THE UNIVERSITY OF HULL

The Cardiorespiratory and Vascular Adaptations to a Routine UK
Exercise Based Cardiac Rehabilitation Programme

Being a Thesis submitted for the Degree of Doctor of Philosophy
in the University of Hull

Department of Sport, Health & Exercise Science

by

Simon J. Nichols BSc

December 2015

Acknowledgements

I would like to express my profound gratitude to my supervisor, Prof. Lee Ingle for his encouragement, support and guidance. His knowledge of, and interest in cardiac rehabilitation, exercise testing and prescription have been invaluable in my time as a PhD student. I would also like to thank Prof. Sean Carroll and Dr James Hobkirk for their supervision and advice which has undoubtedly helped shape and facilitate my programme of research.

Many aspects of my research would not have been possible without the support of nursing and management staff working for City Health Care Partnership CIC. I wish to extend my thanks to Toni Goodman for facilitating our research project and, for supporting me in my decision to undertake this PhD. I would also like to express my appreciation to Wendy, Lesley and Emma who have promoted my study to their patients. The input and support of the cardiac rehabilitation physiotherapy staff has also been greatly valued.

Thank you to all of the staff at Academic Cardiology who have so freely offered their support and advice, specifically Prof. Clark who has kindly allowed me to use his laboratory and, Anna Bennet who conducted echocardiograms on all of my patients. I would also like to express my gratitude to Claire Taylor who has so keenly invested her time into to this project.

Finally, the support of my family and friends has been greatly appreciated. They have given me the determination to complete this work to the best of my ability. This thesis is dedicated to my wife Nerys and my son, Joshua.

List of Publications

NICHOLS, S., TAYLOR, C. & INGLE, L. 2015. A clinician's guide to cardiopulmonary exercise testing 2: test interpretation. *British Journal of Hospital Medicine,* 76**,** 281-289.

TAYLOR, C., NICHOLS, S. & INGLE, L. 2015. A clinician's guide to cardiopulmonary exercise testing 1: an introduction. *British Journal of Hospital Medicine,* 76**,** 192-5.

NICHOLS, S., MILNER, M., MEIJER, R., CARROLL, S. & INGLE, L. 2014. Variability of automated carotid intima-media thickness measurements by novice operators. *Clinical Physiology and Functional Imaging*.

Published Abstracts

NICHOLS, S., MILNER, M., MEIJER, R., CARROLL, S. & INGLE, L. 2014a. Automated carotid Intima-media thickness measurements in healthy, young- to middle-aged adults: immediate and 1-week inter- and intra-observer variability by novice operators. *Journal of Sports Sciences,* 32**,** s78-s86.

Presentations

NICHOLS, S., MILNER, M., MEIJER, R., CARROLL, S. & INGLE, L. 2014c. Automated carotid Intima-   media thickness measurements in healthy, young- to middle-aged adults: immediate and 1-week inter- and intra-observer variability by novice operators. *British Association of Sport and Exercise Sciences.*

Letters to the Editor

NICHOLS, S., CARROLL, S. & INGLE, L. 2014a. *Automated Carotid IMT Measurements Undertaken by Novice Operators* [Online]. European Heart Journal - Cardiovascular Imaging: Oxford University Press. Available: http://ehjcimaging.oxfordjournals.org/content/15/6/637.explore.

General Abstract

Introduction: Recent data suggests that UK cardiac rehabilitation (CR) programmes do not substantially improve cardiorespiratory fitness (CRF) or patient survival. The exercise dose prescribed as part of a routine CR programme may be insufficient. The aims of the thesis were to (i) investigate whether a routine UK CR exercise training programme could improve peak oxygen consumption (VO_{2peak}) and, (ii) reduce carotid intima-media thickness (C-IMT) progression in patients with coronary heart disease (CHD) and, (iii) determine whether higher exercise training doses prescribed to patients with CHD through a tele-monitoring system elicit superior VO_{2peak} improvements compared to routine CR alone.

Study One: We recruited n=34 patients (85.3% male; age 62.1 ± 8.8 years; body mass index [BMI] 29.5 ± 4.5 $Kg·m^{-2}$) who had recently been diagnosed with CHD. n=22 patients formed an exercise training group (TG) and undertook an eight week (16 session) low to moderate intensity (40-70% peak heart rate reserve), routine CR exercise training programme. n=12 patients declined routine CR and were assigned to a non-exercise control group (CG). Patients in the training group were followed up after completing their exercise training programme. Controls were followed up approximately 8 to 10 weeks after their initial visit (visit 2). Both groups were followed up 12 months later. VO_{2peak} change was determined in all patients via "gold standard" maximal cardiopulmonary exercise testing (CPET) using the modified Bruce treadmill protocol. C-IMT progression was also determined using B-mode ultrasound.

In the UK, submaximal exercise tests such as cycle ergometry are typically used to assess CRF change following CR. Submaximal cycle ergometry (intensities up to 70% heart rate reserve) was used to estimate changes in CRF. Submaximal cycle ergometry showed a mean improvement of 1.64 METs (95% CI 1.20 to 2.09 METs; p<0.001). However, "gold standard" maximal CPET showed that this equated to no significant change in VO_{2peak} (Δ change: 0.12 $ml·kg^{-1}·min^{-1}$; 95% CI -1.00 to 1.24 $ml·kg^{-1}·min^{-1}$). No VO_{2peak} improvement was detected in controls (Δ change: 0.15 $ml·kg^{-1}·min^{-1}$; 95% CI -1.37 to 1.66 $ml·kg^{-1}·min^{-1}$; p=0.978). VO_{2peak} remained unchanged after 12 months amongst patients in the TG (Δ -0.94 $ml·kg^{-1}·min^{-1}$; range -6.09 to 2.10 $ml·kg^{-1}·min^{-1}$; p=0.846). Controls experienced C-IMT progression in the right lateral aspect of their common carotid artery (CCA) at the end of the eight week CR period (Δ change: 0.070 mm; range -0.060 to 0.200 mm; p=0.038). Patients in the TG experienced C-IMT reduction in the left lateral aspect of their CCA between CR programme completion and their 12 month follow-up (Δ change: 0.054 mm; range -0.160 to 0.020 mm; p=0.015).

Study Two: We recruited n=50 healthy volunteers (60% male; age 26.2 ± 5.0 years; BMI 24.6 $kg·m^{-2}$) to examine the intra and inter-operator variability of automated c-IMT measurements when taken by novice operators. Two novice operators performed serial bilateral C-IMT ultrasound measurements using the CardioHealth Station (Panasonic Biomedical Sales Europe BV, Leicestershire, UK). Immediate inter-operator variability was determined by comparing operators' initial measurements. Immediate retest variability was determined by comparing consecutive measurements (<10 minutes apart). Longer-term variability was determined by comparing operators' initial measurements to a third set of measurements conducted one week later. Bland-Altman analysis and intraclass correlations were conducted. The limits of agreement (LoA) for immediate *inter*-operator variability were -0.063 to 0.056 mm (mean bias -0.003 mm). Operator 1's immediate retest *intra*-operator LoA were -0.057 to 0.046 mm (mean bias was -0.005 mm). Operator 1's *intra*-operator LoA at one week were -0.057 to 0.050 mm (mean bias -0.003 mm). Operator 2's LoA were similar to those of operator 1. Novice operators produce acceptable short-term and one week inter- and intra-operator C-IMT measurement variability in healthy, young to middle aged adults using the Panasonic CardioHealth Station.

Study Three: We recruited n=27 patients with a diagnosis of CHD (88.9% male; age 59.5 ± 10.0 years; BMI 29.6 ± 3.8 $kg·m^{-2}$). VO_{2peak} change was quantified in n=10 patients receiving routine CR plus personalised exercise training based on maximal CPET data delivered via a bespoke tele-monitoring device. VO_{2peak} change was also determined in n=17 patients receiving routine CR only. CPET was performed using a 25W stepped cycle ergometry protocol. The combination of routine CR and a bespoke exercise training programme significantly increase VO_{2peak} (Δ change: 2.08 $ml·kg_{-1}·min_{-1}$; 95% CI 1.88 to 3.97 $ml·kg_{-1}·min_{-1}$; p=0.014) compared to routine CR alone (Δ change: -0.29 $ml·kg_{-1}·min_{-1}$; 95% CI -1.75 to 1.16 $ml·kg^{-1}·min^{-1}$; p=0.841).

Conclusions: An eight week (16 session) low to moderate intensity (40-70% peak heart rate reserve) CR exercise training programme, typical of many programmes in the UK, does not improve direct measurements of VO_{2peak} on treadmill or cycle ergometer protocols. Current assessment methods utilising submaximal exercise testing may be overstating the effect of CR exercise interventions on CRF. Current UK recommendations for exercise training doses may also be inadequate. Data within study three indicates that a minimum of 13 sessions over a 12 week period may be required to improve VO_{2peak}. Limited evidence indicates that routine CR with structured exercise training may attenuate C-IMT progression compared with usual care control participants. This anti-atherosclerotic effect may be related to lower coronary risk factors and better adherence to other secondary prevention measures. Overall, higher exercise training doses and personalised exercise prescription derived from maximal CPET data appeared necessary for attaining significant CRF improvements in patients with CHD.

List of Abbreviations

a-vO$_2$ diff	Arterio-Venous Oxygen Difference
AACVPR	American Association of Cardiovascular and Pulmonary Rehabilitation
ACPICR	Association of Chartered Physiotherapists in Cardiac Rehabilitation ACE Angiotensin Converting Enzyme
ACS	Acute Coronary Syndrome
ACSM	American College of Sports Medicine
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
Ant	Anterior
AR	Active Recovery
AUC	Area under the Curve
BACPR	British Association for Cardiovascular Prevention and Rehabilitation
BACR	British Association for Cardiac Rehabilitation
BMI	Body Mass Index
BP	Blood Pressure
BPM	Beats per Minute
C-IMT	Carotid Intima-Media Thickness
CABG	Coronary Artery Bypass Graft
CCA	Common Carotid Artery
CG	Control Group
CHD	Coronary Heart Disease
CHF	Chronic Heart Failure
CHS	CardioHealth Station
COPD	Chronic Obstructive Pulmonary Disease
CoV%	Coefficient of Variation
CPET	Cardiopulmonary Exercise Test
CR	Cardiac Rehabilitation
CRF	Cardiorespiratory Fitness
CRT	Cardiac Resynchronisation Therapy
CV	Cardiovascular
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
DXA	Duel X-Ray Absorptiometry
ECG	Electrocardiogram
EF	Ejection Fraction
eMVV	Estimated Maximal Voluntary Ventilation
ERY	East Riding of Yorkshire
ETT	Exercise Tolerance Testing
FEV$_1$/FVC	Ratio of Forced Expiratory Volume in one second to Forced Vital Capacity
FEV$_1$	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GEx	Guided Exercise
GTN	Glyercyl Trinitrate
HDL	High Density Lipoproteins
HIIT	High Intensity Interval Training
HR	Heart Rate
HR$_{max}$	Maximum Heart Rate
HRR	Heart Rate Reserve
ICC	Intraclass Correlation

ICD	Implantable Cardioverter Defibrillator
IMT	Intima-Media Thickness
IQR	Interquartile Range
ISWT	Incremental Shuttle Walk Test
IVUS	Intravenous Ultrasound
Kg	Kilograms
$Kg \cdot m^{-2}$	Kilograms per metre squared
Lat	Lateral
LDL	Low Density Lipoproteins
LoA	Limits of Agreement
LV	Left Ventricular
MCID	Minimal Clinically Importance Difference
METs	Metabolic Equivalents
MI	Myocardial Infarction
$ml \cdot kg^{-1} \cdot min^{-1}$	Millilitres per Kilogram per Minute
mmHg	Millimetres of Mercury
MMV	Maximum Voluntary Ventilation
NACR	National Audit for Cardiac Rehabilitation
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSTEMI	Non-ST Elevation Myocardial Infarction
NYHA	New York Heart Association
O1	Operator 1
O2	Operator 2
O_2	Oxygen
O_2/HR	Oxygen Pulse
OR	Odds Ratio
OUES	Oxygen Uptake Efficiency Slope
PaO_2	Partial Pressure of Arterial O_2
$PaCO_2$	Partial Pressure of Arterial CO_2
PCI	Percutaneous Coronary Intervention
PDA	Personal Digital Assistant
POBA	Plain Old Balloon Angioplasty
POS	Posterior
PPCI	Primary Percutaneous Coronary Intervention
Q	Cardiac Output
RER	Respiratory Exchange Ratio
RHR	Resting Heart Rate
ROC	Receiver Operating Characteristics
ROI	Region of Interest
RPE	Rating of Perceived Exertion
RPP	Rate Pressure Product
RR	Relative Risk
SBP	Systolic Blood Pressure
SD	Standard Deviation
Secs	Seconds
SPO_2	Peripheral Capillary Oxygen Saturation
STEMI	ST Elevation Myocardial Infarction
SV	Stroke Volume
TC	Total Cholesterol
TG	Treatment Group
TIA	Transient Ischaemic Attack
TM	Tele-Monitoring

UK	United Kingdom
VAT	Ventilatory Anaerobic Threshold
VCO_2	Volume of Expired Carbon Dioxide
V_D	Ventilatory Dead Space
VE	Minute Ventilation
VE_{log10}	Log 10 Transformed Minute Ventilation
VE/VCO_2 Slope	Slope-Relationship between Minute Ventilation and Carbon Dioxide Elimination
VO_2	Oxygen Uptake
VO_{2max}	Maximum Oxygen Uptake
VO_{2peak}	Peak Oxygen Uptake
V_T	Ventilatory Tidal Volume
W	Watt
WHO	World Health Organisation
W/H Ratio	Waist to Hip Ratio
95% CI	95% Confidence Interval
η_p^2	Partial Eta Squared
$\Delta VO_2/\Delta WR$ Slope	Change in Oxygen Uptake versus Change in Work Rate Slope [La$^-$]b Blood Lactate

Table of Contents

Chapter 1: Introduction

2.1 Background

In the UK More than 161,000 people die from cardiovascular disease (CVD) each year, of which, approximately 73,000 deaths can be attributed to coronary heart disease (CHD). More than 2.3 million people in the UK are currently living with CHD with an associated financial cost of £1.6 billion (Townsend et al., 2014). Cardiovascular (CV) risk factor reduction plays an important role in reducing CHD related morbidity and mortality (Unal et al., 2004). Multiple interventions have been shown to improve CV risk factors including poor cardiorespiratory fitness (CRF), psychosocial health, diet, dyslipidaemia, hypertension and, smoking status (Arrigo et al., 2008, Ornish et al., 1998, Gayda et al., 2008, Milani and Lavie, 2007, Timin et al., 2002, Ades et al., 2009b, Wilson et al., 2000, Carroll et al., 2011, Sandercock et al., 2011). Following a cardiac event, interventions designed to address these CV risk factors can be delivered as a programme of secondary prevention, collectively, known as cardiac rehabilitation (CR).

In the UK, CR is recommended for most patients with CHD. The aim of CR is to improve survival, reduce morbidity and hospital admissions, improve functional capacity, quality of life and, facilitate early return to work (BACPR, 2012b, Bethell et al., 2009, Heran et al., 2011, Jolliffe et al., 2001, Uddin et al., 2015). Although no longer the sole component of CR, exercise training is still identified as one of the primary elements (BACPR, 2012b). Exercise training may make the single largest contribution to improving patient survival (Jolliffe et al., 2001). Taylor et al. (2006) suggested that exercise training alone leads to a 28% mortality reduction in patients undertaking routine short-term CR. This may be in part attributed to VO_{2peak} improvement. A 1% VO_{2peak} increase may confer a 2% reduction in mortality (Vanhees et al., 1995). Improving VO_{2peak} should be a primary therapeutic objective of all CR teams. However, to achieve this, adequate exercise training doses are required (Haskell, 2001).

It has been suggested that the dose of exercise prescribed in some UK CR programmes may be

insufficient to improve CRF (Ingle and Carroll, 2013, Sandercock et al., 2013a). UK exercise training guidelines themselves acknowledge their conservative nature (ACPICR, 2015) in relation to evidence from existing studies (Belardinelli et al., 2001, Bethell et al., 1983, Fletcher et al., 1994, Seki et al., 2008, Seki et al., 2003). The impact of conservative guidance on exercise training efficacy may also be confounded by chronic CR programme under funding (O'Driscoll et al., 2007) leading to limited programme availability and inadequate exercise dose. Brodie et al. (2006) reported that UK CR programmes only include an average of 11.6 exercise sessions conducted over 4 to 12 weeks (approximately one to three sessions per week). The ACSM (2013) recommend delivering four to seven structured exercise sessions per week (32 to 56 sessions over eight weeks to patients with CHD. CHD patients participating in international exercise training studies who received approximately 36 exercise sessions experience a three-fold greater CRF improvement (1.55 metabolic equivalents [METs]) compared to UK patients who conduct between 6 and 16 sessions [0.52 METs] (Sandercock et al., 2011, Sandercock et al., 2013b). Fewer than 50% of patients completing a 'typical' UK CR programme may achieve minimal clinically important improvements to CRF (Houchen-Wolloff et al., 2014). UK CR exercise training programmes may be severely 'under dosed'. Furthermore, there is evidence that exercise doses greater than those delivered in UK CR programmes (ACPICR, 2015) are needed to attenuate the underlying coronary atherosclerotic process (Hambrecht et al., 2004, Niebauer et al., 1997).

If reduced all-cause and cardiovascular mortality, hospital readmissions, and coronary disease recurrence are serious aims of CR (BACPR, 2012b), a reduction in the atherosclerotic phenotype is desirable. A dose-response relationship between VO_{2peak} improvement and exercise training volume exists (Vanhees et al., 1995) with higher doses conferring greater VO_{2peak} improvement. Higher exercise training doses may underpin CHD regression (Hambrecht et al., 2004). The modest improvements to UK CR patients' CRF (Sandercock et al., 2013b) could indicate that the training dose in routine CR is too low to meaningfully affect CHD progression. However, to

determine this, a measurement of atherosclerosis progression is needed.

