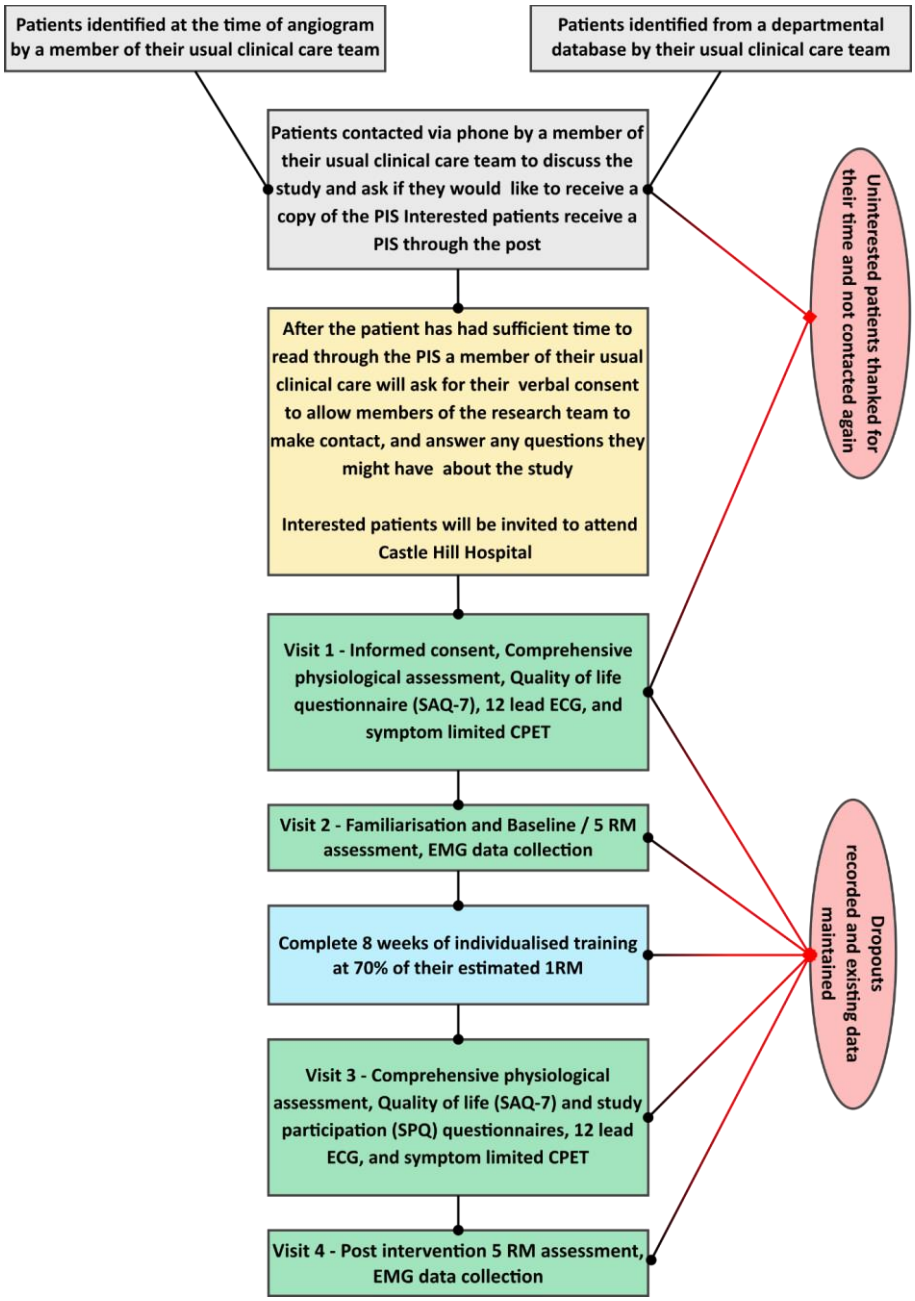

Figure 3. Flow chart of study protocol.

Inclusion criteria

- Diagnosed coronary artery disease with a chronic total occlusion, as identified on coronary angiography performed within the preceding 24 months.
- Willingness to undertake maximal cardiopulmonary and resistance exercise test.

- Resting systolic blood pressure <180mmHg.
- Resting Diastolic blood pressure <100mmHg.
- Aged >18yrs.
- Normal resting left ventricular function.
- Able to provide written informed consent.

Exclusion criteria

- Lower limb amputation.
- Pre-existing musculoskeletal or joint injury that would prevent participation in resistance-based exercise training.
- Change in cardiac medications within previous two weeks.
- Unstable angina.
- Myocardial infarction within the preceding 6 weeks.
- Canadian classification system for angina class IV.
- Chronic heart failure.
- Significant valvular pathology.
- Resting ejection fraction <40%.
- Severe orthopaedic limitations.
- Past history of Complex / uncontrolled arrhythmias.
- Atrial fibrillation.
- Severe COPD.
- Symptoms of intermittent claudication.
- Unable to provide written informed consent.
- Previous permanent pacemaker implant.
- Use of short-term GTN within 30 minutes of exercise testing.
- Abdominal Aortic Aneurism (AAA)
- Known Cerebral Aneurism

Sample size

The aim of the study is to assess the feasibility of prescribing resistance based exercise in a cohort of CTO patients. There is currently no published literature detailing the use if this technique; therefore Julious (2005) recommends recruiting n=12. However, to allow for a 10-20% rate of attrition amongst study participants I will aim to recruit n=15

If participants dropout from the research they will be recorded and reported in the results of the study. The study will aim to re-recruit to fulfil the sample size, however as this is research related to a PhD thesis it is time sensitive and as such this may not be possible. Any dropout due to adverse event or injury will be recorded in the safety analysis.

Withdrawal Criteria

Participants wishing to withdraw from the study will be permitted to do so at any time. Whilst no reason for their withdrawal is required, participants will be asked if they would like to record a reason, as this will assist the research team in determining adherence rates in this population. Any data collected from a patient prior to their withdrawal will be retained by the research team and reported in the studies' findings.

Expected Duration

From the time of their first test (visit 1) each individual patient will maintain active participation in the study for a maximum of 4 months.

Study procedures - Visit 1 & 3

Brief medical assessment & anthropometric data collection

Patients will be invited to the Academic Cardiology Department of Castle Hill Hospital to undergo baseline testing.

Prior to baseline CPET each patient will be asked to confirm that neither their health status, nor medication has altered significantly since they were invited to partake in

the study. Researchers will collect baseline demographic information and will then collect measures of resting pulse, blood pressure, height, weight, and ECG.

Quality of life questionnaire (SAQ-7)

Patients will be asked to complete the validated short from version of the Seattle Angina Questionnaire (SAQ-7) (Chan et al., 2014).

Symptom limited cardiopulmonary exercise test

The patient will be asked to ride a stationary bike against increasing resistance until they can no longer maintain the specified rpm or until volitional exhaustion (approx. 8-12 minutes). During this exercise they will have their exhaled breath (collected via face mask), heart rate, blood pressure and ECG measured throughout.

- Breath-by-breath gas analysis
- Continuous ECG monitoring
- 3-minute unloaded cycling phase at 40-60 rpm
- Personalised ramp protocol using cycle ergometer (60rpm)
- Follows (American Thoracic Society & American College of Chest Physicians, 2003) guidelines

Measurements taken during the CPET will include;

- Peak Oxygen uptake (VO2peak)
- Respiratory Exchange Ratio (RER)
- Ventilatory Anaerobic Threshold (VAT)
- Ventilatory Efficiency (VE/VO2 slope)
- Oxygen Uptake Efficiency Slope (OUES)
- Oxygen Pulse (O2 Pulse)
- Oxygen Uptake, Work Rate relationship (ΔVO2/ΔWR)

- Heart Rate (HR)
- Work Rate (WR)
- CPET duration
- Rating of perceived exertion (Borg, 1982)

Determination of Oxygen Pulse and ΔVO2/ΔWR

Following symptom limited maximal CPET, breath-by-breath data will be exported for offline analysis (15 second mean time average). The instantaneous ration of oxygen uptake to heart rate (O2/HR) will be plotted against work rate (WR). A plateau or reduction in the (O2/HR) despite increasing work rate will be considered indicative of myocardial ischaemia. ΔVO2/ΔWR slope will also be calculated as peak VO2-unloaded VO2/T-0.75×S, where peak VO2 is VO2 at peak exercise, T is the time of incremental exercise, S is the slope of work rate increment in watts per minute. A ΔVO2/ΔWR slope will be deemed abnormal if an inflection in VO2 is observed with respect to WR despite evidence of a normal slope (~10 ml.min-1.watt-1) from the onset of exercise start to the inflection point, and a flattened slope. An inflection in the O2/HR or ΔVO2/ΔWR slope will not be deemed abnormal if it occurs during the last 30 seconds of exercise as this can result from normal physiological limitations to exercise (VO2 plateau). This protocol reflects the seminal work by (Belardinelli et al., 2003).

Study procedures - Visit 2 & 4

Five repetition maximal testing

Patients will attend a familiarisation / baseline assessment session (Visit 2). During the session each patient will have the prescribed resistance exercises explained and demonstrated to them. After a 10 minute warm up on the cycle ergometer they will be instructed on how to perform the exercise with correct form and tempo. Each patient will be coached to avoid performing the Valsalva manoeuvre during lifting. Patients will begin the session with a 10-15 minute warm-up consisting of mobility and light aerobic exercise, followed by 1-2 set of 10 repetitions with a light load on the exercise

to act as a movement specific warm-up prior to testing. When the patient has demonstrated sufficient understanding and competence with each lift, they will determine a 5 repetition maximum weight (5RM) for each movement. 5RM will be defined as the maximal resistance for a given exercise with proper lifting / breathing technique and no additional unwanted compensatory movements (Levinger et al., 2009). Patients will set 5RM benchmarks in the belt squat, leg extension, hamstring curl, single arm biceps curl, bench press, single arm triceps extension and low cable row (exercise images and descriptions beginning on page 25). Lower body exercises will be a combination of uni- and bilateral movements. In contrast, all upper body exercises will be unilaterally executed due to the placement of the continuous blood pressure monitoring device. Once patients have determined 5RM values for each exercise the 8-week intervention can begin.

Electromyography (EMG) data collection

Prior to 5RM testing in visit 2 patients will have EMG surface electrodes bilaterally placed on their rectus femoris / biceps femoris and unilaterally placed on their dominant biceps brachii / triceps brachii (lateral head). Electrical activity will subsequently be measured during each upper and lower body exercise for the remainder of the session. After the 5RM load has been determined for each lift maximal data will be analysed to determine peak and mean signal amplitude. These procedures will be repeated during visit 4, however in this instance if the 5RM value has changed both the old and new 5RM will be recorded for comparison during data analysis.

Study Participation Questionnaire (SPQ)

Patients will be asked to report their feelings on the study with regards to their reasons for, and experience of participation, how well they believe they tolerated both testing and training sessions, and what barriers they can envisage to future patients completing the study.

Resistance-based exercise intervention

- Frequency – 2x per week / 8 weeks
- Intensity – 70% of estimated 1 repetition maximal (1RM)
- Time – ≈50-60 minutes
- Type – Free weights, modified cable pulley system

Resistance training will be performed 2 times per week following an upper / lower body split. Partitioning the sessions in this manner will ensure the musculature of the upper and lower body is not over fatigued prior to each new session. Training sessions will be conducted individually under the supervision of a qualified sports scientist trained in immediate life support. Sessions will take place in the sports science laboratory located on the University of Hull campus. Each patients' involvement in the intervention will last 8 weeks, or until they have performed 16 sessions. Each patient will be permitted to miss 2 non-consecutive training sessions throughout the intervention before being withdrawn. Attendance and absence to scheduled training sessions will be recorded for each patient.

Training days will comprise 4 working sets of 8-12 repetitions at 70% estimated 1RM on each of the 4 upper body, and 3 lower body movements respectively. The procedure for estimating 1RM from the established 5RM will be based on the previous research by (Reynolds, Gordon, & Robergs, 2006). Prior to performing their working sets each patient will be taken through a 10 minute warm-up consisting of mobility and light aerobic exercise. During the working sets of each resistance exercise the patient will receive verbal encouragement from the researcher to perform the desired repetitions whilst maintaining proper technique and breathing. The tempo for each lift will follow a 2:1:1-3:1 protocol (2 second eccentric, 1-3 second concentric, 1 second isometric top and bottom) and rest between sets will be ad libitum. Patients performing 12 repetitions with perceived ease will have their working weight increased until no more than 12 repetitions are possible. Throughout each training session patients will be fitted with a heart rate monitor. Patients will also have beat-to-beat continuous blood pressure measured during the first and last training sessions. This data will be used to assess the haemodynamic profiles of resistance training in CTO.

Belt Squat

Patients will have a weight belt and attachment placed around their waist, the belt will be secured to a modified pulley system. At the onset of each rep the patient will begin standing with feet just outside shoulder width apart, toes flared slightly out to the sides. The patient's knees and hips will be extended. From this position the patient will descend down into a squat, simultaneously flexing at the hips and knees, this will represent the eccentric portion of the repetition. The concentric portion of the lift will begin when the hip and knee are in roughly 80-90 degrees of flexion (depending upon individual flexibility, comfort, and anthropometry). From this position patients will begin to extend both the hip and knee in concert to lift the weight. The patient will continue to press with the legs until the hip and knee reach a point just prior to full extension, this will represent the end of the concentric phase. Patients will be coached to inhale during the eccentric, and exhale during the concentric portion of each lift. The repetitions will follow a 2:1 tempo (2 second eccentric, 1 second concentric), and patients will be coached to maintain some muscular contraction (tension) at maximal flexion.

Figure 4. Example of the starting and finish positions in the Belt Squat.

Leg Extension

Patients will position themselves seated upright on a firm bench with both legs dangling freely (feet not in contact with the ground). The exercising limb will be attached via neoprene cuff to the cable pulley (resistance). The patient will maintain an upright torso, with one hand loosely gripping the seat for stability and the knees at roughly 135º of flexion. The repetition will be initiated by strongly contracting the quadriceps musculature, thus extending the knee through a full range of motion (≈135º). When the shank is parallel with the ground (knee at 0º) the concentric phase of the lift will cease. From this position the patient will eccentrically lengthen the quadriceps returning the limb to the starting position. Patients will be coached to inhale during the eccentric, and exhale during the concentric portion of each lift. The repetitions will follow the previously established tempo, and patients will be coached to maintain some muscular contraction (tension) at maximal flexion.

Figure 5. Example of the starting and finish positions in the Leg Extension.

Hamstring Curl

Patients will position themselves prone on the ground with a weight attachment fixed around their ankle. At the onset of each repetition the patient will forcefully contract the musculature of the hamstring, thus drawing the heel up towards the glute. This will represent the terminus of concentric muscular activity for each rep. From here the knee will be extended back to the starting position (eccentric phase). Patients will be

coached to inhale during the eccentric, and exhale during the concentric portion of each lift. The repetitions will follow the previously established tempo, and patients will be coached to maintain some muscular contraction (tension) in the hamstring at the bottom of the movement.

Figure 6. Example of the starting and finish positions in the H.

Single Arm Biceps Curl

Patients will begin in a standing position securely gripping the dumbbell in one hand. The weight will be resting at the side of the body with the elbow extended. At the onset of each repetition the patient will forcefully contract the musculature of the biceps brachii, thus drawing the hand in a supinated position up towards the anterior deltoid. This will represent the terminus of concentric muscular activity for each rep. From here the elbow will be extended back to the starting position (eccentric phase). Patients will be coached to inhale during the eccentric, and exhale during the concentric portion of each lift. The repetitions will follow the previously established tempo, and patients will be coached to maintain some muscular contraction (tension) in the hamstring at the bottom of the movement.