Investigations such as coronary angiography or intravascular ultrasound permit the quantification of changes in coronary atherosclerosis (Amato et al., 2007). These procedures are highly invasive and impractical in many research settings. A non-invasive surrogate marker of sub-clinical atherosclerosis, such as carotid intima-media thickness (C-IMT) is a practical, valid and reliable alternative (Pignoli et al., 1986, Nichols et al., 2014c, Amato et al., 2007). Whilst some data suggest that exercise training may reduce C-IMT in patients at elevated CV risk (Feairheller et al., 2014, Kim et al., 2006), no UK study has investigated whether a routine CR exercise training programme can achieve this goal.

There is a clear mandate to investigate the efficacy of routine CR in the UK and the limited existing evidence requires verification. A multi-centre study by Sandercock et al. (2013b) examined CRF changes in patients receiving outpatient CR in the UK. However, this study adopted an estimative approach to determining CRF using METs derived from serial exercise testing. The appropriateness of using METs to evaluate CRF change in CHD cohorts is not well validated (Milani et al., 1995). Furthermore, the absence of control groups limits the inferences that can be drawn from Sandercock and colleagues' work (2013b). Routine CR may not substantially improve CRF but it may prevent clinical deterioration. The finding that UK CR patients may only experience a 0.52 MET CRF increase (VO$_2$ increase = 1.8 ml$\cdot$kg$^{-1}\cdot$min^{-1}) requires substantiating (Sandercock et al., 2013b) through a controlled trial using 'gold standard' maximal cardiopulmonary exercise testing (CPET). The effect of exercise training clinically-imaged atherosclerosis should also be investigated. Only by evaluating changes to CV health and CRF is it possible to determine the true efficacy of routine CR in the UK.

2.2 Aims

The aim of this thesis was to determine the CV and CRF adaptations in response to a routine CR exercise training programme. Specifically, using 'gold standard' maximal CPET we aimed to determine whether an eight week (16 session) low to moderate intensity UK CR exercise training programme could improve VO_{2peak}. We also investigated whether C-IMT progression, a marker of sub-clinical atherosclerosis was attenuated as a result of participating in the same regime. A personalised exercise training regime using a higher 'exercise dose' was then prescribed to patients undertaking routine CR to assess whether enhanced VO_{2peak} improvements were attained.

2.3 Hypotheses

2.3.1 Study 1 (Chapter 3)

Research Hypothesis (H_1):

A low to moderate intensity (40-70% heart rate reserve) routine cardiac rehabilitation exercise training programme conducted twice weekly for eight weeks will significantly improve VO_{2peak} assessed via maximal cardiopulmonary exercise testing.

2.3.2 Study 2 (Chapter 4)

Research Hypothesis (H_1):

A low to moderate intensity (40-70% heart rate reserve) routine cardiac rehabilitation exercise training programme conducted twice weekly for eight weeks will attenuate carotid intima-media thickness progression (assessed via B-mode ultrasound) in participants compared to controls.

2.3.3   Study 3 (Chapter 5)

Research Hypothesis (H_1):

An increased exercise training dose (routine cardiac rehabilitation combined with a personalised tele-monitored exercise prescription) will significantly improve directly- determined VO_{2peak} compared to changes evident in participants undertaking routine cardiac rehabilitation alone.

2.4   References

ACPICR 2015. Standards for physical activity and exercise in the cardiovascular population.   *In:* HEATHER, P., HELEN, B., SAMANTHA, B., JOHN, B., LAURA BURGESS, KERI, G., FIONA, G., TIM GROVE, SALLY TURNER & CATRIN, W. (eds.) 3rd ed.: Association of Chartered Physiotherapists in Cardiac Rehabilitation (ACPICR).

ACSM 2013. *ACSM's Guidelines for exercise testing and prescription,* Philadelphia, Wolters Kluwer/Lippincott Williams & Wilkins Health.

ADES, P. A., SAVAGE, P. D., TOTH, M. J., HARVEY-BERINO, J., SCHNEIDER, D. J., BUNN, J. Y., AUDELIN, M. C. & LUDLOW, M. 2009. High-calorie-expenditure exercise: a new approach to cardiac rehabilitation for overweight coronary patients. *Circulation,* 119**,** 2671-8.

AMATO, M., MONTORSI, P., RAVANI, A., OLDANI, E., GALLI, S., RAVAGNANI, P. M., TREMOLI, E. & BALDASSARRE, D. 2007. Carotid intima-media thickness by B-mode ultrasound as surrogate of coronary atherosclerosis: correlation with quantitative coronary angiography and coronary intravascular ultrasound findings. *European Heart Journal,* 28**,** 2094-2101.

ARRIGO, I., BRUNNER-LAROCCA, H., LEFKOVITS, M., PFISTERER, M. & HOFFMANN, A. 2008. Comparative outcome one year after formal cardiac rehabilitation: the effects of a randomized intervention to improve exercise adherence. *European Journal of Cardiovascular Prevention & Rehabilitation,* 15**,** 306-311.

BACPR. 2012. Standards and Core Components for Cardiovascular Disease Prevention and Rehabilitation. Available: http://www.bacpr.com/resources/.

BACR 2006. *British Association For Cardiac Rehabilitation: Exercise instructor training   module,* Leeds, Human Kinetics.

BETHELL, H., LEWIN, R. & DALAL, H. 2009. Cardiac rehabilitation in the United Kingdom. *Heart,* 95**,** 271-275.

BRODIE, D., BETHELL, H. & BREEN, S. 2006. Cardiac rehabilitation in England: a detailed national survey. *European Journal of Cardiovascular Prevention & Rehabilitation,* 13**,** 122-128.

BYRNE, N. M., HILLS, A. P., HUNTER, G. R., WEINSIER, R. L. & SCHUTZ, Y. 2005. Metabolic equivalent: one size does not fit all. *Journal of Applied physiology,* 99**,** 1112-1119.

CARROLL, S., TSAKIRIDES, C., HOBKIRK, J., MOXON, J. W. A., MOXON, J. W. D., DUDFIELD, M. & INGLE, L. 2011. Differential Improvements in Lipid Profiles and Framingham Recurrent Risk Score in Patients With and Without Diabetes Mellitus Undergoing Long-Term Cardiac Rehabilitation. *Archives of Physical Medicine and Rehabilitation,* 92**,** 1382- 1387.

FEAIRHELLER, D. L., DIAZ, K. M., KASHEM, M. A., THAKKAR, S. R., VEERABHADRAPPA, P., STURGEON, K. M., LING, C., WILLIAMSON, S. T., KRETZSCHMAR, J. & LEE, H. 2014. Effects of moderate aerobic exercise training on vascular health and blood pressure in African Americans. *The Journal of Clinical Hypertension,* 16**,** 504-510.

GAYDA, M., BRUN, C., JUNEAU, M., LEVESQUE, S. & NIGAM, A. 2008. Long-term cardiac rehabilitation and exercise training programs improve metabolic parameters in metabolic syndrome patients with and without coronary heart disease. *Nutrition, Metabolism and Cardiovascular Diseases,* 18**,** 142-151.

HAMBRECHT, R., WALTHER, C., MÖBIUS-WINKLER, S., GIELEN, S., LINKE, A., CONRADI, K., ERBS, S., KLUGE, R., KENDZIORRA, K., SABRI, O., SICK, P. & SCHULER, G. 2004. Percutaneous Coronary Angioplasty Compared With Exercise Training in Patients With Stable Coronary Artery Disease: A Randomized Trial. *Circulation,* 109**,** 1371-1378.

HASKELL, W. L. 2001. What to look for in assessing responsiveness to exercise in a health context. *Med Sci Sports Exerc,* 33**,** S454-8; discussion S493-4.

HERAN, B. S., CHEN, J., EBRAHIM, S., MOXHAM, T., OLDRIDGE, N., REES, K., THOMPSON, D. R. & TAYLOR, R. S. 2011. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev,* 7.

HOUCHEN-WOLLOFF, L., BOYCE, S. & SINGH, S. 2014. The minimum clinically important improvement in the incremental shuttle walk test following cardiac rehabilitation. *European Journal of Preventive Cardiology*.

INGLE, L. & CARROLL, S. 2013. Cardiac rehabilitation and exercise training. *Heart*.

JOLLIFFE, J., REES, K., TAYLOR, R. R., THOMPSON, D. R., OLDRIDGE, N. & EBRAHIM, S. 2001. Exercise-based rehabilitation for coronary heart disease. *The Cochrane Library*.

KIM, S. H., LEE, S. J., KANG, E. S., KANG, S., HUR, K. Y., LEE, H. J., AHN, C. W., CHA, B. S., YOO, J. S. & LEE, H. C. 2006. Effects of lifestyle modification on metabolic parameters and carotid intima-media thickness in patients with type 2 diabetes mellitus. *Metabolism,* 55**,** 1053-1059.

MILANI, R. V. & LAVIE, C. J. 2007. Impact of Cardiac Rehabilitation on Depression and Its Associated Mortality. *The American Journal of Medicine,* 120**,** 799-806.

MILANI, R. V., LAVIE, C. J. & SPIVA, H. 1995. Limitations of estimating metabolic equivalents in exercise assessment in patients with coronary artery disease. *The American journal of cardiology,* 75**,** 940-942.

NICHOLS, S., MILNER, M., MEIJER, R., CARROLL, S. & INGLE, L. 2014. Variability of automated carotid intima-media thickness measurements by novice operators. *Clinical Physiology and Functional Imaging*.

NIEBAUER, J., HAMBRECHT, R., VELICH, T., HAUER, K., MARBURGER, C., KÄLBERER, B., WEISS, C., VON HODENBERG, E., SCHLIERF, G., SCHULER, G., ZIMMERMANN, R. & KÜBLER, W. 1997. Attenuated Progression of Coronary Artery Disease After 6 Years of Multifactorial Risk Intervention: Role of Physical Exercise. *Circulation,* 96**,** 2534-2541.

O'DRISCOLL, J. M., SHAVE, R. & CUSHION, C. J. 2007. A National Health Service Hospital's cardiac rehabilitation programme: a qualitative analysis of provision. *Journal of Clinical Nursing,* 16**,** 1908-1918.

ORNISH, D., SCHERWITZ, L. W., BILLINGS, J. H. & ET AL. 1998. Intensive lifestyle changes for reversal of coronary heart disease. *JAMA,* 280**,** 2001-2007.

PIGNOLI, P., TREMOLI, E., POLI, A., ORESTE, P. & PAOLETTI, R. 1986. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. *Circulation,* 74**,** 1399-406.

SANDERCOCK, G., CARDOSO, F. & ALMODHY, M. 2013a. Cardiorespiratory fitness changes in patients receiving comprehensive outpatient cardiac rehabilitation in the UK: a multicentre study. *Heart,* 99**,** 1298-1299.

SANDERCOCK, G., CARDOSO, F., ALMODHY, M. & PEPERA, G. 2013b. Cardiorespiratory fitness changes in patients receiving comprehensive outpatient cardiac rehabilitation in the UK: a multicentre study. *Heart,* 99**,** 785-790.

SANDERCOCK, G., HURTADO, V. & CARDOSO, F. 2011. Changes in cardiorespiratory fitness in cardiac rehabilitation patients: A meta-analysis. *International Journal of Cardiology*.

TAYLOR, R. S., UNAL, B., CRITCHLEY, J. A. & CAPEWELL, S. 2006. Mortality reductions in patients receiving exercise-based cardiac rehabilitation: how much can be attributed to cardiovascular risk factor improvements? *European Journal of Cardiovascular Prevention & Rehabilitation,* 13**,** 369-374.

TIMIN, M. T., SHORES, K. V. & REICKS, M. 2002. Behaviour change outcomes in an outpatient cardiac rehabilitation program. *Journal of the American Dietetic Association,* 102**,** 664-671.

TOWNSEND, N., WILLIAMS, J., BHATNAGAR, P., WICKRAMASINGHE, K. & RAYNER, M. 2014. Cardiovascular Disease Statistics 2014. *British Heart Foundation. London*.

UNAL, B., CRITCHLEY, J. A. & CAPEWELL, S. 2004. Explaining the decline in coronary heart disease mortality in England and Wales between 1981 and 2000. *Circulation,* 109**,** 1101-7.

VANHEES, L., FAGARD, R., THIJS, L. & AMERY, A. 1995. Prognostic value of training-induced change in peak exercise capacity in patients with myocardial infarcts and patients with coronary bypass surgery. *The American journal of cardiology,* 76**,** 1014-1019.

WILSON, K., GIBSON, N., WILLAN, A. & COOK, D. 2000. Effect of smoking cessation on mortality after myocardial infarction: Meta-analysis of cohort studies. *Archives of Internal Medicine,* 160**,** 939-944.

Chapter 2 - Review of literature

3.1   Prevalence and Cost of Cardiovascular and Coronary Heart Disease

3.1.1   Cardiovascular Disease

The term cardiovascular disease (CVD) encompasses all diseases of the cardiovascular (CV) system (American Association of Cardiovascular and Pulmonary Rehabilitation [AACVPR], 2006) and is the largest cause of death in Europe (Mendis et al., 2011). Although no longer the largest cause of premature death in the UK, more than 161,000 people died from CVD in 2012, of those, more than 73,000 were attributable to coronary heart disease (CHD). The financial implication of CHD to primary and secondary care providers is approximately £1.6 billion (Townsend et al., 2014) making it one of the most significant financial costs to the UK health care system.

3.1.2   Heart Disease

Heart disease describes any condition affecting the coronary vasculature, electrical or anatomical structures of the heart. This includes valvular heart disease, heart failure, cardiomyopathy, arrhythmias or congenital heart disease (AACVPR, 2006).

3.1.3   Coronary Heart Disease

CHD is a term used to encompass a range of diseases with common pathology, namely, narrowing of the coronary arteries due to atherosclerotic lesions known as plaques. Arthrosclerosis is thought to be a dynamic, inflammatory process initiated by endothelial damage caused by one or more CV risk factors (Section 2.7). Advanced lesions can restrict the supply of oxygenated blood to the myocardium causing myocardial ischaemia (Angina). Lesions may also rupture resulting in a myocardial infarction [MI] (Jairath, 1999, Lindsay and Gaw, 2004,

Stanner, 2008). For the sake of simplicity, the literature frequently refers to a lone CHD diagnosis, however, patients' past medical history is often complex. Patients may present with multiple co-morbidities including previous CV events which necessitates bespoke patient care.

3.2 Manifestation of Heart Disease

3.2.1 Coronary Heart Disease Pathogenesis

Arthrosclerosis is an inflammatory process propagated by exposure to independent and dependent CV risk factors including hypertension, low-density lipoproteins (LDL), physical inactivity, ethnicity, gender and age (Libby and Theroux, 2005). Exposure to CV risk factors can cause changes to the arterial endothelial monolayer which incites expression of adhesion molecules and attracts leukocytes to the vessels surface. Increased vessel permeability and matrix changes below the endothelium allow LDL, monocytes and T-lymphocytes to move into the intima. Monocytes then express scavenger receptors that result in the uptake of oxidised LDL (oxLDL) through endocytosis. This process causes the conversion of macrophages to foam cell and, cholesterol accumulation between the intima and medial boundary (Libby et al., 2011). The first visible signs of CHD appear as yellow spots along the artery. Once established, these continue to develop through proliferation of extracellular matrix and smooth muscle cells within the arterial wall before forming a fibrous cap (Stanner, 2008).

3.2.2 Stable Angina

Angina (angina pectoris) is a symptom of myocardial ischaemia caused by flow limiting atherosclerotic lesions (Kurz et al., 2014). Any factor that increases myocardial oxygen (O_2) demand may trigger symptoms of angina. Typical triggers include physical activity, eating, extremes of temperature, fever, tachycardia, anaemia and hypoglycaemia. Stable angina is typified by reproducible patters of pain in terms of severity and duration. (Lindsay and Gaw,

2004, Jairath, 1999, Kurz et al., 2014). Symptoms include substernal chest pain, relayed arm, neck, jaw and/or back pain (Jairath, 1999). Clinically, angina may be verified by observing electrocardiogram (ECG) changes, specifically ST segment depression (Ehrman et al., 2013). However ECG cannot reliably discern the severity of ischaemia or the degree of discomfort caused to the patient. Despite its subjectivity, the pre-eminent tool for rating the severity of angina is the Canadian Classification System [Table 1] (Campeau, 1976). Classes I to IV characterise the increasing functional limitation caused by angina. The former characterises angina symptoms after prolonged exertion and the latter on minimal exertion or rest. Whilst this tool provides a quick and inexpensive means of evaluating functional limitation, it relies on accurate symptom reporting and interpretation. Determining the degree of patients' functional limitation can be aided using investigations such as cardiopulmonary exercise testing [CPET] (Section 2.13).

Table 1 – Canadian Classification System for Angina

Grade	Symptoms
I	Angina occurs only with strenuous, rapid or prolonged exertion at work or recreation
II	Slight limitation of ordinary activity, such as walking uphill, walking more than 2 blocks on level surface and climbing more than 1 flight of stairs; walking or stair climbing after meals, in the cold or wind, under emotional stress, or within a few hours of walking
III	Marked limitation of normal physical activity, such as walking 1 to 2 blocks and climbing 1 flight of stairs
IV	Inability to carry on any physical activity without discomfort, and angina may be present at rest

3.2.3   Acute Coronary Syndrome

Acute coronary syndrome (ACS) encompasses a range of diagnoses including unstable angina, ST segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction [NSTEMI] (Kurz et al., 2014, Dzau et al., 2006). The symptoms of ACS (Table 2) require immediate investigation (Cooper et al., 2010):

Table 2 – Symptoms of Acute Coronary Syndrome

Symptom
Chest pain lasting longer than 15 minutes
Nausea, vomiting, sweating and/or breathlessness
Haemodynamic instability
New onset chest pain, abrupt deterioration in previously stable angina or, frequent recurrent pain that occurs with little or no exertion

3.2.4 Unstable Angina

In contrast to stable angina, the symptoms of unstable angina are more unpredictable and may occur without provocation. Unstable angina is not relieved by rest or nitrates and may last for prolonged periods of time (Swanton, 2003). Also termed 'crescendo angina', it is common for episodes of unstable angina to precede MI (Braun Wald, 1989, Swanton, 2003) and should be treated as an emergency (Kurz et al., 2014). In addition to clinical symptoms, transient ECG ST segment elevation/depression or, T wave inversion may be observed during episodes of unstable angina. However, it is not uncommon for an ECG to remain normal (Swanton, 2003).