Figure 7. Example of the starting and finish positions in the Single arm Biceps Curl.

Dumbbell Bench Press

The patients will position themselves in a supine position on a flat weight bench, making sure the glutes and back are in full contact with the padded rests. These will remain in constant contact throughout the lift. A dumbbell will be grasped in one hand approximately inline with the sternum, this position along with individual flexibility, comfort, and anthropometry will dictate the angle created at the elbow. Throughout the exercise the other hand will be held at chest level to ensure accurate blood pressure data is recorded when necessary. At the onset of each repetition the patient will forcefully contract the musculature of the chest, anterior deltoid and triceps to extend the elbow and take the shoulder through horizontal adduction. The concentric phase of the lift will terminate at full elbow extension. Patients will be coached to inhale during the eccentric, and exhale during the concentric portion of each lift. The repetitions will follow the previously established tempo, and patients will be coached to maintain some muscular contraction (tension) in the target musculature between repetitions.

Figure 8. Example of the starting and finish positions in the Dumbbell Bench Press.

Single Arm Triceps Extension

Patients will begin in a standing position with feet staggered and a forward leaning torso. The triceps of the working arm will be placed against a padded bench for support and stability. With the working arm patients will securely grip the handle of the modified pulley system placing the elbow in a flexed position at approximately 45º. At the onset of each repetition the patient will forcefully contract the musculature of the triceps, thus drawing the hand in a neutral position down until the heel of the hand is in contact with the padded bench. This will represent the terminus of concentric muscular activity for each rep. From here the elbow will be flexed back to the starting position (eccentric phase). Patients will be coached to inhale during the eccentric, and exhale during the concentric portion of each lift. The repetitions will follow the previously established tempo, and patients will be coached to maintain some muscular contraction (tension) in the hamstring at the bottom of the movement.

Figure 9. Example of the starting and finish positions in the Single arm Triceps Extension.

Low Cable Row

The patients sits on mats with their feet against a support block. One hand will be placed outstretched on the handle of the pulley machine approximately inline with the sternum, this position may vary due to individual flexibility, comfort, and anthropometry. Throughout the exercise, the other hand will be held at chest level to ensure accurate blood pressure data is recorded when necessary. At the onset of each repetition the patient will forcefully contract the musculature of the back (rhomboid, latissimus dorsi, trapezius), posterior deltoid and biceps. This musculature will take the arm through horizontal abduction with the humerus at an approximate 45º angle in relation to the torso. The concentric phase of the lift will terminate at approximately 90-130º of elbow flexion or until the handle of the pulley machine is in line with the torso. Patients will be coached to inhale during the eccentric, and exhale during the concentric portion of each lift. The repetitions will follow the previously established tempo, and patients will be coached to maintain some muscular contraction (tension) in the target musculature between repetitions.

Figure 10. Example of the starting and finish positions in the Low Cable Row.

Safety Considerations

Throughout the research the safety and tolerability of both exercise interventions will be recorded, this will include; patient reported symptoms of angina, musculoskeletal / soft tissue injuries and joint problems.

In the event of patients reports chest discomfort prior to, or during training or testing, this test will be ceased.

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing does increased the chance of adverse events, however the likelihood of this happening is low, occurring in <0.16% of tests (Skalski, Allison, & Miller, 2012).

Whilst there is no research to date that directly assesses the safety of CPET in CTO patients, the aforementioned study by (Skalski et al., 2012) did recruit a cohort comprising 5060 high-risk cardiac patients. As per the clinical diagnosis pathway most of the patients recruited to the study will have already performed exercise stress testing, therefore in the clinical opinion of the principle investigator (Dr Angela Hoye) there are no significant clinical concerns (e.g. risk of participation) associated with the protocol. To mitigate the chances of adverse events during the CPETs they will be conducted at the cardiology research department of Castle Hill Hospital. Participants will be encouraged to exercise to the limit of their capacity in an environment where they are closely monitored and immediate medical care is on hand. This could provide

participants intimidated by or reluctant to exercise with the chance to test their physical capabilities in a safe and secure manner, thus alleviating some of the stress and anxiety caused by their condition.

Resistance Training

Resistance training does acutely increase systolic and diastolic arterial pressure (MacDougall, Tuxen, Sale, Moroz, & Sutton, 1985b). However, research comparing maximal treadmill and resistance exercise in CAD patients found that whilst there was no electrocardiographic signs of myocardial ischemia during resistance training, 5 of 12 patients did show signs of ischemia during maximal treadmill testing (Featherstone et al., 1993).

The finding that resistance exercise can be completed by CAD patients with no evidence of ischemia is a consistent finding within the literature (Butler, Beierwaltes, & Rogers, 1987; Haslam et al., 1988). Resistance training has since become a widely accepted component of cardiac rehabilitation (American College of Sports Medicine, 2013; McCartney, 1999; Wise & Patrick, 2011), with The American Association of Cardiovascular and Pulmonary Rehabilitation first recommended its implementation for selected CAD patients in 1991 (Karlsdottir, Foster, Porcari, Palmer-mclean, et al., 2002).

The safety and efficacy of the trial will be monitored by the cardiology governance team. Any adverse event occurring during participation in the trial will be reported directly to Dr Benjamin Davison (Consultant Cardiologist) who is independent of the study and will act as an impartial reviewer. In the event of any serious adverse event occurring (such as death or unexpected hospitalisation) the study will be halted until the clinical governance team have reviewed the event and considered whether the study may or may not continue.

Statistical Analysis and Data Management

All confidential and identifiable information will be stored securely with the NHS trust in accordance with information governance policies. Only data classified as essential to the research will be collected as part of the tests and this will be anonymised at the earliest possible convenience. Any subsequent analysis will be conducted without the presence of the participants' identifiable information. All data will be stored in accordance with the data protection act of 1998. Patient medical records will remain with the NHS trust currently responsible for their safekeeping, and policies pertaining to information governance from said trust will be observed. Any data generated from these records that is transported to an alternate location will first be anonymised and stripped of personal information, before being stores on encrypted external hard drives / memory sticks and stored in a secure lockable room.

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11.6 Appendix F - RARE Study

11.6.1 RARE Ethics Approval

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PRIVATE AND CONFIDENTIAL
Thomas Nickolay
Faculty of Health Sciences
University of Hull
Via email

12th November 2019

Dear Thomas

REF FHS194 - Does resistance training influence markers of central and peripheral efficiency in older sedentary individuals.

Thank you for your responses to the points raised by the Faculty of Health Sciences Research Ethics Committee.

Given the information you have provided I confirm approval by Chair's action.

Please refer to the Research Ethics Committee web page for reporting requirements in the event of any amendments to your study.

I wish you every success with your study.

Yours sincerely

Dr Tim Alexander
Deputy Chair, FHS Research Ethics Committee

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11.6.2 RARE Protocol

Does resistance training influence markers of central and peripheral efficiency in older sedentary individuals? (RARE)

Study Protocol

General Information

Title - Does resistance training influence markers of central and peripheral efficiency in older sedentary individuals?

Version number – 3

Date – 12/01/2020

Name of Sponsor – University of Hull

Address – Cottingham Road, Hull HU6 7RX

Investigators - Dr Angela Hoye (Clinical Lead / Principle Investigator)

Tom Nickolay BSc (Hons) (Investigator)

Prof Lee Ingle (Investigator)

Dr Simon Nichols (Investigator)

Name and Address of research site – Sports Science Department, University of Hull, Cottingham Road, Hull HU6 7RX.

Telephone number of research site – 01482 466314

Rationale and Background Information

Skeletal muscle accounts for approximately 40% of total body weight making it the most abundant tissue in the human body (Frontera & Ochala, 2015; McArdle et al., 2007). This dynamic tissue comprise 75% water and 20% protein, with the remaining 5% a mixture of fats, carbohydrates, amino acids, salts and minerals etc. (McArdle et al., 2007). Skeletal muscle contributes to numerous bodily functions, perhaps most notably generating movement (Frontera & Ochala, 2015; Hamill & Knutzen, 2009). The proximal and distal end of a skeletal muscle are fixed to opposing sides of a joint, thus contracting the muscle decreases the joint angle and moves the limb segment and/or an external load. Skeletal muscle also acts as a storage reservoir for glycogen and vital amino acids required by organs such as the skin brain and heart (Frontera & Ochala, 2015). There is a significant positive correlation between the amount of skeletal muscle and peak oxygen uptake (VO2peak) (Sanada et al., 2005). This association is important, as age related reductions in cardiorespiratory fitness are themselves associated with all cause and cardiovascular mortality (Sui et al., 2007).