3.2.5 Non-ST Elevation Myocardial Infarction

NSTEMI typically refers to the full occlusion of a minor coronary artery or sub-total occlusion of a major coronary artery. Although blood (and O_2) flow is significantly restricted during a NSTEMI, the affected area is often sub-endocardial rather than transmural. Although in the early stages of development, NSTEMI may be indistinguishable from unstable angina it is more serious and can lead to myocardial necrosis (Dzau et al., 2006). As the name suggests NSTEMI cannot be diagnosed using through observable elevations to the ST segment on an ECG, instead the detection of cardiac necrosis enzymes (e.g. Troponin T) are required. Infarct location and factors reducing ECG sensitivity such as prior coronary artery bypass graft (CABG), bundle branch block or, previous infarct may all cause an MI to be categorised as NSTEMI as opposed to STEMI (Bode and Zirlik, 2007).

3.2.6   ST Elevation Myocardial Infarction

NSTEMI's differ to STEMI's on the bases that the latter is often the result of a total occlusion of a major coronary artery causing extensive regional obstruction to the myocardial O_2 supply. Because the affected myocardial area is larger than that of a NSTEMI, a STEMI may be diagnosed through characteristic ECG ST elevation and/or T wave inversion as well as raised cardiac necrosis enzymes (Bode and Zirlik, 2007). If untreated, the area of the myocardium distal to the occluded artery will suffer transmural necrosis (Swanton, 2003) which may lead to abnormal cardiac pumping function and chronic heart failure (CHF).

3.2.7   Chronic Heart Failure

CHF is a clinical syndrome characterised by abnormal heart structure or function and, inadequate perfusion commensurate with the body's metabolic demands (McMurray J et al., 2012). CHF exists on a severity continuum and some patients with CHD may have undiagnosed early stage CHF. Indeed, one of the most common causes of CHF is an MI (Cleland et al., 2011) resulting in myocardial necrosis and cardiac remodelling initiating a cascade of haemodynamic compensatory mechanisms.

In CHF, stroke volume (SV) is maintained via the Frank-Staling mechanisms. Blood volume is increased through water retention and decreased urine output. Up-regulation of neurohormones also serves to compensate for inadequate cardiac output (Q) and perfusion by means of vasoconstriction. In the short term, Q is preserved, however, prolonged exposure to these mechanisms is deleterious to cardiac and pulmonary performance as well as skeletal musculature and kidney function (Lymperopoulos et al., 2013). Increased total peripheral resistance caused by vasoconstriction increases cardiac afterload propagating cardiac remodelling, cardiac pump inefficiency and, further activation of haemodynamic compensatory mechanisms. Without intervention this will lead to physical disability and irreparable damage to

vital organs (AACVPR, 2006, Mann and Bristow, 2005, Lymperopoulos et al., 2013).

Advanced CHF is characterised by breathlessness, oedema, fatigue, raised jugular pressures and exercise intolerance, the latter of which may be qualitatively assessed using the New York Heart Association (NYHA) classification (McMurray J et al., 2012). Originally devised in 1928, a more recent characterisation of the NYHA classification system was advocated as a physicians' approximation (opinion) of a patients' functional status [Table 3] (New York Heart Association, 1964). The NYHA classification system suffers from many of the same limitations as the Canadian Classification System for angina in that, it is inherently subjective and lacks sensitivity. More objective functional classification indices obtained from CPET such as peak O_2 uptake [VO_{2peak}; Section 2.14.2] (Weber et al., 1982, Mancini et al., 1991) and VE/VCO_2 slope [Section 2.14.4] (Arena et al., 2007a) have been advocated. However in a clinical setting, NYHA classification remains the pre-eminent stratification tool.

Table 3 – New York Heart Association Classification of Heart Failure

NYHA Class	Symptoms
I (asymptomatic)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnoea
II (mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnoea
III (moderate)	Marked limitation of physical activity. Comfortable at rest but less than ordinary physical activity results in fatigue, palpitation or dyspnoea
IV (severe)	Unable to carry out physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased

3.3 Cardiovascular Risk Factors

3.3.1 Cardiovascular Risk

The incidence of CHD is associated with exposure to CV 'risk factors' which are thought to initiate, propagate and accelerate the atherosclerotic process. CV risk factors coincide with the incidence of CHD (Stanner, 2008) and can be divided in to modifiable and non-modifiable risk factors (AACVPR, 2006). Scientific interest in CV risk factors can be attributed to the Framingham and Framingham offspring studies (Kannel et al., 1979). Some of the most significant advances in the treatment of CHD have developed as a result of our understanding of CV risk factors.

Despite the emergence of novel risk factors, a group of 'classic' risk factors have repeatedly been shown to predict poor clinical outcomes (McQueen et al., 2008, Yusuf et al., 2004). The interaction of these risk factors can be complex with changes to one risk factor causing reciprocal changes to another. However, through the modification of CV risk factors, morbidity and mortality reduction is achievable (Yusuf et al., 2004). Many risk factors respond positively to lifestyle changes and consequently remain therapeutic targets for primary and secondary prevention programmes.

3.3.2 Smoking

The link between cigarette smoking and CHD is well established. Smoking can augment the effects of other risk factors, cause plaque instability, reduce endothelial function, incite blood clot formation and cause oxidative stress (Stanner, 2008). The risks associated with smoking are incrementally related to the number of cigarettes smoked. Smoking >40 cigarettes per day for example is associated with greater incidence of MI (OR 9.16; 99% CI 6.18 to 13.58). Smoking cessation however, reduces all-cause mortality (RR 0.64; 95% CI; 0.58-0.71) irrespective of age, gender or ethnicity (Anthonisen et al., 2005, Critchley and Capewell, 2003).

3.3.3 Hypertension

Hypertension (high blood pressure) is a major risk factor for CHD causing endothelial dysfunction and exacerbating the atherosclerotic process (Stanner, 2008). Blood pressure (BP) is normally distributed across the UK population. Although "cut-off" values are widely cited [Table 4] (Grabowski and Tortora, 2003), the point at which someone suffers from hypertension is difficult to define. The National Institute for Health and Care Excellence (NICE) state that a 2 mmHg increase in systolic BP (SBP) is associated with a 7% increase in CHD risk (National Institute for Health and Care Excellence, 2011), however, hypertension is amenable to treatment with pharmacological and lifestyle interventions.

Dietary and exercise therapy are effective treatments for hypertension. The Dietary Approaches to Stop Hypertension (DASH) trials (Appel et al., 1997, Sacks et al., 2001) showed that reduction of dietary sodium significantly reduced blood pressure. In secondary prevention populations, exercise training may reduce resting BP by approximately 3 mmHg (Taylor et al., 2004), however results are often variable (Hofman-Bang et al., 1999). These variations may reflect differences in exercise training dose or cardiac diagnosis.

Table 4 – Blood pressure classification system

Category	Systolic (mmHg)	Diastolic (mmHg)
Normal	<120	<80
Prehypertension	120-139	80-89
Stage 1 Hypertension	140-159	90-99
Stage 2 Hypertension	>160	>100

mmHg = Millimetres of Mercury

3.3.4 Dyslipidaemia

Dyslipidaemia describes abnormal changes to blood lipids and is an independent CV risk factor (AACVPR, 2006). The modification of lipoproteins such as low-density lipoproteins (LDL) are implicated in the pro-atherogenic process. Others, such as high-density lipoproteins (HDL) are

thought to aid the removal of cholesterol from the blood (Libby and Theroux, 2005, Stanner, 2008). Ratios of apolipoprotein B100 (associated with LDL) to apolipoprotein A1 (associated with HDL) have also been shown to predict MI incidence (McQueen et al., 2008). These measures are not yet routinely used in clinical practice. Current UK guidelines recommend the measurement of total cholesterol (TC), high-density lipoprotein (HDL) cholesterol and triglyceride concentrations. The evaluation of non-HDL cholesterol as opposed to low-density lipoproteins (LDL) is also now advocated [TC minus HDL] (National Institute for Health and Care Excellence, 2014).

Blood lipids are amenable to lifestyle and medical intervention. Carroll et al. (2011) showed that long-term exercise training in patients with CHD significantly improved lipid profiles whilst the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT Gemfibrozil drug trial) showed that a HDL increase (6%) and a triglyceride decrease [31%] reduced non-fatal MI or CHD related death by 22% [95% CI 7 to 35%; $p=0.006$] (Rubins et al., 1999, Rubins and Robins, 2000).

3.3.5 Diabetes Mellitus

Diabetes mellitus (DM) is defined by the World Health Organisation (WHO) as a fasting glucose plasma ≥7.0 mmol/l (World Health Organisation, 2006) and is considered to be 'CHD equivalent'. Even if a patient is free from symptomatic CHD, once a diagnosis of DM is given the risks of a patient suffering a cardiac event are similar to those who have previously sustained one (Juutilainen et al., 2005). DM is independently associated with the occurrence of dyslipidaemia, pro-inflammatory reactions, endothelial dysfunction, oxidation reactions, insulin resistance and accelerated atherogenesis. DM can be managed with appropriate dietary intervention, weight reduction, medication and exercise (AACVPR, 2006).

3.3.6 Abdominal Obesity

Obesity increases CV risk and may exacerbate other CV risk factors including dyslipidaemia, hypertension and type 2 DM. Obesity and over-weight individuals may defined as having a body mass index (BMI) >30 kg·m^{-2} and 25 to 29.9 kg·m^{-2} respectively (Lavie et al., 2009). Despite BMI's long standing association with CV risk, body fat distribution may be more significant in the prediction of MI. The INTERHEART study (Yusuf et al., 2004) found that abdominal obesity (waist/hip ratio) was a stronger predictor of MI (OR 2.24; 95% CI 2.06 to 2.45) compared to BMI [data not reported] (Lavie et al., 2009). A combined approach to classifying obesity may be prudent for adequate risk stratification. Diet and exercise training are both effective at reducing weight and/or attenuating the metabolic and CV impact of obesity (Clément et al., 2004, Ades et al., 2009b).

3.3.7 Sedentary Lifestyle

Maintaining physical activity and higher levels of cardiorespiratory fitness [(CRF: defined as "the capacity to take in and process O2 for the production of energy for physical activity via aerobic metabolism" p53 (AACVPR, 2006)] are associated with lower rates of mortality (Kavanagh et al., 2002, Kavanagh et al., 2003). A 1% improvement in peak oxygen uptake (VO$_{2peak}$; Section 2.14.2) or 1 metabolic equivalent (MET) increase may confer a 2 to 12% improvement in survival outcomes respectively (Myers et al., 2002, Vanhees et al., 1995). Current UK physical activity guidelines state that adults should participate in 150 minutes of moderate physical activity, or 75 minutes of vigorous activity per week in addition to reducing sedentary activities. Adults should be encouraged to undertake activities that improve muscular strength on at least two days per week (Department of Health, 2011).

3.3.8 Age

Advanced age is associated with adverse changes to cells and tissues within the body that increase the risk of developing many diseases including CHD and CHF (Kregel and Zhang, 2007). Regarded as a major CV risk factor, aging is accompanied with prolonged exposure to other CV risk factors, thus older individuals have greater propensity to arterial damage (British Association for Cardiac Rehabilitation [BACR], 2006). Although widely considered non-modifiable, a recent review by Najjar, Scuteri and Lakatta (2005) discuss the possibility that aging itself may constitute a collection of changes to the vascular tree which are wholly susceptible to lifestyle and medical intervention. However aging can be regarded as a relative risk factor to the *individual* and it is difficult to argue that the effects of advancing age can be anything other than non-modifiable.

3.3.9 Gender

CHD is traditionally perceived to be a male disease. CHD incidence is significantly greater in younger men than younger women (Anand et al., 2008). At age 40, the risk of suffering a cardiac event for men and women is 48.6% (95% CI 45.8 to 51.3%) and 31.7% (95% CI 29.2 to 34.2%) respectively (Lloyd-Jones et al., 1999). The risk of presenting as an acute MI in men (60.6%) and women (33.0%) younger than 60 years is also disparate and, on average, women defer their first cardiac event by nine years. However, the gender gap (27.6%) has been shown to significantly narrow when adjusting for geographic region (difference: 23.2%), geographic region and smoking prevalence (difference 18.2%) and, the nine 'classic' CV risk factors [4.7%] (Anand et al., 2008). Thus a large proportion of male CV risk can be attributed to early and prolonged exposure to CV risk factors. It is possible that males make poorer lifestyle choices than their female counterparts. However female sex hormones appear to play an important cardioprotective role in moderating the impact of the same CV risk factors.

Beyond the menopause, the risk of women dying from CHD becomes similar to that of men. A reduction in cardioprotective gender specific sex hormones has been implicated in this phenomenon (van Lennep et al., 2002). Importantly, there is evidence to suggest that in both postmenopausal women and elderly men, regular physical activity exerts greater cardioprotective benefits than seen in their younger counterparts. This shows that regardless of gender and/or age, the effects of CV risk factors can be attenuated by exercise training (Anand et al., 2008).

3.3.10 Heredity

An individual with a first-degree relative who has received a CHD diagnosis is at increased risk of MI [OR: 1.81; 95% CI: 1.69 to 1.94]. If both of an individual's parents have suffered a premature MI (defined by the INTERHEART study as <50 years of age) the risk of sustaining an MI increases further [OR: 6.56; 95% CI: 1.39 to 30.95] (Chow et al., 2011). In addition to familial factors, ethnicity plays a major role in CHD risk. In the UK, people of South Asian decent have a particular predisposition to CHD and are at 1.5 times greater risk of dying from the disease. Similarly, African-Americans suffer an unusually high incidence of hypertension and CHD compared to their Caucasian counterparts (Chaturvedi, 2003).

3.4   Interventions and Surgical Treatments for Coronary Heart Disease

3.4.1   Percutaneous Coronary Intervention

Evolving from the balloon angioplasty, the percutaneous coronary intervention (PCI) is a cardiology procedure for the relief of myocardial ischaemia and symptoms of angina. During a PCI a sheath is inserted into the femoral, radial or less commonly, the brachial artery through which, a 'guide catheter' is threaded retrograde to the coronary circulation. A 'guide wire' is then fed to the lesion that is occluding coronary blood flow. A balloon attached to the wire's tip

is inflated against the lesion displacing the plaque into the abluminal space (AACVPR, 2006). Although coronary blood flow is acutely restored, further intervention is often needed to avoid re-stenosis (Swanton, 2003). A metallic support structure (stent) designed to keep the vessel patent is inserted by mounting them on a second angioplasty balloon. Although the modern elective PCI is effective for the purpose of relieving symptoms of angina, studies have been unsuccessful in showing any mortality benefit over conservative medical management (Boden et al., 2007). Despite this, the PCI has revolutionised the treatment of an acute MI.

3.4.2   Primary Percutaneous Coronary Intervention

Until recently, patients suffering an MI were treated with thrombolysis, a drug designed to dissolve blood clots and restore coronary blood flow. Since the 1990's however, the use of PCI as a primary treatment for STEMI (known as the PPCI) and an early aggressive treatment for NSTEMI has become increasingly common. A PPCI's application is similar to that of an elective PCI but is used to displace coronary thrombi. Its advent has been associated with reduced hospital stay, fewer readmissions due to re-infarction within one year and, lower mortality rates at seven days, thirty days and one year (Stenestrand et al., 2006). PPCI however is not always suitable or available at some medical facilities. Under such circumstances a clinician may choose to administer an antithrombotic agent.

3.4.3   Thrombolysis

Antithrombotic agents are delivered via a coronary 'guide wire' and are given to dissolve the occlusive thrombus associated with an MI. Like a PPCI, the early restoration of blood flow to the myocardium reduces infarct size and significantly reduces mortality. However in the scenario of a STEMI, PPCI has been shown to produce more favourable outcomes (Keeley et al., 2003).

3.4.4 Coronary Artery Bypass Graft

CABG is a surgical revascularisation operation that bypasses coronary occlusions by attaching one or more *non-coronary* arterial conduits to the coronary vasculature. For example, the left internal mammary artery is often used for left anterior descending occlusions because its origin can remain attached to the subclavian artery. Despite this, many patients will also require one or more venous conduits such as the saphenous vein to be completely removed from their donor site and grafted on to an arterial blood supply (Swanton, 2003).

The advent of PCI's has resulted in fewer CABG procedures (Townsend et al., 2014) however the need for further revascularisation remains higher amongst people receiving PCI compared to CABG (Hoffman et al., 2003). However, with the exception of elderly or diabetic patients (Hlatky et al., 2009), the risk of death within the first five years from both interventions is equivocal, irrespective of the number of diseased vessels (Hlatky et al., 2009).

3.5 Cardiac Secondary Prevention

3.5.1 Cardiac Rehabilitation

Cardiac rehabilitation (CR) is a comprehensive intervention for people with heart disease. CR aims to facilitate the timely recovery of patients and reduce the risk of recurrent cardiac events (Bethell et al., 2009). Following the WHO technical report on 'rehabilitation after myocardial infarction' (World Health Organisation, 1993), CR has become standard therapy for many patients in the UK who have sustained a cardiac event and has been defined by the WHO as:

"The sum of activities required to influence favourably the underlying cause of the disease so that people may, by their own efforts preserve or resume when lost, as normal a place in the community..." (p.1)

There is now compelling evidence that in well controlled environments, 'the sum' of secondary

prevention interventions may modulate CV risk factors including poor CRF, psychosocial health, diet, dyslipidaemia, hypertension and smoking rates (Arrigo et al., 2008, Ornish et al., 1998, Gayda et al., 2008, Milani and Lavie, 2007, Timin et al., 2002, Ades et al., 2009b, Wilson et al., 2000, Carroll et al., 2011, Sandercock et al., 2011). Consequently, modern CR has been embraced as a beneficial 'package' of secondary prevention initiatives aimed at reducing CV risk factors. CV risk factor reduction is largely responsible for improved survival outcomes amongst patients completing CR in recent years (Taylor et al., 2006). Although CR in the UK has broadly adopted a multifaceted approach to CV risk factor reduction, the implementation of CR is far from comparable to interventions documented in clinical trials.

3.5.2 Cardiac Rehabilitation in the United Kingdom

The UK's national governing body for CR recommends a seven component (Table 5) multidisciplinary approach to the delivery of CR (British Association for Cardiac Prevention and Rehabilitation [BACPR], 2012). Based on evidence supporting their role in secondary prevention, these components are supposed to advocate a comprehensive evidence based approach to CR. However, whether such 'comprehensive' CR programmes occur throughout the UK is questionable.

Table 5 – Seven Core Components of UK Cardiac Rehabilitation

Core Component
Health behaviour change and education,
Medical risk factor management,
Lifestyle Risk Factor Management
Psychosocial health,
Cardioprotective therapies,
Long-term management
Audit and evaluation

Brodie et al. (2006) highlight a number of constraints facing UK CR teams which includes a lack of input from professionals such as dieticians, psychologists, doctors and pharmacists. They also show a particularly poor record of patient referral to long-term maintenance programs. This is possibly the most pivotal step in ensuring patient adherence to lifestyle changes and effective CR. Although only 11% of UK CR centres were included in this study, the National Audit or Cardiac Rehabilitation (NACR) also makes it clear that many UK CR teams fail to meet the minimum service specifications outlined by the BACPR (British Heart Foundation, 2014, BACPR, 2012b). The consequences of doing so may undermine the quality of patient care and reduce any measurable health benefits that CR can hope to achieve. The inequality in CR service provision is not however limited to the availability of appropriately trained staff.
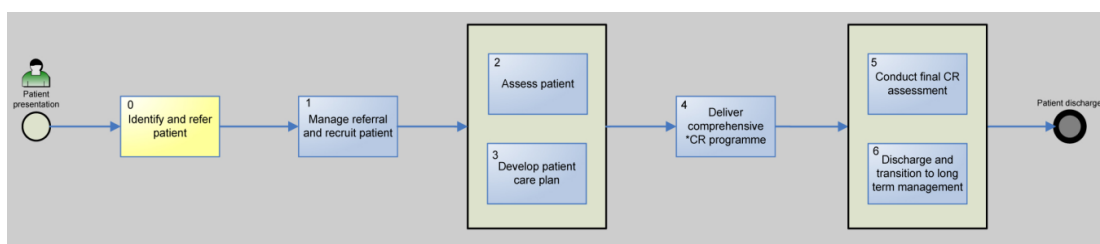
Figure 1 – The 'best care pathway' for CR has recently replaced the traditional phased approach. Stage four of this diagram represents the stage in a patient's recovery where comprehensive CR should occur.

In addition to varied service provision, local referral criteria also dictate who can receive CR. Patients recommended for referral to CR include MI, PCI, stable angina, CABG, cardiac valve replacement, device implantation and CHF (BACPR, 2012b, Bethell et al., 2009). In practice, substantial variations in CR eligibility exist with MI patients most likely to be referred and patients with angina or implantable devices least likely (British Heart Foundation, 2014). Whilst UK CR guidelines appear both comprehensive and evidence based, its implementation is far from complete.

It is apparent that UK CR is not operating optimally, however there is documentable evidence of change. Recently, CR in the UK has undergone significant restructuring with the aim of

developing a more equitable system. For instance, UK CR programmes have traditionally been described in terms of phases [I to IV] (BACR, 2006). These phases were originally coined in the USA to determine what level of health care patients were entitled to according to the health insurance policy. However, because all patients should be entitled to CR, the Department of Health recently adopted a staged approach described as the 'best practice care pathway' (Department of Health, 2010). These stages (Figure 1) are now endorsed by NICE and the BACPR (NICE, 2013a, BACPR, 2012b). The new frame work details the staffing and component requirements of CR and makes it clear that all patients with heart disease (not just CHD) should be offered CR. Stage four of the flow diagram covers the secondary prevention measures that should be offered by UK CR programmes. Whether or not this step change in approach has produced any materialistic improvement to CR is yet to be determined.

3.5.3 Cardiac Rehabilitation Improves Survival

Multiple meta-analyses have confirmed the benefits of CR on a range of clinical outcomes (Davies et al., 2010, Taylor et al., 2004, Dalal et al., 2010, Jolly et al., 2006, Rees et al., 2004, Beauchamp et al., 2013). A Cochrane report recently demonstrated that CR reduced all-cause (RR 0.87; 95% CI: 0.75-0.99) *and* CV mortality (RR 0.74; 95% CI: 0.63-0.87) in studies lasting longer than 12 months (Heran et al., 2011), a finding echoed by others [all-cause mortality; HR 0.65; 95% CI 0.46 to 0.92; p=0.015; number needed to treat = 17 per 2 years] (Piepoli et al., 2004). However, these findings are not consistently reported in a number of large studies.

Although Davies et al. (2010) found improved hospitalisation rates amongst CHF patients undertaking exercise based CR (RR 0.72; 95% CI 0.52 to 0.99; p=0.04) mortality was unaffected (RR 1.02; 95% CI 0.70 to 1.51; p=0.90), something others (HF-Action) have also reported [HR 0.96; 95% CI, 0.79-1.17; p=0.70] (O'Connor et al., 2009). CHF often has complex presentation and poor survival outcomes *potentially* making improved mortality an unrealistic expectation. However the inconsistent effect of CR in CHF also extends into CHD populations bringing into

question its efficacy (Erdman et al., 1986, Heller et al., 1993, Hage et al., 2003).

In contrast to CHF, the prognosis for patients with CHD is often good, particularly with recent advances in medical treatment. A review of published meta-analyses showed that whilst exercise training provided a survival benefit to patients with CHD, the 95% CI of effect where wide (OR 0.89; 95% CI 0.76 to 1.04) and less credible than specific secondary prevention medications (Naci and Ioannidis, 2013). In CR, medical treatment is prescribed concurrently with exercise training and the profound effect that secondary prevention medications has on survival may therefore negate any cumulative effect of conducting exercise training. However, studies predating recent advances in medical treatments have also frequently failed to report any survival benefit of exercise based CR. It is therefore unlikely that exercise has become irrelevant in the treatment of CHD.

Early research from landmark studies such as those conducted by the WHO (1983) "failed to provide an answer to the question of whether comprehensive programmes, as applied in separate centres, could reduce mortality and morbidity after MI in the long term". It is particularly pertinent that the only two UK studies (Hugh and Mullee, 1990, Carson et al., 1982) to be included in a Cochrane report on exercise based CR (Heran et al., 2011) also found no discernible effect on mortality. At the time of publication Heran and colleagues (2011) could present no evidence to suggest that any UK CR programme could improve survival. The findings of a more recent UK CR study (West et al., 2012) not included in the original report makes it clear that irrespective of advances to our understanding of exercise physiology or medicine, the UK model of CR continues to underperform. The study by West et al. (2012) arguably represents an outdated version of UK CR (BACPR, 2012a), however many UK CR exercise training practices since the onset of West and colleague's (2012) study remain unchanged. Of greater relevance is the failure of the study to reach its recruitment target (Doherty and Lewin, 2012) which reduces the statistical power and the likelihood of finding a significant mortality effect. Nonetheless, the only contemporary data reporting on UK CR programmes shows that CV risk factors, exercise

habits and mortality in both the short (2 year: RR 0.98; 95% CI 0.74 to 1.30) and longer-term (7 to 9 year: RR 0.99; 95% CI 0.85 to 1.15) are unaffected by comprehensive CR. Whilst the potential benefits of exercise based CR are not widely contended, the study by West et al. (2012) has catalysed a debate about the efficacy of UK CR (Ingle and Carroll, 2013, Sandercock et al., 2013a, BACPR, 2012a, Doherty and Lewin, 2012, Taylor, 2012, Conraads et al., 2012, West and Henderson, 2013, West, 2012). Because many studies outside of the UK have documented a significant survival benefit following *exercise* based CR, it is a logical step to investigate whether the exercise component of UK CR is prescribed sufficiently to elicit meaningful changes to patient health. The challenge of doing so however remains largely overlooked.

3.5.4 UK Cardiac Rehabilitation Exercise Training

Despite CR being considered a multidisciplinary therapy (Association of Chartered Physiotherapists in Cardiac Rehabilitation [ACPICR], BACR, 2006; Wenger, 2008), exercise training may confer the single greatest benefit to patients undertaking CR. Jolliffe and colleagues (2001) reported that exercise training alone (OR 0.74; 95% CI 0.56 to 0.98) provided superior survival outcomes compared to comprehensive CR (OR 0.87; 95% CI 0.71 to 1.05).

In the UK, exercise training should form the core component of a comprehensive CR programme (Taylor et al., 2006). If patients are to receive optimal benefits this component should be delivered to a high standard. This however, may not be the case as Sandercock et al. (2013a) demonstrated. Their large scale multicentre study showed that on average, patients completing CR could expect to experience a modest 0.52 MET CRF increase. The retrospective design and use of estimated CRF change are clear study limitations. However Sandercock and colleagues' (2013b) findings suggest that UK CR patients will experience smaller CRF changes than previously reported (Sandercock et al., 2011, Balady et al., 1996). Multiple factors may have contributed to these findings including the complex medical presentation (particularly in the

early stages of CR) of some patients undertaking CR in clinical practice compared to those involved in clinical trials. Patients may present with orthopaedic limitations, respiratory disease or one of many other co-morbidities rather than an isolated case of CHD or CHF which may limit their ability to improve CRF. However for most, co-morbidities will not preclude effective exercise training and it is more likely that poor exercise provision and prescription are responsible for Sandercock and colleagues (2013b) findings.

CR provision across the UK is disparate (Doherty and Lewin, 2012, Brodie et al., 2006) but can broadly be characterised as a programme conducted one to three times per week over four to twelve weeks. Despite CPET being considered the "gold standard" test to base exercise prescriptions on, submaximal cycle ergometry protocols, the Chester step test, incremental shuttle walk test or the six-minute walk test are most frequently used (Section 2.12.1). Despite its frequent use, the utility of the submaximal exercise test may be undermined by prescribing exercise at approximately 40-60% (up to a maximum of 70%) of a patient's predicted heart rate reserve (HRR) rather than at an intensity obtained during the test. Although not without its flaws, prescribing exercise at a workload eliciting an appropriate Borg score (Borg, 1982) and heart rate (HR) observed during submaximal exercise testing for example should be considered. This may be of particular value in cardiac patients where unreliable HR training estimations may be compounded by the unquantifiable effect of beta-blockades on HR (Brubaker and Kitzman, 2011). The effect of inaccurate exercise prescriptions could in principle be attenuated by higher exercise doses. Current UK CR guidelines may not recommend the level of exercise needed to improve CRF.

3.5.5   Exercise Dose and UK Cardiac Rehabilitation Programmes

In the UK, the aim of a CR exercise training regime is to achieve a minimum of 20 minutes CV exercise per session (BACPR, 2012b, ACPICR, 2015) although in practice, this is likely to be dictated by the ability of the patient (or perceived ability of the patient). To allow de-

conditioned patients to achieve greater total CV exercise duration, the BACPR advocate the use of interval circuit training with short duration CV exercises interspersed with active recovery exercises (BACR, 2006). Although UK guidelines do not discourage continuous training where appropriate, many CR programmes use low to moderate intensity (40-70% HRR) interval training as their 'default' prescription. The ACPICR (2015) also suggest that intensities as low as 30-40% HRR/VO$_{2peak}$ may be effective for de-conditioned patients, a position which is unsupported in national guidelines and poorly supported in the literature (Swain and Franklin, 2002). A recent meta-regression analysis by Uddin et al. (2015) not only found that higher exercise doses-conferred greater CRF improvements but demonstrated that it was the only predictor if VO$_{2peak}$ improvement.

UK CR guidelines remain staunchly conservative in their approach to exercise prescription and by their own admission, more so "than the evidence and guidelines from other countries" have shown to be beneficial (ACPICR, 2015). This cautious approach to CR is on the premise that maximal exercise tolerance testing (ETT) is not routinely conducted in the UK. However, there is a paucity of evidence showing that low to moderate exercise training intensities (<40% to 60%) conducted over short training periods [11.6 days] (Brodie et al., 2006)] can improve CRF. The ACPICR (2015) rightly conclude that the majority of studies included in a recent Cochrane review (Heran et al., 2011) consisted of training regimes conducted two to three times per week. Despite this, little consideration is given to the fact that duration per session was often >30 minutes for >12 weeks at intensities equal to or greater than 70 HRR or VO$_{2peak}$ (Seki et al., 2003, Seki et al., 2008, Hofman-Bang et al., 1999, Dugmore et al., 1999, Fletcher et al., 1994). Existing research appears to have been manipulated to fit the existing model of UK CR rather than striving to implement CR protocols known to be effective.

In recommending exercise intensities of approximately 40% maximal aerobic capacity, the ACPICR (2015) refer to multiple other organisation's guidelines (Scottish Intercollegiate Guidelines Network), one of which does not discuss exercise training at 40% of a maximal

aerobic capacity (Piña et al., 2003). A second citation refers to their previously published self-authored book (American College of Sports Medicine [ACSM], 2013). A third citation clearly states that if an exercise intensity of 40% VO_{2max} is chosen for exercise prescription, longer term adherence is needed for CRF improvements (Fletcher et al., 2001). The only relevant original training study cited by the ACPICR (2015) shows that for training intensities of 45-55% HRR to improve VO_{2peak}, frequency needed to be greater than five days per week (30 minutes per session) for six months (Duncan et al., 2005). Whilst exercise doses as low as 40% HRR/VO_{2peak} may be sufficient to elicit a VO_{2peak} improvement, its impact following a CR programme lasting an average of 11.6 sessions (Brodie et al., 2006) is likely to be small. The failure to implement sufficient exercise training dose may provide answers to the apparent lack of impact that CR appears to have on morbidity and mortality (West et al., 2012).

3.6   Exercise Dose Manipulation

Training specificity underpins quality exercise prescription and refers to the purposeful activation of specific metabolic and mechanical systems within the body for a desired outcome. When appropriately stressed, these systems will adapt favourably by increasing their capacity to undertake the desired task, however insufficient stimulus will evoke little or no effect (Haskell, 2001). The decision of whether or not to implement a training regime should be based on whether or not it is effective. One of the most pertinent statements aimed at guiding practitioners' decision whether or not to implement an exercise training regime was provided by Haskell (2001) who likened exercise to pharmacological treatments. Before implemented, a treatment must first show mechanisms of action, a good adverse event profile, efficacy in a disease state and target population and, a specific recommended dose for the desired outcome. These two final points remain a significant area of controversy within CR as no single standard effective dose has been shown to improve CRF.

When prescribing exercise, interplay between the frequency, intensity and duration of exercise

exists. The sum of these variables can be described as the exercise 'dose' (Kesaniemi et al., 2001) hence in clinical practice, dose manipulation is achieved by altering any of these components. In CR populations as with any other, appropriate training doses are required to elicit CV and muscular training adaptations that result in improved aerobic fitness. A specific 'threshold dose' below which no training response occurs has not been defined however, a dose-response relationship does exist between exercise training and VO_{2peak} increase, as well as VO_{2peak} and mortality reduction (Vanhees et al., 1995). The findings that UK CR appears does not improving survival (West et al., 2012) and, only results in modest CRF improvements (Sandercock et al., 2013b) therefore likely reflects an inadequate exercise training dose, a concern highlighted by others (Sandercock et al., 2013b, Ingle and Carroll, 2013, Sandercock et al., 2013a). Greater doses of exercise than currently advocated may be needed. However, with the exception of non-NHS long term CR maintenance programmes, CR teams are often constrained by service specifications that dictate programme duration. Consequently, the most feasible way of increasing exercise dose may be through frequency, time per session (minutes) and intensity manipulation, not programme duration.

Warburton (2005) showed that in CHD, high intensity interval training [HIIT] (2 minutes at 90% VO_2 reserve followed by 2 minutes at 40% VO_2 reserve) significantly improved VO_{2peak} and ventilatory anaerobic threshold (VAT) to a greater extent than continuous moderate training (65% VO_2 reserve). The superior training response most likely reflects greater dependence on anaerobic metabolism to sustain exercise during HIIT compared to the steady metabolic state achieved during moderate intensity continuous aerobic training. Improving an individual's VAT may have profound beneficial impact on a patients' ability to conduct daily activities due to an in increase in fatigue threshold i.e. the point at which symptoms of fatigue manifest during daily activities. The findings of Warburton (2005) are not isolated. Similar results have been repeatedly demonstrated in sedentary healthy individuals (O'Donovan et al., 2005), patients with CHD (Cardozo et al., 2015) and in patients with CHF even when energy expenditure is matched between exercise groups.

Wisloff et al., (2007) showed that both VO_{2peak} and VAT improved in CHF patients undertaking high intensity aerobic interval training (three times per week for 12 weeks) to a greater extent than those completing moderate continuous training (70 to 75% Peak HR). However Wisloff et al., (2007) 'four minutes on/four minutes off' interval protocol at 80% VO_{2peak} may be considered an unrealistic expectation for many UK CR programmes. Perhaps more importantly, HIIT has not gained acceptance within UK CR establishments. Despite the prospect of improving patient health and wellbeing, HIIT's implementation in the short term is unlikely and an alternative approach to dose manipulation may be to increase the number of exercise sessions per week (frequency).