Human ageing is associated with a loss in muscle mass and function that leads to reductions in both strength and power (Doherty, 2003; McGuigan et al., 2006). Muscular strength, classed as the amount of force a muscle can produce, is believed to peak at around 20-30 years of age, before gradually declining from the fifth decade of life (Liu & Latham, 2009; Peterson et al., 2010). The mechanisms underlying age related reductions in muscle mass are not completely understood (Fujita & Volpi, 2004). However, it is believed to be a multifaceted process influenced by factors such as; reduced physical activity, reduced nutritional absorption / malnutrition, altered hormonal balance and reduced muscle quality (Doherty, 2003; Fujita & Volpi, 2004).

It is possible that the physical dysfunction associated with reduced skeletal muscle mass in older adults could be attenuated with the addition of adequate resistance training (RT)(Vlietstra et al., 2018). The term "resistance training" is used to describe modalities of exercise in which the skeletal muscle is required to exert force against an external resistance (either static or dynamic) (Kraemer et al., 2017). It is widely acknowledged that RT results in skeletal muscle hypertrophy (increasing cross-sectional area) (Schoenfeld, 2013). However, hypertrophy alone does not fully account for increases in muscular strength. The initial stages of a RT intervention (≈4 weeks) are often accompanied by increases in strength that are independent of muscle hypertrophy (McArdle et al., 2007). These adaptations are neural in nature, resulting from improved motor neuron recruitment, synchronisation and firing rate (Hamill & Knutzen, 2009).

Skeletal muscle mass is indirectly and non-invasively measured through a number of different methods, ranging in their accuracy from; bioelectrical impedance analysis (Janssen et al., 2000), to the gold standard air displacement plethysmography (McArdle et al., 2007). Muscular strength is usually measured in absolute terms (sometimes estimated) as one repetition maximal load lifted (1RM). In addition to assessing the strength of the muscular contraction by recording the mass of the externally applied load, researchers can non-invasively measure the electrical activity within the muscle during contraction using electromyography (EMG). EMG allows researchers to quantify the magnitude of the electrical activity within the muscle in response to a given external load (Hamill & Knutzen, 2009).

A recent meta-analysis incorporating 6 studies and 1494 nursing home residents reported that sarcopenia (reduced muscle mass) was significantly associated with a higher all-cause mortality risk (pooled hazard ratio 1.86, 95% confidence interval 1.42-2.45, P<0.001) (Zhang et al., 2018). Similarly, Nichols and colleagues (2019) found that skeletal muscle mass (appendicular lean mass), expressed as a percentage of total body mass was inversely associated with 5-year all-cause mortality in coronary artery disease (CAD) participant s (r=-0.365, P=0.006). The researchers also investigated the

association between measures of skeletal muscle mass (skeletal muscle index = SMI and appendicular skeletal mass = ASM) and aerobic capacity, concluding that muscle mass was positively correlated with VO2peak and peak oxygen pulse in CAD participant s (SMI; r=0.431 & ASM; r=0.473, P=0.001).

A meta-analysis conducted in 2012 revealed that 67% (6/9) of studies assessing RT induced changes in aerobic capacity (VO2max) of older (>60) participants reported significant improvements (Ozaki et al., 2013). The authors suggest that the variability in outcome is not attributable to training load, intensity or volume, but is instead dependent upon the individual's initial aerobic capacity. Indeed, they reported a significant negative correlation (r=0.632; P=0.001) between baseline VO2max and magnitude of RT induced change in VO2max. The authors conclude that RT may increase aerobic capacity in older participants if baseline VO2max values are ≈≤5 ml/kg/min that of untrained age group norms (Ozaki et al., 2013). A study investigating the metabolic demands of daily living tasks in older participants, found that 26 weeks of heavy RT significantly reduced (P=≤0.05; 6%) the oxygen cost (VO2) of carrying a pre-determined load (aimed at stimulating carrying a bag of groceries) (Hartman et al., 2007). Furthermore, following the resistance training intervention the participants (n=29) perceived level of exertion for all tests (3mph walking, 2mph walking with load and stair climbing) was significantly (P=≤0.05) reduced.

The aforementioned study by Hartman and colleagues (2007) demonstrates RT's capacity to increase metabolic economy, sometimes referred to as work efficiency or mechanical efficiency (Hoff et al., 2006; Karlsen et al., 2009). When spoken about in these terms economy or efficiency can be considered as the oxygen cost required to generate a given work load/output (Karlsen et al., 2009). There is a minimal threshold of muscular strength required to perform tasks associated with daily living, such as; walking, carrying, standing and stair climbing, if this threshold is not met due to age related declines in muscle mass and strength, disability may arise (Karlsen et al., 2009). Similar to the findings of Hartman and colleagues (2007) research by Barrett-O'Keefe, Helgerud, Wagner, & Richardson (2012) demonstrated that maximal strength training

(RT) reduced pulmonary VO2, single-leg VO2 (measured via blood gasses) and single leg blood flow (measured via thermodilution) in response to sub-maximal steady state exercise.

As previously mentioned RT influences not only muscle architecture but also neural input. One study in 2010 recruited 23 healthy older participants (men 65 ± years) to undertake either RT alone (n=8), concurrent training (n=8) (RT and aerobic training) or solely aerobic training (n=7) three times per week for 12 weeks (Cadore et al., 2010). The authors used EMG to determine changes in neuromuscular activation following interventions. Data analysis revealed that muscle activation to the same submaximal load was significantly reduced (P=<0.05) only in the RT group. Interestingly, this coincided with a significant increase in maximal muscle activation (P=<0.05).

Exercise interventions are often categorised as either supervised or non-supervised (often home-based). Supervised exercise programs allow the researcher / trainer to have a direct impact on the session intensity, duration and execution. However, in order to facilitate these sessions the participant may be required to sacrifice their own time and money to travel to the training venue (laboratory, gymnasium, sports hall etc), this has the potential to reduce recruitment / adherence (Orange et al., 2019b). Whilst unsupervised home-based interventions do not provide the researcher / trainer with the same degree of in session control, there is evidence to suggest they promote comparable functional adaptations (Orange et al., 2019a).

Study Design

The study protocol is outlined in Figure 1. This will be a single centre, feasibility study recruiting sedentary participants >50 years of age. Twelve participants fitting the inclusion criteria will be recruited to take part in the study. A participant information leaflet (PIL) will be provided if the participant expresses interest. After the participant has had time to consider their involvement (>24 hours later) they will be followed up by a member of the research team to ask if they would like to proceed with study

participation. The researcher will answer any questions they may have about the protocol and invite them for a baseline assessment (visit 1) where informed consent will be obtained.

Visit one will be a baseline assessment consisting of a brief medical evaluation involving the collection of resting pulse rate, blood pressure, height, weight, waist / hip circumference and spirometry. Following these measures, the participant will complete a symptom limited maximal cardiopulmonary exercise test (CPET).

Following visit one the cohort will attend a familiarisation / baseline strength assessment (Visit 2). During the session the participant will be introduced to the equipment that will be utilised during their training intervention. The participant will then be instructed on how to perform each exercise with proper technique to reduce the risk of injury during the study period. Following this familiarisation, participants will establish a 5 repetition maximum (5 RM) lift on the belt squat, single arm biceps curl and triceps extension (unilateral). Each repetition will be standardised as described in more detail below. Prior to the session patients will complete a 10 minute warm up on the cycle ergometer in which expired gas will be collected for analyses. During the session participants will have electromyography (EMG) recorded from the rectus femoris / biceps femoris during lower body exercises and biceps brachii / triceps brachii (lateral head) during upper body exercises.