Nieuwland and colleagues (2000) showed that greater CRF improvements may be achieved by undertaking twice daily training five days per week (total daily duration >160 mins) when compared to one session performed two times per week. Exercise frequency is clearly linked to the magnitude of CRF improvements experienced by CR patients. Hence, the observation that UK CR programmes result in smaller CRF improvements than their international counterparts (approximately one third) to a degree proportional to the number of fewer exercise sessions conducted (approximately one third) is unlikely to be coincidental (Sandercock et al., 2013b, Sandercock et al., 2011, Brodie et al., 2006). The poor performance of UK CR (Sandercock et al., 2013b, West et al., 2012) may be attributable to the low number of exercise sessions [one to three sessions per week; four to twelve weeks duration] (Brodie et al., 2006). Despite this, Nieuwland et al. (2000) still showed that exercise conducted twice per week (for six weeks) significantly improved VO_{2peak} and VAT. Contrary to suggestion, these findings indicate that UK CR frequency should be substantial enough to induce meaningful CRF improvements. However, there are significant differences between total exercise duration in UK CR programmes (recommended >20 mins per session) and that of the study by Nieuwland et al. (2000) [approximately 85 minutes per session]. In addition, the exercise intensity range (60-70% HRR) was determined from a maximal CPET which enhances the accuracy of exercise prescription.

Furthermore, this is the highest recommended exercise intensity for UK CR patients (ACPICR, 2015). Consequently, although exercise frequency was similar to that of a UK CR programme, the overall dose was substantially greater. CRF improvements are achievable when exercise is conducting twice per week. However, the duration (mins) that exercise is prescribed at should be substantially greater than the minimum current UK recommendations. This is particularly relevant to UK CR programmes that may not be able to easily increase exercise training frequency due to service specifications.

An appropriate sustained exercise dose is integral to improving and maintaining CRF in patients attending CR programmes. It is unreasonable to expect that CR could meaningfully reduce premature mortality or morbidity without an appropriate exercise dose because the physiological adaptations to exercise training likely underpin any survival benefit. However, even when training adaptations do occur, the mechanisms are difficult to map and often disputed.

3.7 Exercise Intolerance and Training Adaptations

Peak CRF improvements, specifically VO_{2peak} are independently linked with premature morbidity and mortality reduction (Kodama et al., 2009) and as such is one of the primary therapeutic targets of a CR programme. Exercise training in CHD, CHF and healthy populations can elicit VO_{2peak} increases via favourable changes to one or more components of the Fick equation (Section 2.14.1). The determining factors of the respective aspects of the Fick equation are many however they can be broadly categorised by characteristics of muscle O_2 supply (central determinants) or muscle O_2 use [peripheral determinants] (Wasserman et al., 2011) [Table 6]. In clinical populations, the precise mechanisms through which exercise training improves VO_{2peak} and other markers of CRF are diverse and may depend on disease aetiology and/or clinical co-morbidities.

Basset and Howley's paper (2000) on "limiting factors for maximal oxygen uptake..." has led to

the wide assumption that SV limits VO_{2peak} in both older and younger sedentary healthy men and women. However the supposition that improvements to Q are the primary determinant of exercise training adaptations in healthy populations irrespective of age may be flawed. In older females (69 ± 7 years) in particular, a-vO_2 difference (65%) may be the most significant contributor to VO_{2peak} increases following exercise training (Spina et al., 1993, Murias et al., 2010a).

Table 6 – Primary determinants of oxygen uptake

Muscle O_2 Supply (Central)	Muscle O_2 Use (Peripheral)
Cardiac Output	Adequate red cell-sarcoma O_2 diffusion gradient
Perfusion of O_2 to muscle	Muscle fibre type
Capillary PO_2	Muscle fibre size
Haemoglobin concentration	Muscle oxidative capacity
Haemoglobin's affinity for O_2	

O_2 = Oxygen; PO_2 = Partial Pressure of Oxygen;

By contrast, using the same exercise regime in healthy older men (68 ± 7 years), Murias, Kowalchuk and Paterson (2010b) showed that SV augmentation was the predominant contributor to VO_{2peak} increase with two thirds attributable to improved maximal SV (SV week 0: 122.1 ± 21.7 ml/beat; SV week 12: 140.2 ± 19.4 ml/beat; p<0.05). Only one third as attributable to increased a-vO_2 difference (week 0: 13.5 ± 2.2; week 12: 14.7 ± 2.1; p<0.05). The widely held assumption that VO_{2peak} is limited by Q should not be misinterpreted as the determining factor for training adaptations. Indeed matched exercise stimuli may elicit varied training responses dependent on the population and, even if Q does limit VO_{2peak}, other factors may be the first to respond to exercise training.

Where augmented SV or Q has been shown to underpin increased VO_{2peak}, factors such as enhanced left ventricular (LV) contraction and/or diastolic function have been proposed as mechanisms, the latter of which may underpin exercise capacity in post MI patients (Dekleva et al., 2014). Patients with CHD or CHF may have slow LV relaxation times due to myocardial dysfunction. Consequently high LV pressures may result in a low atrial-LV pressure gradient and abnormal LV filling, characteristics of diastolic dysfunction. Diastolic dysfunction affects

determinants of LV filling efficiency such as peak early mitral inflow velocity (E; units = ml/sec), E wave deceleration time (dec t E), peak early diastolic annular velocity (e'; units = mm/sec) and, increases the reliance on atrial contraction for LV filling. Diastolic efficiency may be an important determinant of the hearts ability to augment SV in response to demands of exercise (Little and Oh, 2009).

Through linear regression, Dekleva et al. (2014) demonstrated that indices of diastolic dysfunction such as E/e' (Beta =-0.486; p=0.001) and dec t E (Beta = 0.270; p=0.008]) were strongly related to decline in VO_{2peak}, furthermore, E/e' was found to correlate with circulatory power, an indirect measure of exercise Q [Section 10] (E/e: r=0.48; p<0.001]. This most likely reflects the hearts inability to optimally fill the LV with blood at increasing work rates resulting in a lower Q response. Indeed, patients with normal LV filling pressures were shown to have a significantly higher VO_{2peak} than those with elevated LV filling pressures (normal LV filling pressure VO_{2peak}: 1931 ± 501 ml; elevated LV filling pressure VO_{2peak}: 1630 ± 464 ml; p=0.025). Multivariate regression also showed that diastolic dysfunction was a significant predictor of VE/VCO$_2$ slope elevation (E/e: Beta = -0.479; p<0.001; LVEDD: Beta =-0.290; p=0.013), findings supported by data from the HF-ACTION group (Gardin et al., 2009). The most likely reason for this is the negative impact that diastolic dysfunction could have on lung perfusion and pulmonary dead space (V_D). Despite presenting valuable data, both Dekleva et al. (2014) and Gardin et al. (2009) rely heavily on correlations to sustain their argument. Correlation does not imply cause. Moreover, as demonstrated by Murias et al. (2010a) the limiting mechanisms of VO_{2peak} of (Bassett and Howley, 2000) may not be the first to respond to exercise training. In fact central cardiac factors *including* diastolic dysfunction may have little impact on exercise intolerance in cardiac populations (Shelton et al., 2010, Clark et al., 1996) and may therefore not underpin CRF improvements in CR patients.

Shelton and colleagues (2010) found that at submaximal workloads, Q was comparable amongst patients with and without CHF leading the authors to conclude that Q may not limit exercise capacity. However, if Shelton and colleague's (2010) cardiac index data (Q standardised to body

35

surface area) are held true instead of absolute change in Q, central haemodynamic performance during exercise appears significantly worse amongst CHF patients than non-CHF controls. Furthermore, because a-vO_2 difference is determined by the O_2 perfusion-diffusion ratio (Roca et al., 1992, Critoph et al., 2014), a reduction in perfusion can widen the a-vO_2 difference (as seen in this study) without a measurable improvement in muscle O_2 use. Hence, an alternative interpretation to Shelton and colleagues (2010) data is that central factors may limit exercise capacity in patients with impaired cardiac function. Indeed, Critoph, Patel, Mist, and Elliott (2014) found that hypertrophic cardiomyopathy patients displayed an impaired Q-VO_2 relationship and SV response at each stage of CPET. A similar pattern of a-vO_2 difference widening reported by Shelton and colleagues (2010) was also observed. However a limiting factor of VO_2 or VO_{2peak} does not necessitate its improvement following exercise training.

A case study by Bellotto et al. (2011) showed that a patient with a totally artificial heart was able to increase their VO_{2peak} in spite of near complete inotropic and chronotropic incompetence. Such findings indicate that factors other than Q are able to play a significant role in training adaptations in cardiac patients. VO_2 determinants such as vascular conductance and a-vO_2 difference have the potential to limit VO_2 or VO_{2peak}.

Table 6 shows that poor vasodilator capacity has the potential to limit VO_2 and/or VO_{2peak} due to a reduction in muscle O_2 perfusion. It is reasonable to suggest that improving impaired vasodilator capacity will improve VO_{2peak}. Supporting this 'perfusion hypothesis', Goodman et al. showed that the majority of the VO_{2peak} improvement seen in CABG patients undertaking exercise training (pre training: 19.0 ± 0.6 ml·kg^{-1}·min^{-1}; post training: 21.0 ± 0.7 ml·kg^{-1}·min^{-1}) were attributable to central haemodynamic determinants including peak vascular conductance [16% increase; $p<0.01$] and maximal calf blood flow (18%; $p<0.01$). Others have rejected central perfusion as a significant contributor to improved VO_{2peak} (Ades et al., 1996). However studies using direct invasive techniques (as opposed to indirect measures such as inert rebreathing) to assess central parameters consistently highlight the important role of central perfusion in improvement VO_{2peak}.

The neatly designed study by Motohiro et al. (2005) showed that three weeks of exercise training following an MI increased SV, Q, peripheral vasodilator capacity and, VO_{2peak} without a change in absolute $a\text{-}vO_2$ difference. Importantly, unlike Shelton et al. (2010) and Critoph et al. (2014) direct measures of limb blood flow, Q and $a\text{-}vO_2$ difference were made. Increases in vasodilator capacity appeared strongly related to the improvements in central haemodynamics (peak Q: r=0.51; SV: r=0.55; p=<0.001) inferring that muscle exercise VO_2 may be dictated by an appropriate redistribution of Q. Like Motohiro et al. (2005), Beere et al. (1999) indicate that inadequate redistribution of blood flow to the working muscle plays a major role in determining VO_{2peak}. In their study the ratio of leg blood flow to Q was considerably lower in older participants than younger participants. The invasive sampling techniques used to assess muscle O_2 extraction showed that whilst *systemic* (global) $a\text{-}vO_2$ difference was lower in older individuals than their younger counterparts, *leg* $a\text{-}vO_2$ difference was similar. Exercise training failed to improve leg O_2 extraction despite increasing systemic $a\text{-}vO_2$ difference, VO_{2peak} and femoral blood flow. Central factors including perfusion may limit exercise tolerance and dictate training adaptations in patients with a cardiac diagnosis. However, results of studies in CHF populations often contradict those in CHD and healthy elderly cohorts. A distinction between CHF and CHD must be made.

CHF represents the 'worst case' scenario for the CV system and it is clear that the mal-adaptations associated with this syndrome are worse than those seen in normal age related functional decline and CHD. In the absence of symptomatic exercise induced myocardial ischaemia, many patients with CHD have a well preserved VO_{2peak} by comparison (Zafrir et al., 1999). The beneficial effects of new cardiology based treatments such as thrombolysis and primary angioplasty (Unal et al., 2004) often prevent permanent myocardial damage. An increasing number of patients with CHD diagnoses do not suffer high level cardiac dysfunction thought to initiate peripheral mal-adaptation observed in established CHF (Poole et al., 2012). Whilst the two diseases often share common aetiology, the severity of their respective pathology is dissimilar and may explain discrepancies between the findings of multiple studies.

In contrast to the conclusions of Beere et al. (1999) and Motohiro et al. (2005), Sullivan et al. (1989a) found that in CHF, exercise training decreases femoral venous O_2 content at the VAT and suggests that improved muscle O_2 extraction rather than central haemodynamics were responsible. However, the later work of Coats and colleagues (1992) found that in CHF patients, eight weeks of exercise training improved systemic vascular resistance and increased both submaximal and maximal Q. Despite this, Coats et al. (1992) did not specifically examine peripheral determinants of O_2 extraction and the conclusions of Sullivan et al. (1989) cannot be dismissed. Despite conflicting physiological evidence, it is important to note that the hearts of patients with CHF are often substantially dilated making it unlikely that myocyte growth and SV changes can be achieved via the Frank-Staling mechanism. In addition, the inotropic and chronotropic incompetence of many may limit the gains achievable through improved HR or cardiac contractility (Duscha et al., 2008). By contrast, peripheral abnormalities seen in cardiac disease extending far beyond those seen through physical deconditioning alone (Vescovo et al., 1996). This may make training induced skeletal muscle adaptations and increased a-vO_2 difference a primary mechanism of improving aerobic capacity (Clark et al., 1996). However, the exact role that peripheral adaptations play in improving VO_{2peak} is complex (Poole et al., 2012).

Abnormal haemodynamics resulting from cardiac injury almost certainly initiate a cascade of events leading to abnormal vascular and skeletal function/structure (Poole et al., 2012, Duscha et al., 2008). Reduced capillary and mitochondrial density, transition to type IIb muscle fibres and muscle atrophy are all common features of CHF that lead to reduced aerobic fitness (Duscha et al., 2008). Reversal of some of these characteristics following exercise training is consistently reported in the literature. For example, Hambrecht et al. (1995) showed that six months of exercise training in CHF patients significantly increased oxidative capacity and mitochondrial density, factors strongly correlated with VO_{2peak}. As well as showing improved VO_{2peak}, the study also documents an increase in VAT and, a reduction in blood lactate, a finding also shown by Sullivan and colleagues (1989a). Changes to skeletal muscle biochemistry and mitochondrial activity may therefore play an important role in attenuating

early metabolic acidosis and improving exercise tolerance.

A twelve month training study by Ades and colleagues (1996) found capillary density and oxidative enzyme activity improved at three and twelve months. Muscle fibre area remained unchanged at three months but significantly increased at twelve months. Although Ades et al. (1996) did find evidence of improved end-diastolic volumes and peak LV performance, enhanced muscle O_2 diffusion and utilisation appeared to be the main contributor to VO_{2peak} increase in *older* patients with CHD. Importantly, no changes in vascular conductance or other measures of perfusion were found suggesting that that enhanced diffusion occurred independently of central determinants of VO_2. Hence, the training responses of older men with CHD may be similar to those of a CHF population (Sullivan et al., 1989a, Clark et al., 1996) opposed to healthy older men (Murias et al., 2010b). When superimposed on normal age-related functional decline, CHD appears to alter the manner in which exercise training improves VO_{2peak} and patients may have greater propensity to experiencing changes to a-vO_2 difference than *Q*.

Advanced age is associated with a number of deleterious physiological changes including reduced endothelial dependent vasodilation. Improved endothelial function is now a widely accepted response to exercise training (Seals et al., 2008). Wisloff and colleagues (2007) recently demonstrated that both moderate continuous and aerobic interval training (high intensity) improved endothelial function. Unlike Motohiro et al. (2005) who maintain that improved *Q* dictated changes to vascular conductance, Wisloff et al, (2007) state that improved endothelial function may in fact mediate cardiac anti-remodelling. Anti-remodelling may have occurred as a consequence of decreased afterload. However whilst increased vascular conductance may have caused this, evidence suggests that improved endothelial function (and vascular conductance) is predicated on exposure to greater laminar shear stress exerted by increased *Q* during exercise (Hambrecht et al., 2003, Hambrecht et al., 1998). Subsequently, it is pertinent that whilst both moderate and aerobic interval training improved

endothelial function, only participants in the latter group experienced significant cardiac anti-remodelling effects.

Because high intensity training is associated with greater vascular shear stress, factors exclusively related to training intensity may be important in dictating whether or not cardiac anti-remodelling occurs. Yet, Vasiliauskas and colleagues, (2007) showed that PCI patients undertaking six months of moderate intensity exercise training (90% of VO_2 attained at 75% predicted HR_{max} during submaximal exercise testing; three times per week) also experienced cardiac anti-remodelling. This training intensity was substantially less than that used in Wisloff and colleague's (2007) aerobic interval training group. However the length of the programme was significantly longer. Intensity may therefore not specifically dictate whether anti-remodelling occurs, rather, an overall greater dose of exercise. Although central adaptations do appear to occur in response to exercise training, improved resting cardiac function may not result in improved VO_2 during exercise.

Even though resting cardiac parameters are prognostically important, neither Wisloff et al. (2007) nor Vasiliauskas et al. (2007) adequately substantiate the link between their improvement and VO_{2peak} changes. Indeed, resting measures of cardiac function are widely regarded as poor predictors of aerobic capacity (Franciosa et al., 1981). This is unsurprising because areas of the myocardium prone to dyskinesis function differently during exercise. SV responses during exercise are therefore less predictable than at rest. Although Goodman et al. (1999) showed that resting ejection fraction (EF) remained unchanged following exercise training, EF at 40% and 70% VO_{2max} coincided with a significant improvement in VO_{2peak} (40% VO_{2peak}: 60 ± 3% versus 63 ± 2%; $p<0.05$; 70% VO_{2peak}: 61 ± 3% versus 64 ± 3%; $p<0.05$). This suggests that dynamic markers of cardiac function are needed to assess changes in cardiac performance following exercise training. However, despite an increase in at fixed submaximal workloads, no corresponding change in absolute Q was observed implying that enhanced a-vO_2 difference was responsible for improving VO_{2peak}.

Following exercise training, MI and angina patients may have *lower Q* at fixed submaximal workloads. Reduction in *Q* during exercise has been attributed to decreased dependence of HR for VO_2 augmentation and increased dependence on a-vO_2 difference with the effect of reducing myocardial stress (Detry et al., 1971). A decrease in HR at fixed workloads suggests reduced myocardial O_2 requirements. This may also explain observed increases in patients' ischaemic threshold by a factor of one third. Improved coronary endothelial function or retardation of CHD progression may also increase coronary perfusion and reduce angina symptoms (Ehsani et al., 1981, Hambrecht et al., 2004). Improvements in clinical symptoms at submaximal workloads may be of greater value to clinicians and patients than changes to peak exercise performance owing to the impact on patients' ability to conduct daily activities and subsequent quality of life.