The resistance-based exercise intervention will consist of 8 weeks of progressive home-based resistance training. Following this training period, all 12 participants will attend the laboratory on two further occasions to complete follow-up assessments identical to those undertaken during visit 1 (visit 3) and visit 2 (visit 4).

Objectives

- To assess the rate of recruitment and adherence to a progressive home-based resistance exercise intervention in older (≥50 years) sedentary participants.
- To assess the ease of data collection for potential outcome measures.

- To determine a suitable primary outcome measure for future a randomised controlled trial (RCT).
- To explore patients' experiences of the study protocol and how this may influence future recruitment to a definitive RCT.

Study flow chart

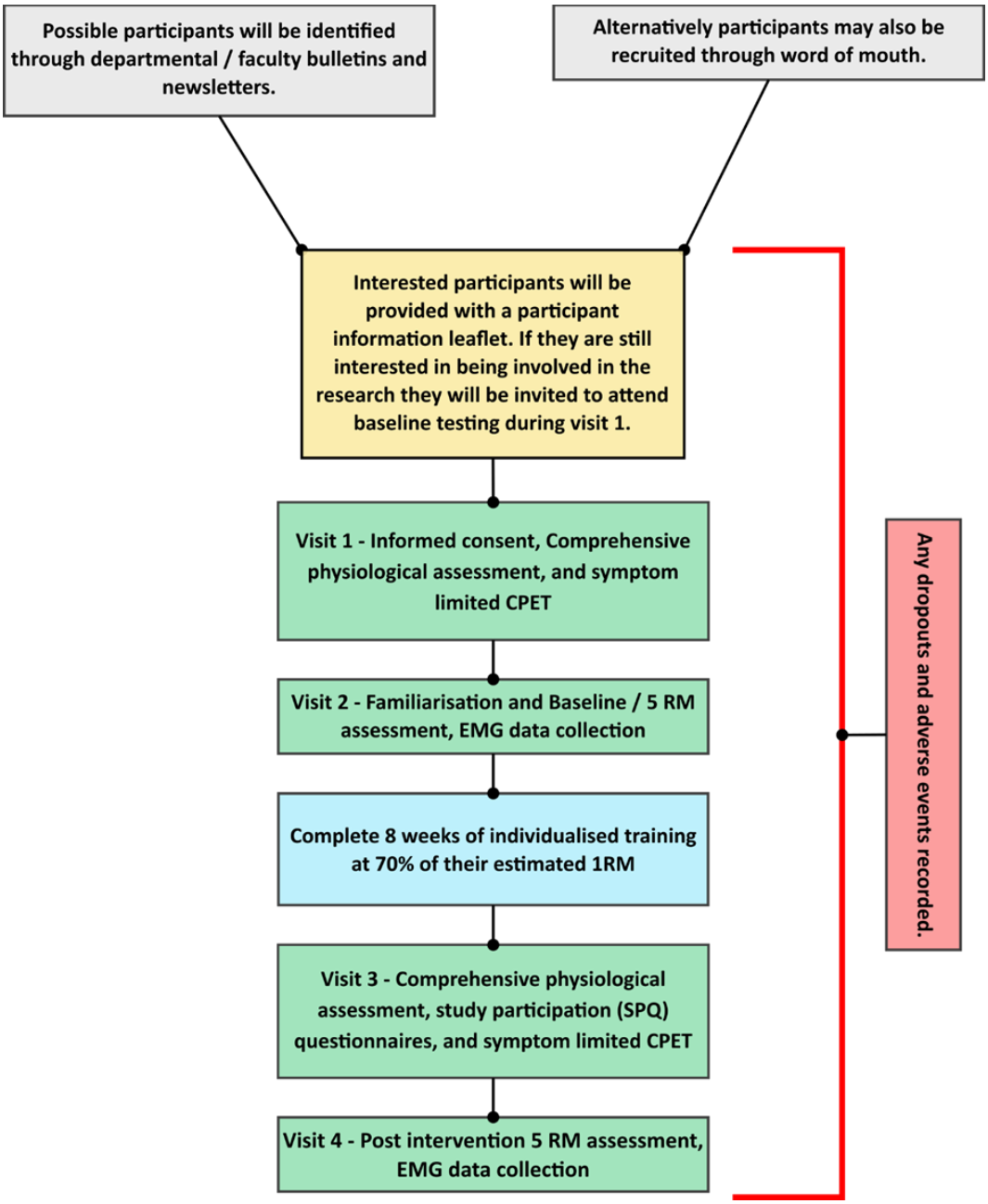

Figure 1. Flow chart of study protocol.

Inclusion criteria

- Self-reported as sedentary with no involvement in physical exercise regimen.
- Willingness to undertake maximal cardiopulmonary and resistance exercise test.
- Resting systolic blood pressure <180mmHg.
- Resting Diastolic blood pressure <100mmHg.
- Aged >50yrs.
- Normal resting left ventricular function.
- Able to provide written informed consent.

Exclusion criteria

- History of Coronary / Heart Disease
- History of Stroke
- Diabetes Mellitus
- Limb amputation
- Pre-existing musculoskeletal or joint injury that would prevent participation in resistance-based exercise training.
- Severe orthopaedic limitations.
- Past history of Complex / uncontrolled arrhythmias.
- Atrial fibrillation.
- Severe COPD.
- Unable to provide written informed consent.
- Previous permanent pacemaker implant.
- Abdominal aortic aneurism (AAA)
- Cerebral aneurism
- Embolism

Sample size

The aim of the study is to assess the feasibility of prescribing resistance-based exercise in older sedentary populations to increase muscular and cardiovascular efficiency.

There is currently no published literature detailing the use if this technique in participants of this age with this duration of intervention; therefore Julious (2005) recommends recruiting n=12.

If participants dropout from the research they will be recorded and reported in the results of the study. The study will aim to re-recruit to fulfil the sample size, however as this is research related to a PhD thesis it is time sensitive and as such this may not be possible. Any dropout due to adverse event or injury will be recorded in the safety analysis.

Withdrawal Criteria

Participants wishing to withdraw from the study will be permitted to do so at any time. Whilst no reason for their withdrawal is required, participants will be asked if they would like to record a reason, as this will assist the research team in determining adherence rates in this population. Any data collected from a participant prior to their withdrawal will be retained by the research team and reported in the studies' findings.

Expected Duration

From the time of their first test (visit 1) each individual participant will maintain active participation in the study for a maximum of 4 months.

Study procedures - Visit 1 & 3

Brief medical assessment & anthropometric data collection

Participants will be invited to the bio-mechanics laboratory of Hull University to undergo baseline testing.

Prior to baseline CPET researchers will collect measures of resting pulse, blood pressure, wait-hip ratio, height and weight.

Symptom limited cardiopulmonary exercise test

The participant will be asked to ride a stationary bike against increasing resistance until they can no longer maintain the specified rpm or until volitional exhaustion (approx. 8-12 minutes). During this exercise they will have their exhaled breath (collected via face mask), heart rate, and blood pressure measured throughout.

- Breath-by-breath gas analysis
- 3-minute unloaded cycling phase at 40-60 rpm
- Personalised ramp protocol using cycle ergometer (60rpm)
- Follows (American Thoracic Society & American College of Chest Physicians, 2003) guidelines

Measurements taken during the CPET will include;

- Peak Oxygen uptake (VO2peak)
- Respiratory Exchange Ratio (RER)
- Ventilatory Anaerobic Threshold (VAT)
- Ventilatory Efficiency (VE/VO2 slope)
- Oxygen Uptake Efficiency Slope (OUES)
- Oxygen Pulse (O2 Pulse)
- Oxygen Uptake, Work Rate relationship slope (ΔVO2/ΔWR)
- Heart Rate (HR)
- Work Rate (WR)
- CPET duration
- Rating of perceived exertion (Borg, 1982)

Study procedures - Visit 2 & 4

Five repetition maximal testing

Participants will attend a familiarisation / baseline assessment session (Visit 2). During the session each participant will have the prescribed resistance exercises explained and demonstrated to them. After a 10 minute warm up on a cycle ergometer they will be instructed on how to perform the exercise with correct form and tempo. Each participant will be coached to avoid performing the Valsalva manoeuvre during lifting. Participant s will begin the session with a 10-15 minute warm-up consisting of mobility and light aerobic exercise, followed by 1-2 set of 10 repetitions with a light load on the exercise to act as a movement specific warm-up prior to testing. When the participant has demonstrated sufficient understanding and competence with each lift, they will determine a 5 repetition maximum weight (5RM) for each movement. 5RM will be defined as the maximal resistance for a given exercise with proper lifting / breathing technique and no additional unwanted compensatory movements (Levinger et al., 2009). Participant s will set 5RM benchmarks in the belt squat (Figure 2), single arm biceps curl (Figure 3) and, single arm triceps extension (Figure 4) (exercise images and descriptions beginning on page 22). Once participants have determined 5RM values for each exercise, they will have the home-based intervention and equipment explained to them.

Electromyography (EMG) data collection

Prior to 5RM testing in visit 2 participants will have EMG surface electrodes bilaterally placed on their rectus femoris / biceps femoris and unilaterally placed on their dominant biceps brachii / triceps brachii (lateral head). Electrical activity will subsequently be measured during each upper and lower body exercise for the remainder of the session. After the 5RM load has been determined for each lift maximal data will be analysed to determine peak and mean signal amplitude. These procedures will be repeated during visit 4, however in this instance if the 5RM value has changed both the old and new 5RM will be recorded for comparison during data analysis.

Home-based Resistance Exercise Intervention

- Frequency – 2x per week / 8 weeks
- Intensity – RPE 4-7
- Time – ≈30-40 minutes
- Type – Bodyweight with / without banded resistance

Resistance training will be performed twice per week with each session recruiting whole body musculature. Sessions will be separated by a minimum of 48 hours to reduce excessive soreness and fatigue.

Table 1. Sequence of exercises performed during each training session.

Movement Pattern	Primary Exercise	Week	Sets / Repetitions
Lower body triple extension	Bilateral squat (bodyweight)	1-4	2 / 8-12
		5-8	3 / 8-12
Upper body horizontal press	Bilateral push-up (bodyweight)	1-4	2 / 8-12
		5-8	3 / 8-12
Upper body horizontal pull	Bilateral seated row (resistance band)	1-4	2 / 8-12
		5-8	3 / 8-12
Lower body hip extension	Bilateral hip thrust (bodyweight)	1-4	2 / 8-12
		5-8	3 / 8-12
Upper body vertical press	Bilateral shoulder press (resistance band)	1-4	2 / 8-12
		5-8	3 / 8-12
Upper body horizontal shoulder abduction	Bilateral banded pull-aparts (resistance band)	1-4	2 / 8-12
		5-8	3 / 8-12
Lower body hip hinge	Bilateral deadlift (resistance band)	1-4	2 / 8-12
		5-8	3 / 8-12
Upper body elbow extension	Unilateral triceps extension (resistance band)	1-4	2 / 8-12
		5-8	3 / 8-12
Upper body elbow flexion	Bilateral biceps curl (resistance band)	1-4	2 / 8-12
		5-8	3 / 8-12
Upper body torso anti-rotation	Bilateral pallof press (resistance band)	1-4	2 / 8-12
		5-8	3 / 8-12
Upper body torso anti-extension	Plank (bodyweight)	1-4	2 / max duration
		5-8	3 / max duration

The sequence of exercises performed during each session is outlined in Table 1. The primary exercise aligned with each movement pattern represents the desired prescription. However, if the participant does not possess the requisite strength, flexibility of stability to perform the movement safely, an alternative will be provided that remains consistent with the movement pattern.

Prior to performing their working sets each participant will complete a 10 minute warm-up consisting of mobility and light aerobic exercise (jogging on the spot). During weeks 1-4 each session days will comprise 2 sets of 8-12 repetitions, this will progress to 3 sets of 8-12 during weeks 5-8. The tempo for each lift will follow a 2:1:1-3:1 protocol (2 second eccentric, 1-3 second concentric, 1 second isometric top and bottom) and rest between sets will be ad libitum (≤3 minutes). The intensity of each set will be monitored by assessing the reps in reserve based rating of perceived exertion (RPE) scale outlined by Zourdos and colleagues (2016). Participants performing 12 repetitions with perceived ease (RPE <4) during their second or third set, will have either the resistance band tension increased, or the exercise difficulty progressed (unilateral glute bridge to bilateral hip thrust / push-up to feet elevated [incline] push-up) until no more than 12 repetitions are possible. Throughout each training session participants will be fitted with a heart rate monitor.

5 Repetition Maximal Lifts

Belt Squat

Participants will have a weight belt and attachment placed around their waist, the belt will be secured to a modified pulley system. At the onset of each rep the participant will begin standing with feet just outside shoulder width apart, toes flared slightly out to the sides. The participant's knees and hips will be extended. From this position the participant will descend down into a squat, simultaneously flexing at the hips and knees, this will represent the eccentric portion of the repetition. The concentric portion

of the lift will begin when the hip and knee are in roughly 80-90 degrees of flexion (depending upon individual flexibility, comfort, and anthropometry). From this position participants will begin to extend both the hip and knee in concert to lift the weight. The participant will continue to press with the legs until the hip and knee reach a point just prior to full extension, this will represent the end of the concentric phase. Participants will be coached to inhale during the eccentric, and exhale during the concentric portion of each lift. The repetitions will follow a 2:1 tempo (2 second eccentric, 1 second concentric), and participants will be coached to maintain some muscular contraction (tension) at maximal flexion.

Figure 2. Example of the starting and finish positions in the Belt Squat.

Single Arm Biceps Curl

Participants will begin in a standing position securely gripping the dumbbell in one hand. The weight will be resting at the side of the body with the elbow extended. At the onset of each repetition the participant will forcefully contract the musculature of the biceps brachii, thus drawing the hand in a supinated position up towards the anterior deltoid. This will represent the terminus of concentric muscular activity for each rep. From here the elbow will be extended back to the starting position (eccentric phase). Participant s will be coached to inhale during the eccentric, and exhale during the

concentric portion of each lift. The repetitions will follow the previously established tempo, and participants will be coached to maintain some muscular contraction (tension) in the hamstring at the bottom of the movement.

Figure 3. Example of the starting and finish positions in the Single arm Biceps Curl.

Single Arm Triceps Extension

Participants will begin in a standing position with feet staggered and a forward leaning torso. The triceps of the working arm will be placed against a padded bench for support and stability. With the working arm participants will securely grip the handle of the modified pulley system placing the elbow in a flexed position at approximately 45º. At the onset of each repetition the participant will forcefully contract the musculature of the triceps, thus drawing the hand in a neutral position down until the heel of the hand is in contact with the padded bench. This will represent the terminus of concentric muscular activity for each rep. From here the elbow will be flexed back to the starting position (eccentric phase). Participants will be coached to inhale during the eccentric, and exhale during the concentric portion of each lift. The repetitions will follow the previously established tempo, and participants will be coached to maintain some muscular contraction (tension) in the hamstring at the bottom of the movement.

Figure 4. Example of the starting and finish positions in the Single arm Triceps Extension.

Primary Home-based Resistance Exercises

Squat

At the onset of each rep the participant will begin standing with feet just outside shoulder width apart, toes flared slightly out to the sides. The participant's knees and hips will be extended. From this position the participant will descend down into a squat, simultaneously flexing at the hips and knees, this will represent the eccentric portion of the repetition. The concentric portion of the lift will begin when the hip and knee are in roughly 80-90 degrees of flexion (depending upon individual flexibility, comfort, and anthropometry). From this position participants will begin to extend both the hip and knee in concert to lift the weight. The participant will continue to press with the legs until the hip and knee reach a point just prior to full extension, this will represent the end of the concentric phase. Participants will be coached to inhale during the eccentric, and exhale during the concentric portion of each lift. The repetitions will follow a 2:1 tempo (2 second eccentric, 1 second concentric), and participants will be coached to maintain some muscular contraction (tension) at maximal flexion.