The complex interaction of central and peripheral factors of exercise intolerance and training adaptations is clear. Whilst cardiac insult may propagate changes to peripheral musculature, a continuous cascade of mal-adaptation to both appears to result in patients' functional decline. This cycle may however be interrupted by appropriate exercise training interventions. Regardless of mechanism, improving CRF carries prognostic significance. The evaluation of CRF can be done by performing either maximal or submaximal exercise tests.

3.8   Exercise Testing and Interpretation

3.8.1   Maximal and Submaximal Exercise Testing

Exercise testing is an invaluable procedure recommended for most patients referred to CR (ACSM, 2013). Data obtained from an exercise test aids clinical decision making by providing information on cardiac event risk, exercise response and tolerance and, outcomes of exercise training. Maximal CPET protocols are the 'gold standard' technique for the evaluation of CRF (Balady et al., 2010). However, whilst CPET or maximal ETT is common in continental Europe and the USA many UK CR teams opt for submaximal exercise tests without cardiorespiratory gas exchange.

Some of the most widely used submaximal exercise testing protocols in the UK includes submaximal cycle ergometry, the six-minute walk, incremental shuttle walk test (ISWT) and Chester step test (ACPICR, 2015). These protocols are preferred not because of the data quality or volume, but because of equipment portability and cost as well as minimal space and training requirements. In addition, submaximal exercise testing is perceived to reduce the risk of a cardiac event in spite of the fact that the risk during maximal CPET is low [0.16%] (Skalski et al., 2012). Not conducting a maximal ETT equates to not knowing how a patient tolerates exercise across a full range of intensities. This is arguably responsible for the conservative approach to exercise prescription in the UK and as previously mentioned may be one cause of poor UK CR outcomes.

When appropriately applied, CPET provides high quality data for risk stratification, medical treatment/diagnoses and exercise prescription. In fact when compared to maximal or even submaximal CPET, traditional submaximal exercise testing offers limited physiological information to prescribe exercise. For example, whilst the six-minute walk test has been shown to have prognostic value (Ingle et al., 2007b), its utility for exercise prescription is poor for most patients with at least a moderate level of CRF. Similarly, the incremental shuttle walk test may be poorly predictive of CRF due to the manner of workload increase. Because O_2 kinetics in CHD and CHF patients are slow (Mezzani et al., 2009), the substantial increase in non- steady-state work rate observed during progressive levels is likely to lead to an over estimations of CRF. The lack of quality data to construct an exercise prescription from will undoubtedly lead to suboptimal exercise training. In spite of this, valuable information can still be obtained from submaximal exercise test protocols.

Compared to CPET appropriate submaximal exercise testing protocols are inexpensive yet still provide rudimental information on a patient's response to exercise at incremental work rates. Obtained data can include HR, BP, rate pressure product (RPP), O_2 saturation and rating of perceived exertion (RPE) up to a predetermined endpoint such as workload or percentage of predicted maximal HR (e.g. 70% predicted HRR). Direct measurements of HR and BP not only

allow the healthcare professional to observe a normal haemodynamic response to exercise at low work rates but when used properly, aids exercise prescription, as does a patients RPE (Borg, 1982). RPP (the product of BP x HR/100) allows an indirect measure of myocardial VO_2 (AACVPR, 2006) and may be used to assess the effects of exercise training. Following exercise training, patients' ischaemic threshold may increase in concert with a RPP reduction. This suggests a reduction in myocardial O_2 demand. Submaximal exercise testing also facilitates the estimation of VO_2 (reported as METs) however this practice is controversial and potentially inaccurate.

A MET is an estimate of energy expenditure at rest and is widely cited as equating a VO_2 of 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$. However, this value is based on a study conducted in the 1890's with a sample of n=1 male [age 40 years; mass 70 kg] (Wasserman et al., 2011) and consequently, should be used with caution. Despite this, during exercise testing an estimate of VO_2 for a given work rate can be expressed as multiples of a resting MET based on an assumed linear relationship between work rate, HR and VO_2 (Noonan and Dean, 2000). However, each exercise test protocol requires a bespoke predictive MET equation because VO_2 is influenced by factors such as test modality, stage length and work rate increment (Noonan and Dean, 2000). Furthermore, even with test specific equations, there is no uniform metabolic cost for a given activity across a healthy population, less so in a clinical population. Percentage of lean muscle mass, obesity and age can all affect VO_2. Indeed in older frailer populations, the 'average MET' may be closer to 2.6 $ml \cdot kg^{-1} \cdot min^{-1}$ rather than 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$ (Byrne et al., 2005). Nonetheless, the use of the MET is a simple expression of energy cost for physical activities. During submaximal exercise testing, METs up to and including the achieved work rate can be estimated. Beyond this, predicted maximal METs (i.e. estimated VO_{2peak}) can be estimated based on the extrapolation of the aforementioned linear work rate, HR and VO_2 relationship (Noonan and Dean, 2000). The accuracy of doing so is questionable and it should be noted that what is already an estimation of VO_2 (MET) at observed work rates subsequently becomes an estimation based on estimation. If maximal exercise parameters are required, a maximal ETT/CPET should be conducted.

The extension of a submaximal exercise testing protocol to a maximal ETT allows a complete

assessment of a patient's response to exercise. Maximal test data such as maximum HR (HR_{max}) are valuable tools for accurate exercise prescription. Furthermore, unlike submaximal exercise tests, a direct MET estimate for peak exercise can be obtained which can be used for exercise prescription and risk stratification (Kavanagh et al., 2002). It is important however to acknowledge that the assumption of a linear work rate, HR and VO_2 relationship until maximal exertion is flawed. Such an assumption will usually result in an over estimation of VO_2 in cardiac patients (Wasserman et al., 2011). This may be in part due to chronotropic incompetence, beta-blockade, slow O_2 kinetics (Brubaker and Kitzman, 2011, Poole et al., 2012) and exercise induced myocardial ischaemia. Patients with exercise induced myocardial ischaemia may experience HR compensation due to SV reductions at workloads beyond their ischaemic threshold (Chaudhry et al., 2009) resulting in a break in HR/work rate linearity. Belardinelli et al. (2003) demonstrated a distinct breakpoint in the relationship between VO_2 and work rate at the onset of myocardial ischaemia. Under these circumstances METs may over predict VO_2. If this is true, the 0.52 MET increase reported by Sandercock et al. (2013b) study may overstate the CRF improvements that UK CR patients achieve. However because no study has reported VO_{2peak} change using 'gold standard' maximal CPET this remains conjecture. CPET is the only reliable method of detecting changes in peak aerobic fitness (i.e. VO_{2peak}), it enhances the quality and volume of data obtained during exercise testing and, the indices obtained can be used for clinical diagnosis, risk stratification and exercise prescription.

3.9   Cardiopulmonary Exercise Testing

CPET, whether using cycle ergometry or a treadmill protocols is the 'gold standard' method of quantifying CRF (Guazzi et al., 2012). Compared to maximal ETT and submaximal exercise tests, CPET is more expensive, less portable and to conduct competently, takes more time and staff training. Despite this, CPET is one of the most widely used exercise prescription tools, principally because objective phenomenon such as VO_{2peak} and VAT serve as a physiological reference point

to base exercise prescriptions (Sullivan et al., 1989b, Murias et al., 2010a, Wisløff et al., 2007, O'Donovan et al., 2005). In addition, CPET has been shown to reliably detect exercise induced myocardial ischaemia [sensitivity 87%; specificity 74%] (Belardinelli et al., 2003) unlike standard ETT which although still widely used, lacks sensitivity (46%) and specificity (66%). In contrast to ETT and submaximal exercise testing which typically measures fewer exercise variables (Table 7), CPET integrates expired gas analysis to provide a greater volume of objective CRF measures. When used effectively, these can help elucidate the pathophysiology of various disease states that lead to exercise intolerance and, help discern the training responses to exercise (Guazzi et al., 2012, Wasserman et al., 2011). Because CPET is an integrative illustration of whole body CV, pulmonary and metabolic function, its data provides highly valuable prognostic information that can be used for risk stratification in clinical populations (Ingle et al., 2014, Arena et al., 2007a, Agostoni et al., 2013, Davies et al., 2006, Weber et al., 1982).

Table 7 – Standard Exercise Tolerance Test Variables

Variable
ECG morphology
HR Response to Exercise
Peak HR
Recovery HR
BP Response to Exercise
Peak BP
Estimated METs
RPE
Clinical Symptoms

ECG = Electrocardiogram; HR = Heart Rate; BP = Blood Pressure; METs = Metabolic Equivalent; RPE = Rating of Perceived Exertion

3.9.1   Methodological principles

The failure of CPET to gain widespread utilisation is perhaps due to expense and, the apparent complexity and overwhelming volume of data displayed by many metabolic carts. However, the quantification of CRF from CPET can be achieved using a concise list of variables (Table 8) derived from O_2 uptake (VO_2), carbon dioxide elimination (VCO_2), minute ventilation (VE) and HR. A series of integrative graphs commonly referred to as the Wasserman 9-panel plot are widely used to encourage a systematic approach to CPET interpretation (Wasserman et al., 2011).

3.9.2   Protocol

CPET protocols are generally conducted using a treadmill or cycle ergometre. Cycle ergometry may be preferred in individuals who are obese, have orthopaedic limitations and/or balance problems. However, whilst cycle ergometry is sympathetic to the needs of some, able participants will often terminate exercise at a VO_2 approximately 10 to 20% lower than if they had exercised on a treadmill. Particular consideration should be given when choosing an appropriate exercise modality to allow participants to achieve their best possible test scores (Taylor et al., 2015, Balady et al., 2010). Failure to do so may result in suboptimal exercise prescriptions, incorrect diagnosis or inaccurate risk stratification. The quality of results obtained from CPET may also depend on the choice of protocol. CPET should last between eight and twelve minutes to minimise the likelihood of factors such as boredom leading to exercise test termination. However, because changes in ventilatory parameters lag behind work rate changes, ramp or pseudo ramp protocols with work rate increments of 5 to 20w per minute may be required to maintain the relationship between VO_2 and work rate in patients with CHD. Alternatively incremental protocols utilising small work rate changes may be used (Naughton et al., 1963, Balke and Ware, 1959). Protocols that utilise large work rate increments such as 'The Bruce' protocol employs large work rate changes and may cause rapid blood lactate

accumulation leading to premature exercise termination. Even with the addition of a less strenuous 'stage 0', the 'Modified Bruce' protocol (Table 9) may be inappropriate for many CHD and CHF patients. Nearly half of all patients (42%) with suspected CHF may be unable to achieve a respiratory exchange ratio >1 (Ingle et al., 2008). Under these circumstances, submaximal markers of CRF can still be obtained, however important variables dependent on maximal effort cannot. In spite of this, protocols such as the 'Modified Bruce Protocol' continue to be used in cardiology departments and are widely understood in UK CR programmes. This makes data derived from them easily interpretable by those outside of the field of exercise physiology. Nonetheless, careful consideration should be given to balancing the requirement of clinical applicability, VO_2-work rate preservation and unnecessarily prolonged tests.

Table 8 – Key cardiopulmonary exercise test variables and their responses in both health and disease

Variable	Unit	Definition	Technical considerations	Significance	Normal Response	Relevance
VO_{2peak}	$ml \cdot kg^{-1} \cdot min^{-1}$ (also expressed as % of predicted VO_{2max})	Highest O_2 uptake obtained during exercise	Breath-by-breath data averaged over 10-20-s where stages <30-s ; 30-60-s if stages are 3-min	Indicative of cardiovascular, pulmonary and skeletal musculature capacity to deliver and utilise O_2	Dependent on age, sex and genetics	Traditionally defines peak aerobic exercise capacity Indicative of cardiovascular fitness, disease severity Prognostically powerful
VAT	$ml \cdot kg^{-1} \cdot min^{-1}$ (also expressed as % of predicted VO_{2max})	The point at which VCO_2 rises at a greater rate than VO_2	Reflects increased buffering of H^+ by intracellular bicarbonate secondary to increased reliance on anaerobic metabolism	The upper limit of sustainable, moderate intensity exercise for many individuals	VAT usually occurs between 40 -60% of VO_{2peak} Declines with age, physical inactivity and presence of chronic diseases	Can be used as an objective reference point for exercise prescription Increases in response to exercise training Objective marker of CRF Prognostically important
Peak RER	Arbitrary unit	VCO_2 divided by VO_2 at peak exercise	Good practice to average peak RER values over the same period as VO_{2peak}	RER will increase as VCO_2 rises when exercise is conducted beyond VAT	Peak RER of >1.10 is indicative of good participant effort during testing	Indicates patient effort. If VO_{2peak} is abnormal and RER of 1.10 is not achieved, poor effort should be considered as cause in addition to disease pathology
VE/VCO_2 slope	Slope gradient	Ventilatory efficiency of CO_2 elimination	Linear relationship until VE increases in response to exercise acidosis (respiratory compensation) Prognostically superior when data from whole test is included	Reflects matching of pulmonary ventilation and perfusion Susceptible to alterations in peripheral mechano and metaboreflex's	VE/VCO_2 slope <34	Index of disease severity Highly prognostic
Oxygen uptake efficiency slope	Slope gradient	Ventilatory efficiency of O_2 uptake	The slope of the gradient between VO_2 (ml) and log_{10} transformed VE	Reflects matching of pulmonary ventilation and oxygen utilisation	Lower values indicate poor efficiency Values of 1400 or 1.4 are consider indicative of poor prognosis	Less widely established than other prognostic markers. Strong correlation to VO_{2peak} Low variability even when exercise tests are considered submaximal
O_2 pulse	ml O_2/beat	VO_2 divided by heart rate	Sum product of stroke volume and a-vo2 diff	Indirect measure of stroke volume	Increases with work rate Peak values vary	A reduction or plateau despite increased work rates suggests falling stroke volume
Breathing reserve	%	VE_{max} divided by MVV (or eMVV)	MVV manoeuvres are uncomfortable for many individuals and may provoke dizziness - eMVV is often preferred	In patient populations breathing reserve indicates possible lung disease	>20% in healthy populations (non-athletic)	Aids delineation of cardiovascular or respiratory limitation to exercise

VO_{2max} = Maximal Oxygen Uptake; O_2= Oxygen; s= Seconds; VAT = Ventilatory Anaerobic Threshold; VCO_2 = Carbon Dioxide Elimination; H^+= Hydrogen Ion; VO_{2peak} = Peak Oxygen Uptake; CRF = Cardiorespiratory Fitness; RER = Respiratory Exchange Ratio; VO_2= Oxygen Uptake; VE/VCO_2= Ventilatory Equivalent for CO_2; VE =Minute Ventilation; a-vO_2 = Arteriovenous O_2 Difference; SV = Stroke Volume; MVV = Maximum Voluntary Ventilation; eMVV = Maximum Voluntary Ventilation;

Table 9 – Stages of the Bruce and Modified Bruce Protocol

Stage	Bruce Speed (mph)	Bruce Gradient (%)	Modified Bruce Speed (mph)	Modified Bruce Gradient (%)
0	N/A	N/A	1.7	0
1	1.7	5	1.7	5
2	1.7	10	1.7	10
3	2.5	12	2.5	12
4	3.4	14	3.4	14
5	4.2	16	4.2	16
6	5	18	5	18

Mph = Miles per hour; N/A = Not applicable; Grey box denotes additional stage zero

3.10   Cardiorespiratory Fitness Parameters

3.10.1 Maximum Oxygen Uptake

VO_{2max} characterises the uppermost limit of the CV system and is defined by the Fick equation as:

$$VO_{2max} = [HR \times SV] \times (a\text{-}vO_2 \text{ diff})$$

Where HR is heart rate, SV is stroke volume and a-vO_2 is arteriovenous O_2 difference (Balady et al., 2010). VO_{2max} is measured in litres although it is often standardised to an individual's body mass and expressed as $ml \cdot kg^{-1} \cdot min^{-1}$ to allow for inter-individual comparison. The term VO_{2max} and VO_{2peak} are often erroneously interchanged with the former implying that a true observable physiological limit to exercise has been attained as indicated by a VO_2 plateau. A true VO_2 plateau is rarely observed in clinical populations with only one in two patients able to achieve maximal CPET criteria (Ingle et al. 2008). In such circumstances, the term VO_{2peak} may be more appropriate. Consequently, VO_{2max} is generally applied to healthy and athletic cohorts whilst VO_{2peak} is widely reported in clinical studies.

3.10.2 Peak Oxygen Uptake

VO_{2peak} is calculated by averaging breath-by-breath gas exchange data over a defined period. For ramp protocols, periods of 10 to 20 seconds are often used whereas protocols with longer stages

may use 30 to 60 seconds (Guazzi et al., 2012). Attainment of a peak CPET performance as opposed to a submaximal CPET can be verified if a patient achieves any two of the criteria listed in Table 10 (ACSM, 2013). Like VO_{2max}, VO_{2peak} is often expressed in $ml \cdot kg^{-1} \cdot min^{-1}$, Wasserman et al., (2011) also recommend referencing a patient's VO_{2peak} with respect to their predicted maximum VO_{2peak} (Hansen et al., 1984). Attainment of <75% of predicted VO_{2max} despite verification of adequate effort suggests exercise limiting pathophysiology (Wasserman et al., 2011). A pathological reduction in VO_{2peak} in CHD and CHF populations is often linked with poor survival outcomes.