Figure 5. Example of the starting and finish positions in the Squat.

Push-up

At the onset of each repetition the participant will begin face down on the ground with four points of contact (hands & toes / balls of feet). The musculature of the upper and lower body will be contracted isometrically throughout the exercise to maintain posture (straight line through heels, hips, shoulders and head). Beginning with arms outstretched (just outside shoulder width) the participant will flex the elbow and extend the shoulder drawing the chest towards the ground, this represents the eccentric portion of the exercise. When the chest is approximately 1/5 inches from the ground the participant will forcefully contract the chest, deltoids and triceps, reversing the movement at the elbow and shoulder and returning to the starting position, this represents the concentric phase of the exercise. Participants will be coached to inhale during the eccentric, and exhale during the concentric portion of each lift. The repetitions will follow a 2:1 tempo (2 second eccentric, 1 second concentric), and participants will be coached to maintain some muscular contraction (tension) at maximal flexion.

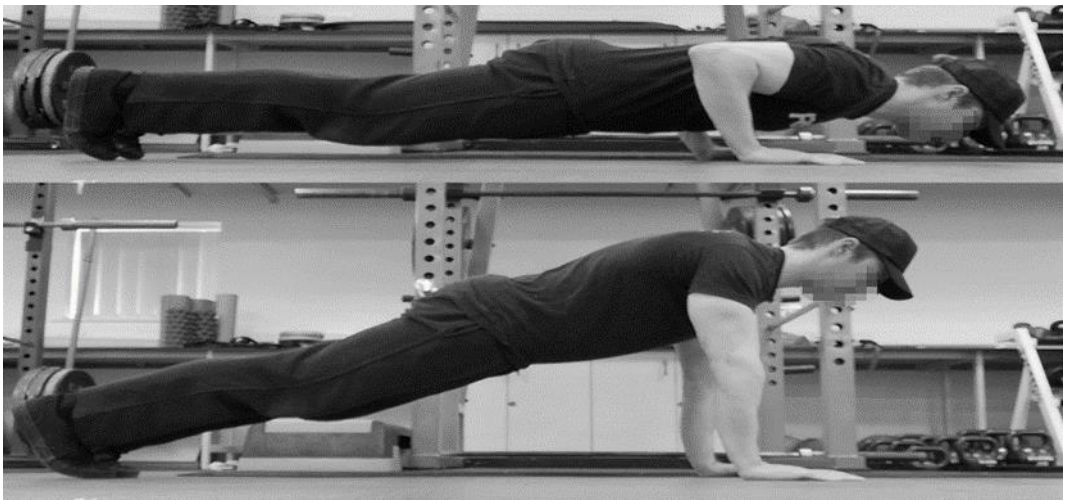

Figure 6. Example of the starting and finish positions in the Push-up.

Seated Row

At the onset of each repetition the participant will begin sat on the ground with their legs straight out in front of themselves. The arms will be outstretched in front of the torso (towards the feet), firmly grasping a resistance band anchored underneath the feet. The concentric portion of the repetition will be initiated when the participant contracts the musculature of the upper back (trapezius. Latissimus dorsi), posterior deltoid and biceps. This contraction will lead to flexion of the elbow and extension of the shoulder. When the hands are in roughly in line with the sternum the eccentric portion of the exercise will begin, reversing the movement at the elbow and shoulder until the participant returns to the starting position. Participants will be coached to inhale during the eccentric, and exhale during the concentric portion of each lift. The repetitions will follow a 2:1 tempo (2 second eccentric, 1 second concentric), and participants will be coached to maintain some muscular contraction (tension) at maximal flexion.

Figure 7. Example of the starting and finish positions in the Bent-over Row.

Hip Thrust

At the onset of each repetition the participant will begin with the feet placed shoulder width apart, upper back (just below shoulder blades) supported roughly 1 foot above the ground, hips and knees flexed at approximately 90 degrees (glutes not in contact with the ground). Throughout the movement the torso will remain in a fixed position, with the participant contracting the abdominal muscles to draw the rib cage down towards the hips. The concentric portion of the lift will be initiated with a strong gluteal contraction to extend the hip. The transition from concentric to eccentric will begin when the hips are fully extended with a slight posterior pelvic tilt (90 degree angle of the knee maintained throughout). Participants will be coached to inhale during the eccentric, and exhale during the concentric portion of each lift. The repetitions will follow a 2:1 tempo (2 second eccentric, 1 second concentric), and participants will be coached to maintain some muscular contraction (tension) at maximal flexion.

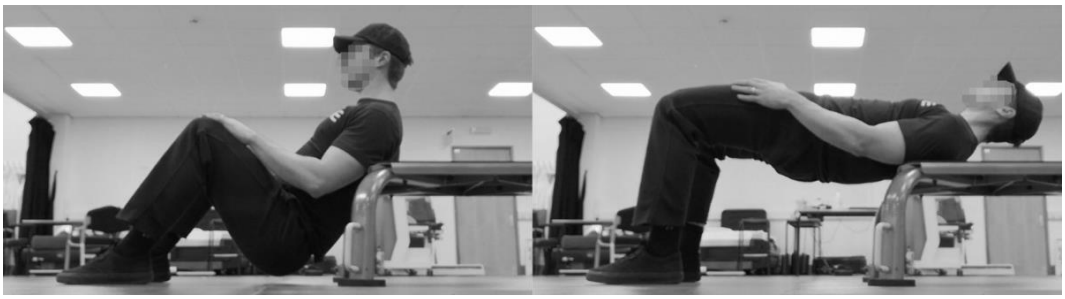

Figure 8. Example of the starting and finishing position in the Hip Thrust.

Shoulder Press

At the onset of each repetition the participant will begin sat on the ground with their legs placed through a resistance band (anchored to the ground under the glute muscles). The participant will clasp the opposing end of the resistance band in each hand, positioning the band between the top of the chest and the chin. The concentric portion of the lift will consist of elbow and shoulder extension. The band will be drawn overhead until the biceps are aligned vertically with the ears, this represents the end of concentric contraction. The process will be reversed until the participant is again in the start position. Participants will be coached to inhale during the eccentric, and exhale during the concentric portion of each lift. The repetitions will follow a 2:1 tempo (2 second eccentric, 1 second concentric), and participants will be coached to maintain some muscular contraction (tension) at maximal flexion.

Figure 9. Example of the starting and finishing position in the Shoulder Press.

Banded Pull-Apart

At the onset of each repetition the participant will begin stood with arms outstretched horizontally in front of the torso. In each hand the participant will clasp a section of resistance band. The hands will be roughly shoulder width apart (with minor flexion of the elbow) applying slight tension to the resistance band. The concentric portion of the lift will begin when the participant forcefully pulls the band apart by horizontally abducting the shoulder. The end of concentric and beginning of eccentric contraction

will be reached when the resistance band comes into contact with the sternum. The shoulders will then pass through horizontal adduction until the participant is once again in the start position. Participants will be coached to inhale during the eccentric, and exhale during the concentric portion of each lift. The repetitions will follow a 2:1 tempo (2 second eccentric, 1 second concentric), and participants will be coached to maintain some muscular contraction (tension) at maximal flexion.