Table 10 – Criteria for attainment of peak effort during cardiopulmonary exercise testing

	Criteria
Failure of HR to increase despite an increasing workload (achieving ≥ 85% of age-predicted HR_{max} is a well-recognised indicator of patient effort)	
A VO_2 plateau (or failure to increase by >150 $ml \cdot min^{-1}$) with an increasing workload	
A RER at peak exercise > 1.10	
A RPE >17 on the 6-20 Borg scale or >9 on the 0-10 Foster scale	

HR = Heart Rate; HR_{max} = Maximum Heart Rate; VO_2 = Oxygen Uptake; RER = Respiratory Exchange Ration; RPE = Rating of Perceived Exertion

In CHD and CHF populations, VO_{2peak} has been widely applied as a prognostic marker. Weber and Colleagues (1982) were the first to classify CHF severity according to VO_{2peak} with functional class A (>20 $ml \cdot kg^{-1} \cdot min^{-1}$), B (16-20 $ml \cdot kg^{-1} \cdot min^{-1}$), C (10-15 $ml \cdot kg^{-1} \cdot min^{-1}$) and D (<10 $ml \cdot kg^{-1} \cdot min^{-1}$) corresponding to NYHA class I, II, III and IV respectively (Table 3). Despite the array of available CPET variables, Mancini et al., (1991) found VO_{2peak} to be the strongest predictor of survival amongst heart transplant candidates. A VO_{2peak} >14 $ml \cdot kg^{-1} \cdot min^{-1}$ conferred acceptable one year survival (94%) allowing clinicians to safely defer cardiac transplantation. Moreover, amongst CHD populations, those with a VO_{2peak} <15 $ml \cdot kg^{-1} \cdot min^{-1}$ have been shown to have poor survival outcomes whilst those with a VO_{2peak} >19 $ml \cdot kg^{-1} \cdot min^{-1}$ can expect *improved* survival outcomes (Keteyian et al., 2008). Importantly, increasing VO_{2peak} by 1% or 1 $ml \cdot kg^{-1} \cdot min^{-1}$ may confer a 1 to 15% reduction in risk of death (Keteyian et al., 2008, Vanhees et al., 1995, Kavanagh et al., 2003, Kavanagh et al., 2002). However many patients are unable to provide a 'near maximal effort' for

reasons such as orthopaedic limitation and motivation. In this scenario, the prognostic significance of their attained VO_{2peak} may be reduced and submaximal markers of CRF such as the VAT may be more useful.

3.10.3 Ventilatory Anaerobic Threshold

When plotted on opposing axes, the initial phases of an incremental CPET elicit a linear VO_2 (X axis) and VCO_2 (Y axis) increase. As exercise intensity increases, energy requirements become such that sufficient adenosine triphosphate (ATP) re-synthesis cannot be achieved through oxidative phosphorylation. Further work rate increments are progressively supplemented by anaerobic glycolysis. The metabolites of this process require immediate removal to maintain adequate homeostasis. Muscular lactate moves into the blood stream and the immediate pH balance is maintained by the buffering of H^+ with intracellular bicarbonate such that:

$$CO_2 + H_2O \rightleftarrows H_2CO_3 \rightleftarrows H^+ + HCO_3^-$$
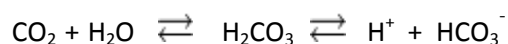
The subsequent dissociation of carbonic acid results in CO_2 and H_2O absorption into the blood where it can be transported to the lungs for elimination. This results in ventilatory CO_2 excess, and a characteristic break point in the linearity of VCO_2 elimination with respect to VO_2 (Beaver et al., 1986a, Wasserman et al., 2011). The VAT may therefore be determined using Beaver and colleagues (1986) V-slope method, where, a trend line is drawn from the initiation of exercise to the point where the slope inflects (gradient of approximately 1). A second line is drawn from the end of exercise to the same deflection point. The data point closest to the intersection of the two lines marks the VAT (Figure 2) and is generally expressed as a VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$) value. The resulting value can also be calculated as a percentage of predicted VO_{2peak}.

The exact point at where the VAT occurs is inherently subjective and has been shown to have wide limits of agreement (~200 ml). Although inter observer mean bias is small (~13 ml), any VAT

measurement could vary by approximately 5 to 10% [coefficient of variation] (Myers et al., 2010). VAT determination requires quality control. By combining other techniques such as the ventilatory equivalent method [Figure 3] (Mezzani et al., 2009) it is possible to verify that the VAT obtained from the V-slope method is accurate. It is however important to note that some patients with CHD and CHF will have an abnormal ventilatory drive (Mezzani et al., 2009) which may impair the accuracy of VAT identification through the ventilatory equivalent methods. Hence, the V-slope method is currently the most widely used and arguably, the 'gold standard' method of identifying VAT.

The VAT has multiple applications including assessment of aerobic fitness, exercise prescription and prognostic evaluation of patients with chronic diseases. Although individuals with superior CRF often achieve a higher VAT, untrained healthy individuals will usually reach their VAT between 40 and 60% of predicted VO_{2max}. Attainment of a VAT corresponding to <40% predicted VO_{2max} is indicative of significant physical deconditioning or disease pathology causing disturbances of the O_2 transport chain (Mezzani et al., 2009, Wasserman et al., 2011). Like $VO_{2peak,}$ VAT holds prognostic value. Non-attainment of the VAT is associated with reduced VO_{2peak} and poor survival outcomes [P<0.01; HR=1.459; CI=1.09-1.10] (Agostoni et al., 2013). A VAT of <13 $ml \cdot kg^{-1} \cdot min^{-1}$ has also been shown to be prognostically significant amongst patients with CHF [log-rank p=0.04] (Lavie et al., 2004) whereas a VAT <11 $ml \cdot kg^{-1} \cdot min^{-1}$ has been shown to identify patients at higher perioperative risk [5.3-fold increase in mortality] (Gitt et al., 2002).
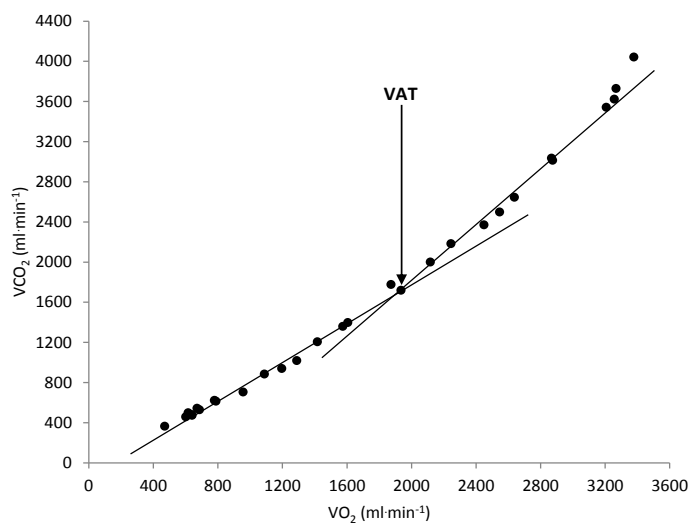
Figure 2 – V-slope method for the detection of the ventilatory anaerobic threshold (VAT). Carbon dioxide elimination (VCO_2) is plotted as a function of oxygen uptake (VO_2), the point where VCO_2 increases disproportionately to VO_2 (marked by the arrow) denotes the VAT.
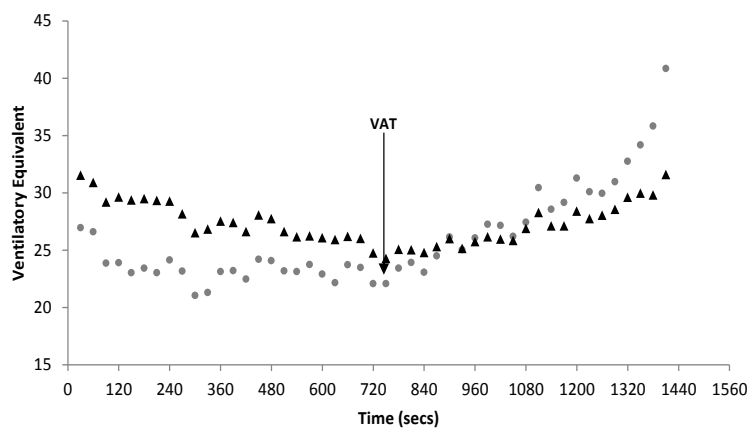
Figure 3 – Ventilatory equivalents method for the detection of the ventilatory anaerobic threshold (VAT). Instantaneous ratio of minute ventilation to carbon dioxide elimination ($VEqCO_2$) and, oxygen uptake ($VEqO_2$) is plotted as a function of time. The point where an observable inflection in $VEqO_2$ (marked by the arrow) denotes the VAT.

Because the VAT may dictate the number of activities that can be conducted without experiencing symptoms of fatigue, improving it may facilitate patients' independence and improve quality of life (Kavanagh et al., 1996). The VAT should be a primary therapeutic target for CR teams prescribing exercise training.

Multiple studies have shown that the VAT increases in response to appropriately prescribed and accurate exercise training interventions (Sullivan et al., 1989b, Wisløff et al., 2007, Keith et al., 1992, Fukuda et al., 2013). However, like any other exercise training regime, adequate exercise dose needs to be applied if the VAT is to increase.

3.10.4 VE/VCO$_2$ Slope

Despite CO_2 ventilatory excess at work rates above the VAT, in healthy individuals, arterial pH and $PaCO_2$ is maintained by proportional ventilatory drive. In CHF and CHD however, ventilation is frequently disproportionate to VCO_2 and may partly explain symptoms of breathlessness at lower levels of exertion. Sullivan and colleagues (1988) were among the first to characterise ventilatory inefficiency in CHF by using the slope-relationship between VE and VCO_2 (VE/VCO$_2$ slope). Subsequent studies have also shown an elevated VE/VCO$_2$ slope in CHD (Van de Veire et al., 2006, McConnell et al., 1998). During CPET, VE/VCO$_2$ slope quantifies the volume of air required to eliminate 1 litre of CO_2 (Figure 4). The modified alveolar equation shows the basic information incorporated into the VE/VCO$_2$ slope:

$$VE = 863 \times VCO_2/PaCO_2 \times (1-V_D/V_T)$$

Where 863 is a constant environmental correction factor and V_D/V_T is ventilatory dead space to ventilatory tidal volume ratio (Whipp, 1983). Consequently, factors such as ventilatory-perfusion mismatch are hypothesised to increased V_D/V_T and steepen the VE/VCO$_2$ slope gradient.
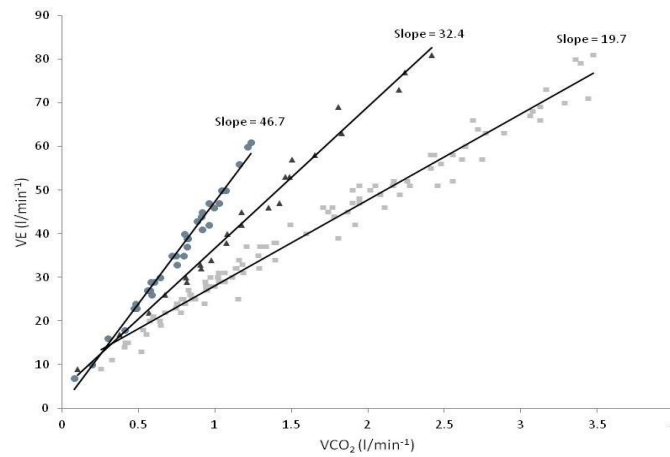
Figure 4 – The slope of the relationship between minute ventilation (VE) and carbon dioxide elimination (VCO_2) (VE/VCO_2 slope). A steeper slope gradient indicates a higher ventilatory drive and poor prognosis. Grey squares show the VE/VCO_2 slope for a healthy individual whilst triangles and circles indicate the slopes of a patient with coronary heart disease and chronic heart failure respectively.

Passino and colleagues (2006) demonstrated that *the* only independent predicted of VE/VCO_2 slope elevation was NT-proBNP, an indicator of myocardial wall stretch and LV dysfunction (AUC 0.768; 95% CI 0.692–0.844). This implicates LV dysfunction (and neurohormonal activation) in ventilatory inefficiency. However, hypersensitive type III (mechanoreceptors) and IV (chemoreceptor) muscle afferents have also been shown to induce an inappropriately high ventilatory response driving down $PaCO_2$ (Wasserman et al., 2011, Guazzi et al., 2012, Piepoli et al., 1995, Mezzani et al., 2009) and thus elevating VE/VCO_2 slope (see VE/VCO_2 slope equation). The relative contribution of these factors remains a debated topic (Poole et al., 2012, Clark et al., 1996, Critoph et al., 2014, Scott et al., 2000) and it is likely that ventilatory inefficiency is product of global cardiopulmonary, CV and muscular changes associated with a cardiac disease state.

Irrespective of cause, a high VE/VCO_2 slope gradient indicates poor prognosis. A gradient of >34 is frequently used to dichotomise those with poor prognosis (Arena et al., 2004, Chua et al., 1997, Cicoira et al., 2001, Corrà et al., 2002, Tsurugaya et al., 2006) although a number of other

values have been advocated. However because the mathematical principle of VE/VCO_2 slope is on a continuous scale, it may be better appreciated as a continuous variable. For the purpose of clinical decision making, a multi-cohort classification system was developed by Arena et al., (2007a). An algorithm based on two year event free risk was recommended for VE/VCO_2 slope gradients of <29.9, 30.0 to 35.9, 36.0 to 44.9, and >45 were associated with <5, ~15, ~30, and ~50% two year risk. Arena et al., (2007a) also recommend specific clinical actions to be taken when patients present with VE/VCO_2 slope within these respective ranges which include serial reassessment, review of medical management and referral to exercise training programmes. However, this model was devised for CHF and many patients with CHD subjected to CPET may also have an observable disproportionate ventilatory drive.

VE/VCO_2 slope elevation has been documented amongst patients with CHD and likely indicates the same myriad of physiological abnormalities observed in CHF. In CHD, VE/VCO_2 slope elevation has been shown to correspond to the degree of cardiac remodelling *and*, neurohormonal activation (Van de Veire et al., 2006). Moreover, limited evidence has also demonstrated that, a VE/VCO_2 slope >34 identifies patients at risk of further cardiac events [3 year event free survival; VE/VCO_2 slope >34 = 65.0%; VE/VCO_2 <34 = 86.7%; p<0.001] (Tsurugaya et al., 2006). Despite its apparent utility, VE/VCO_2, slope like VO_{2peak} may be less useful when patients cannot complete a 'near maximal' exercise test.

The prognostic signal of VE/VCO_2 slope is superior when a linear relationship for the whole CPET is plotted despite ventilatory compensation creating a non-linear component near to participant exhaustion (Ingle et al., 2007a). Ingle et al. (2007a) showed that the prognostics strength of VE/VCO_2 slope is reduced when patients fail to achieve near maximal CPET criteria. The clear implication from this is that to fully harness the prognostic utility of the VE/VCO_2 slope, near maximal effort is required. For many patients however, this may not be achievable due to motivational factors or co-morbidities. Although VE/VCO_2 slope is a highly valued prognosticator, there is a need for reliable indices of CRF obtained when maximal CPET cannot be verified. As already discussed, the VAT is one objective marker of submaximal aerobic fitness

however, the oxygen uptake efficiency slope (OUES) may be more reliable and equally valuable for the purpose of risk stratification or evaluating the effects of exercise training regimes.

3.10.5 Oxygen Uptake Efficiency Slope

The OUES is a method of quantifying ventilatory efficiency with respect to VO_2 (Figure 5). Originally applied to paediatric populations, OUES is calculated by plotting VO_2 against the logarithmically transformed VE [VE_{log10}] (Baba et al., 1996). OUES is significantly correlated with VO_{2peak} in healthy and cardiac populations [r=0.684; p=0.001] (Van Laethem et al., 2005, Van de Veire et al., 2006); a steeper OUES implies superior ventilatory efficiency whereas a lower slope indicates the contrary.

The exponent of the slope provides an index of ventilatory efficiency, muscle O_2 supply and mitochondrial O_2 extraction. Because of this, the pathological specificity of OUES is worse than that of VE/VCO_2 slope. Similar to VE/VCO_2 slope elevation, the mechanisms underpinning OUES can be related to changes in V_D/V_T and $PaCO_2$. The dependency of OUES on ventilation- perfusion matching, CO_2 production, metabolic acidosis and, the increased sensitivity of muscle afferents in response to chemical and mechanical stimuli is intuitive (Antoine-Jonville et al., 2012). Indeed, improvements in V_D/V_T following heart transplantation have been shown to correlate (r=0.55) with subsequent changes in OUES and VO_{2peak} (Van Laethem et al., 2007). However, because OUES also incorporates muscle O_2 perfusion and utilisation, any specific explanations for its elevation are difficult to determine. In spite of this, the incorporation of multiple physiological systems may contribute to the prognostic power of the OUES.
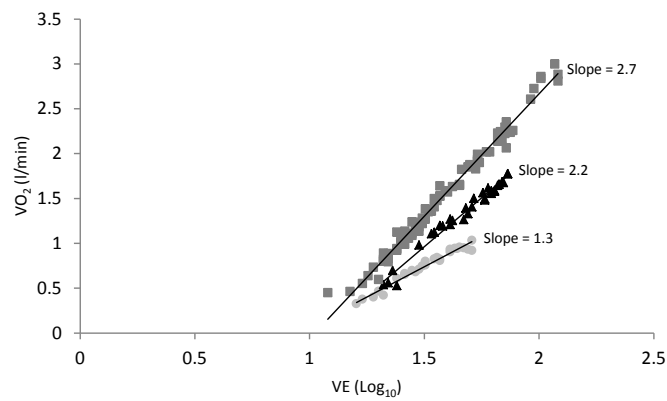
Figure 5 – The oxygen uptake efficiency slope (OUES) shows the relationship between the logarithmically transformed minute ventilation (VE Log_{10}) and oxygen uptake (VO_2). A steeper gradient indicates superior ventilatory efficiency and prognosis. Grey squares show the OUES for a healthy individual whilst triangles and circles indicate the slopes of a patient with coronary heart disease and chronic heart failure respectively.

OUES values of <1.4 to 1.5 have been suggested as predictors of mortality [AUC 0.76; 95% CI 0.68 to 0.83 or AUC 0.82; 95% CI 0.76 to 0.87] (Arena et al., 2007b, Davies et al., 2006) and although OUES responds in a similar manner to VO_{2peak} following exercise training (Defoor et al., 2006, Gademan et al., 2008), whether or not an increase in the OUES reflects improvement event free survival is yet to be established.