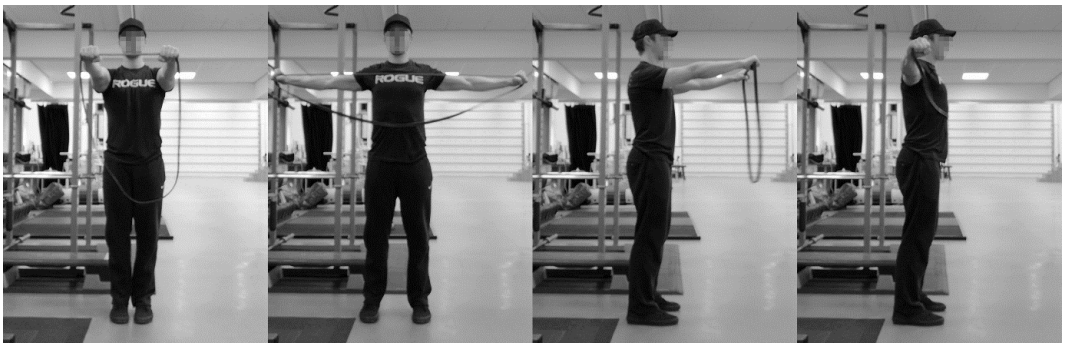

Figure 10. Example of the starting and finishing position in the Banded Pull-Apart.

Deadlift

At the onset of each repetition the participant will begin stood with feet shoulder width apart, knees slightly flexed and spine in a neutral position. A resistance band will be anchored between the ground and the mid foot with each end clasped securely in the hands. At this starting position the band will be stretched and under tension. In contrast to other exercises the movement will be initiated with an eccentric contraction as the participant flexes at the hips (major) and knees (minor). Throughout the movement the upper body will maintain a neutral position with the arms remaining perpendicular to the ground. At the end of the eccentric phase the hips and knees will be flexed to roughly 90-100 and 20-45 degrees respectively. Concentric contraction will primarily occur in the hamstrings and glutes extending the hips and knees to the starting position. Participants will be coached to inhale during the eccentric, and exhale during the concentric portion of each lift. The repetitions will follow a 2:1 tempo (2

second eccentric, 1 second concentric), and participants will be coached to maintain some muscular contraction (tension) at maximal flexion.

Figure 11. Example of the starting and finishing position in the Deadlift.

Triceps Extension

At the onset of each repetition the participant will begin stood in a staggered stance. If the left arm is to be exercised then the left leg must be the rear foot. A resistance band will be anchored under the heel of the rear foot. Both knees will be slightly bent and the torso will remain neutral with a slight forward inclination (≈10-30 degrees). The exercising arm will be fully flexed at the elbow, with the shoulder extended overhead until it lies as close to parallel with the ear as flexibility will permit. The resistance band will be securely clasped in the exercising hand. At the onset of the concentric phase, the triceps will be contracted to extend the elbow overhead. Once the elbow is fully extended, the motion will be reversed until the participant is once again in the start position. Participants will be coached to inhale during the eccentric, and exhale during the concentric portion of each lift. The repetitions will follow a 2:1 tempo (2 second

eccentric, 1 second concentric), and participants will be coached to maintain some muscular contraction (tension) at maximal flexion.

Figure 12. Example of the starting and finishing position in the Triceps Extension.

Biceps Curl

At the onset of each repetition the participant will begin stood with feet shoulder width apart, knees slightly flexed and spine in a neutral position. A resistance band will be anchored between the ground and the mid foot with each end clasped securely in the hands. The participant will contract the biceps thus generating flexion at the elbow joint, this represents the concentric phase of the exercise. Once the hands are in line with the shoulders, the motion will be reversed until the participant is once again in the start position. Participants will be coached to inhale during the eccentric, and exhale during the concentric portion of each lift. The repetitions will follow a 2:1 tempo (2 second eccentric, 1 second concentric), and participants will be coached to maintain some muscular contraction (tension) at maximal flexion.

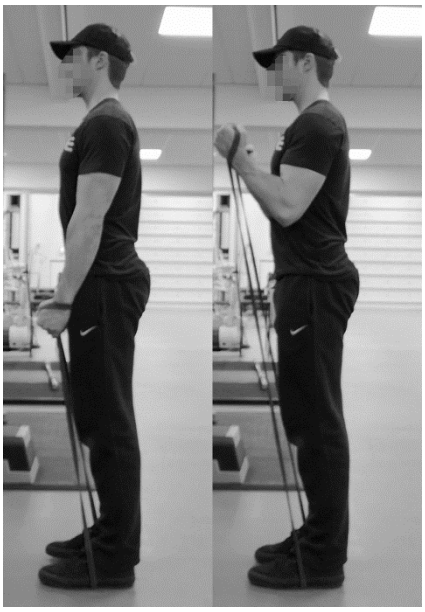

Figure 13. Example of the starting and finishing position in the Biceps Curl.

Pallof Press

At the onset of each repetition the participant will begin stood with feet shoulder width apart, arms outstretched (horizontally), knees slightly flexed and spine in a neutral position. A resistance band will be anchored approximately one meter in front of the participant at a 45 degree angle. The participant will firmly grasp the band with both hands, in this configuration the tension applied by the band will be isometrically challenging the abdominal musculature. From this start position the participant will draw the hands vertically towards the sternum. When the hands are approximately 1-2 inches from the sternum the motion will be reversed until the participant is once again in the start position.

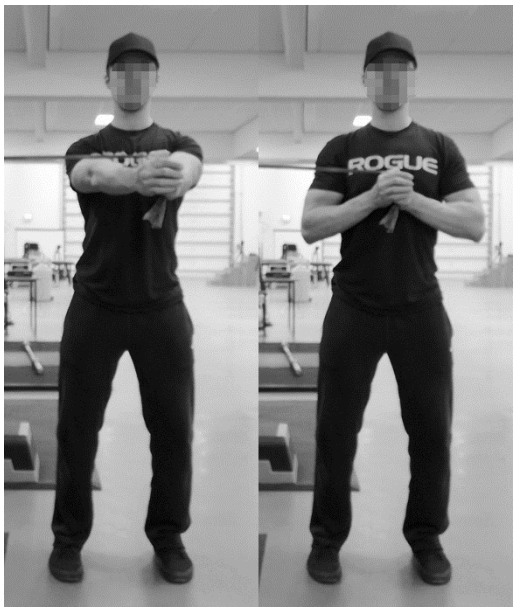

Figure 14. Example of the starting and finishing position in the Pallof Press.

Plank

At the onset of each repetition the participant will begin in a similar position as the push-up. However, as opposed to having their weight supported over the hands, the participant will spread their weight across the forearms. This movement will not contain concentric and eccentric contraction, instead the position will be maintained through isometric contraction for a maximal period of time.

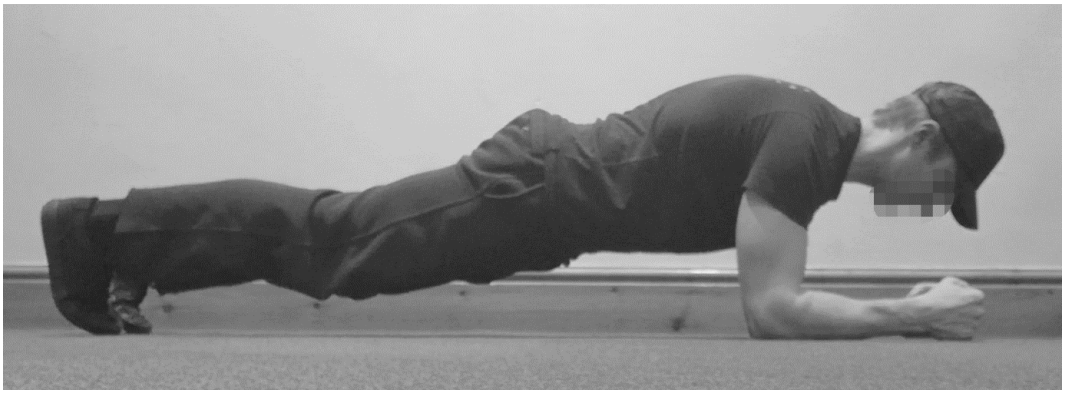

Figure 15. Example of the starting and finishing position in the Plank.

Safety

Maximal strength testing has proven to be a safe procedure in young, old diseased and healthy participants (Adams et al., 2000; Barnard et al., 1999; Faigenbaum et al., 2003).

Cardiopulmonary exercise testing does increased the chance of adverse events, however the likelihood of this happening is low, occurring in <0.16% of tests (Skalski, Allison, & Miller, 2012).

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