Unlike VE/VCO_2 slope, OUES retains similar prognostic significance when calculated from submaximal workloads [OUES 50%; AUC 0.74; 95% CI 0.67 to 0.81] (Arena et al., 2007b) and benefits from greater reproducibility (Van Laethem et al., 2009). OUES values obtained at 50 and 100% of CPET duration may vary by as little as 1% (Davies et al., 2006). Unlike VO_{2peak} and VE/VCO_2 which rely on near maximal efforts to fully harness their prognostic utility (Ingle et al., 2007a, Arena et al., 2003), OUES may be practically applied to CHD and CHF populations where maximal effort is unattainable due to patient anxiety, willingness to exert themselves, significant physical deconditioning or, myocardial ischaemia.

3.10.6 Myocardial Ischaemia

Standard ETT diagnoses myocardial ischemia on the basis of ST segment changes, ventricular arrhythmias, symptoms of angina, or an abnormal haemodynamic response to increasing exercise intensity [SBP drop of >20mmHg] (American Thoracic Society/American College of Chest Physicians, 2003). However, ETT has poor sensitivity (46%) and specificity [66%] (Gianrossi et al., 1989, Belardinelli et al., 2003). Recently, evidence has suggested that the incorporation of metabolic gas exchange substantially improves test sensitivity (87%) and specificity [75%] (Belardinelli et al., 2003). Although the techniques used by Belardinelli et al. (2003) are yet to gain acceptance within the diagnostic setting, there is clear evidence that indirect measures of SV during exercise can be used to demonstrate myocardial ischaemia. In a CR environment, the accurate identification of an ischaemic threshold prior to symptoms of angina would significantly enhance exercise prescription and safety.

3.10.7 Oxygen Pulse and Oxygen Uptake versus Work Rate Slope

Oxygen pulse (O_2/HR) is an indirect measure of SV calculated from a modification of the Fick equation. The principle component of VO_2 is Q, hence an estimation of SV may be made by dividing VO_2 by HR [unit: ml O_2 per beat]. O_2/HR therefore, is the product of SV and a-vO_2 (Whipp et al., 1996). Because myocardial ischaemia has a profound deleterious effect on SV during exercise, changes in the O_2/HR can be used to diagnose suspected exercise induced LV dysfunction and flow limiting CHD (Belardinelli et al., 2003, Chaudhry et al., 2009, Wasserman et al., 2011).

In healthy populations, incremental CPET elicits a linear O_2/HR response, however, in CHD a spontaneous inflection of this response may be observed. Coronary stenosis may inhibit myocardial O_2 supply to the point where ATP re-synthesis is impaired and myocardial contractions become dyssynchronous. Subsequent myocardial wall motion abnormalities cause a reduction in SV causing a compensatory HR increase to sustain Q. HR compensation is

59

unlikely to fully normalise VO_2. The result of increased HR is the compounding of an already inadequate O_2 supply by increasing myocardial work and, reducing diastolic and coronary artery filling times (Ellestad, 1996, Chaudhry et al., 2009, Zafrir et al., 1999). The point at where a HR increase coincides with a spontaneous, premature flattening or inflection of O_2/HR is thought to be indicative of exercise induced myocardial ischaemia (Belardinelli et al., 2003).

Identification of an ischaemic threshold may also be observed to greater effect by combining O_2/HR with the VO_2 versus work rate slope ($\Delta VO_2/\Delta WR$). In healthy individuals a linear increase in $\Delta VO_2/\Delta WR$ of 10 $ml\cdot min^{-1}\cdot watt^{-1}$ is maintained until peak exercise where normal limitation to exercise performance may cause a plateau. A uniform flattening of this relationship (<10 $ml\cdot min^{-1}\cdot watt^{-1}$) is considered indicative of global reduction in CV efficiency and is often seen in CHF (Wasserman et al., 2011). In CHD however, the 10 $ml\cdot min^{-1}\cdot watt^{-1}$ relationship may be maintained until the onset of myocardial ischaemia which causes an abrupt decline in the rate of VO_2 increase. This may manifest as an objective break-point in the $\Delta VO_2/\Delta WR$ slope. Because myocardial wall-motion abnormalities and a subsequent reduction in SV are likely to occur prior to ECG changes and symptoms of angina (Nesto and Kowalchuk, 1987), $\Delta VO_2/\Delta WR$ slope and O_2/HR may be regarded as more sensitive markers of ischaemia.

3.10.8 Prognostic Role of Oxygen Pulse and, Oxygen Uptake versus Work Rate Slope

Although not universally agreed (Cohen-Solal et al., 1997), an absolute peak O_2/HR value of less than 10 to 12 ml/beat has been shown to predict those at greater risk of death (Lavie et al., 2004, Oliveira et al., 2009). Attainment of less than ~80% predicted maximum O_2/HR has also been shown to indicate poor survival outcomes amongst patients with CV and pulmonary disease [HR 1.98; 95% CI 1.16–3.39; p=0.01] (Oliveira et al., 2009). Whether or not peak O_2/HR provides additional prognostic value beyond that offered by VO_{2peak} remains debated (Laukkanen et al., 2006).

Whilst peak O_2/HR may be a valuable prognosticator, the clear limitation of applying this

technique in CHF and CHD populations is that it ignores the role of the periphery i.e. a-vO_2 difference. A correction equation "SV = (peak oxygen pulse/15) x 100" (Mezzani et al., 2009) may be used to remove the peripheral component of O_2/HR at peak (yielding peak SV). However to use this one must assume normal PaO_2 and a-vO_2 at peak which in a number of scenarios would be unwise. In CHF in particular, abnormalities in muscle O_2 extraction have been documented (Shelton et al., 2010, Critoph et al., 2014) and it is not unusual for PaO_2 to be abnormal due to increased V_D, shunt or alveolar perfusion defects (Wasserman et al., 2011). In studies examining O_2/HR as a prognosticator without considering the contributions of the periphery it is reasonable to suggest that peripheral factors may contribute to its prognostic power.

3.10.9 Breathing Reserve

Whilst exercise performance in patients with an isolated diagnosis of CHD or CHF may be limited by CV factors, many patients may also have concurrent respiratory pathology causing exercise intolerance. Poorly controlled asthma and COPD in particular, may limit exercise capacity to a greater extent than a patient's primary cardiac diagnosis. Distinguishing the primary cause of exercise intolerance can be achieved through CPET derived variables.

Breathing reserve is the difference between maximum voluntary ventilation (or estimated MVV; eMVV) and a patients maximum exercise ventilation (VE). eMVV is often preferred over MVV due to unpleasant side effects (e.g. pre-syncope) associated with performing the manoeuvre. eMVV may be calculated as FEV_1 x 40 (Blackie et al., 1991) where FEV_1 is forced expiratory volume in one second obtained from resting spirometry. Breathing reserve is typically >20% in individuals not limited by significant lung pathology (Balady et al., 2010).

3.11 Limitation of Cardiopulmonary Exercise Testing in the Context of Coronary Heart Disease

Although CPET is a highly valuable investigation, data can only determine the overall performance of the CV and cardiorespiratory system. It cannot provide specific information on the physical health of the vascular system. Because a primary goal of CR is to halt or slow down the progression of CHD, a method of quantifying atherogenic rate and CHD severity would be advantageous. Coronary angiography is currently the 'gold standard' method of quantifying coronary arthrosclerosis however its invasive nature and associated risks often make its use inappropriate for many clinical trials. Non-invasive surrogate markers of atherosclerosis such as carotid intima-media thickness (C-IMT) which accurately reflect CHD severity may help determine whether exercise training regimes such as those of a UK CR programme attenuate atherosclerosis progression.

3.12 Carotid Intima-Media Thickness

3.12.1 Clinical significance of Carotid Intima-Media Thickness

It is well established that increased arterial intima-media thickness represent the early stages of atherosclerotic lesions (Pignoli et al., 1986). Although arthrosclerosis is often diffuse throughout the vascular tree, areas prone to low shear stress and oscillatory shear stress such as the bifurcation of the common carotid artery (CCA), have greater propensity to its formation (Chatzizisis et al., 2007). Due to the superficial location of the CCA, B-mode ultrasound imaging provides a simple, non-invasive technique to quantify arthrosclerosis progression.

The distance between two echogenic lines observed when performing B-mode ultrasound imaging on the CCA (Figure 6) has been validated against histopathological samples and is an accurate measure of carotid intima and media thickness [C-IMT] (Pignoli et al., 1986). Increased C-IMT is associated with reduced coronary flow reserve, greater risk of CV events and increased mortality (Lorenz et al., 2007, Rohani et al., 2005, Sonoda et al., 2004). C-IMT significantly

improves CHD prediction when incorporated in to tradition CV risk factor scoring systems tools (Nambi et al., 2010). However, this has been challenged (Lorenz et al., 2012) and the link between C-IMT and coronary plaque severity still remains controversial.
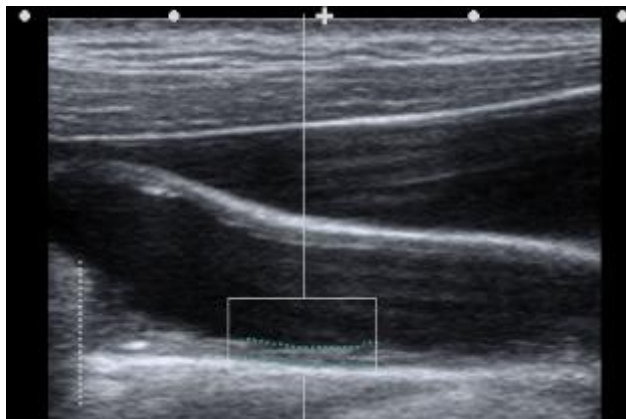
Figure 6 – Insonation of the common carotid artery (CCA) allows the quantification of intima-media thickness as indicated by the two parallel (blue).

Although C-IMT progression indicates the severity of arthrosclerosis in the CCA (Pignoli et al., 1986), *some* studies using coronary angiography have shown a poor association between coronary plaque severity and C-IMT [r=0.19; 95% CI -.53 to 0.20; p=non-significant] (Hulthe et al., 1997). However, a recent study using intravascular ultrasound (IVUS) found that mean C-IMT was in fact strongly correlated with maximal (r=0.53; p<0.0001) and mean (r=0.49; p<0.01) coronary artery IMT (Amato et al., 2007). As well as using a direct measure of coronary arthrosclerosis (IVUS), Amato and colleagues (2007) used a more rigorous C-IMT protocol than Hulthe et al. (1997). C-IMT measurements were obtained at multiple angles of insonation to accommodate the non-uniform distribution of arthrosclerosis around the circumference of the CCA (Tajik et al., 2012). Many studies do not do this (Takashi et al., 2002, Buttitta et al., 2000, Hulthe et al., 1997). Measurements at multiple insonation angles may be needed to accurately quantify and C-IMT and correlate its dimensions with coronary IMT.

Post-mortem studies report strong associations between C-IMT and coronary plaques (Pignoli et al., 1986). It is therefore unsurprising that higher C-IMT values are associated with poorer

survival outcomes. 'Healthy' males over the age of 50 years typically have right and left sided mean C-IMT measurements of 0.460 to 0.620 mm and, 0.530 to 0.700 mm respectively [interquartile range]. 'Healthy' females over the age of 50 years typically have right and left sided mean C-IMT measurements of 0.500 to 0.590 and, 0.520 to 0.640 respectively (Simon et al., 2002).

Normal C-IMT progression in the CCA ranges from 0.001 to 0.030 mm (Lorenz et al., 2012). However patients exposed to CV risk factors experience faster C-IMT progression and higher incidence of CVD. A recent Framingham Heart Study showed that a 1 mm increase in C-IMT substantially elevated the risk of CVD [RR 2.46; 1.18–5.13; p=0.02] and, that a C-IMT >1.5 mm conferred a significant risk of cardiac events [RR 1.92; 95% CI 1.49–2.47; p<0.001] (Polak et al., 2011). However, CVD and CHD are progressive diseases and, incremental risk scoring systems rather than a 'risk cut-off' may better reflect this.

Lorenz et al. (2007) demonstrated that C-IMT increments of as little as 0.1 mm increase the risk of MI by 15%. Although not unequivocally recommended as a CV prognosticator (Lorenz et al., 2012), the IMPROVE study [n=3482] showed that the rate of maximal C-IMT (as opposed to mean C-IMT) progression rate over a 15 month follow-up period was highly predictive of CV events in patients with >3 CV risk factors (Baldassarre et al., 2013). Tracking C-IMT progression and regression in CHD populations appears to have good rational and it is now one of the most widely used surrogate markers of sub-clinical atherosclerosis (O'Leary and Bots, 2010). Until recently however, no guidance on appropriate C-IMT ultrasound protocols had been published. This has led to wide protocol variation and discord regarding the choice of carotid segment or even what constitutes a plaque or thickened intima-media. This has now been addressed. Both Stein et al. (2008) and Touboul et al. (2012) have published consensus statements on how to optimise C-IMT protocols. The latter of these ('The Mannheim Carotid Intima-Media Thickness and Plaque Consensus') provides clear advice for ultrasound operators wishing to measure C-IMT.

3.12.2 Plaque Definition

Plaques are "focal structures" protruding into the lumen by 0.5 mm, 50% of the IMT value or, an IMT thickness of at least 1.5 mm when measured from the intima-lumen interface to the media adventitia interface.

3.12.3 Intima-Media Thickness Definition

The IMT is defined by two, double-line echogenic patterns on both walls of the CCA (Figure 6) when visualised in a longitudinal image. These lines represent the luminal-intima and, media adventitia interfaces and are validated against histopathological samples (Pignoli et al., 1986).

3.12.4 Examination procedure

When performing C-IMT measurements with B-mode ultrasound, the CCA should be visualised in the longitudinal view, perpendicular to the ultrasound beam so that the near and far walls can be visualised. Lateral probe positions are advocated because of the superior 'midfield' resolution. Although multiple angles of insonation are not recommended for clinical practice due to increased examination time, they are promoted in clinical trials for reproducibility and statistical analysis (Touboul et al., 2012). Furthermore, atherosclerosis is not uniformly distributed around the circumference of the CCA and follows an irregular helix-like distribution throughout its different segments (Tajik et al., 2012). Multiple views are advantageous in profiling atherosclerotic regression/progression. The recent advancement in automated and semi-automated ultrasound systems means that reproducing C-IMT protocols is reliable even for the novice operator (Nichols et al., 2014c, Vanoli et al., 2013b, Vanoli et al., 2013a). Monitoring changes in C-IMT following treatment is increasingly accessible and no longer the preserve of experienced sonographers.

3.12.5 Effects of Exercise Training on Carotid Intima-Media Thickness

C-IMT increases through exposure to CV risk factors such as obesity, aging, hypertension, dyslipidaemia and poor CRF (Scholl et al., 2015, Chaubey et al., 2010). Because secondary prevention interventions aim to improve CV risk factors, they may also reduce C-IMT. An inverse relationship between VO_{2max} and C-IMT exists, even in the presence of other CV risk factors. When analysed by quartile, those with a higher VO_{2max} have been shown to have smaller C-IMT values [-0.026 mm per quartile; 95% CI -0.030 to -0.020 mm] (Scholl et al., 2015). Superior CRF may protect against the deleterious effects of other CV risk factors and, attenuate atherosclerosis progression. Those with high levels of CRF and multiple CV risk factors typically still experience faster C-IMT progression than those with high CRF but no/fewer CV risk factors (Scholl et al., 2015). This data does however suggest that structured exercise training might also reduce C-IMT.

Few studies have examined the effects of physical activity on C-IMT (Kadoglou et al., 2008) and the limited existing data is inconclusive. In patients with CHD, Sato et al (2008) demonstrated that the strongest predictors of C-IMT progression were resting systolic BP (p=0.030) and daily walking distance (p=0.024), two well recognised CV risk factors. A six month walking regime showed that C-IMT change was inversely related to daily walking distance ($r=-0.510$; p<0.01). Receiver operating characteristics curve analysis showed that walking more than 4.25 km per day was most likely to inhibit C-IMT progression (sensitivity 64.0%, specificity 73.3%). Amongst treatment responders, the average reduction in C-IMT was -0.018 ± 0.03 mm. Like VO_{2peak} improvements (Duncan et al., 2005), C-IMT reductions following a low intensity exercise training intervention may be small C-IMT (2008). However, some studies have found that higher intensities of exercise training may have no effect on C-IMT.

Tanaka et al. (2002) reported that a three month exercise training regime (average days per week: 5.3 ± 0.3; average session duration: 42.3 ± 1.4 mins; average intensity: 73 ± 1% HR_{max}) did not reduce C-IMT in healthy untrained middle aged and older males (*n*=18). Because Sato et al.

(2008) showed C-IMT reduction over a six month period was small (-0.018 ± 0.03 mm; *n*=40) it is possible that the duration of Tanaka and colleagues (2002) study was insufficient to elicit measurable C-IMT reductions. C-IMT reductions following three months of exercise training are likely to be very small meaning that Tanaka et al. (2002) would need significant more participants to detect a significant change. Furthermore Tanaka and colleagues' (2002) amalgamation of middle aged (38-57 years) and older men (58-77 years) into one group could mask any between-group differences in C-IMT changes. Exercise training may have a greater effect on the elderly and those at elevated CV risk.

Ethnicity is a non-modifiable risk factor. African-Americans are at high risk of CVD (Chaturvedi, 2003). In a study that included hypertensive and obese men and women as well as postmenopausal women, African-Americans undertaking six months of exercise training had a 6.4% reduction in C-IMT. The C-IMT reduction coincided with significantly improved VO_{2max} (baseline VO_{2max}: 27.2 ± 6.3 ml·kg^{-1}·min^{-1}; six months VO_{2max}: 28.9 ± 7.1 ml·kg^{-1}·min^{-1}; p=0.04) as well as a reduction in weight (-2.4%; p=0.02), fasting glucose (-6.6%; p=0.04) and flow mediated dilatation [60%; p<0.001] (Feairheller et al., 2014). Okada et al. (2004) also demonstrated that risk factor management including physical activity guidance ('aerobic' walking for 30 minutes three times per week) could reduce C-IMT (-6.8%; p=0.002) over 2 years. Even though combined drug and lifestyle therapy may provide greater C-IMT reduction (-16.7%; p=0.002), Okada et al. (2004, Feairheller et al. (2014) and Sato (2008) all show that C- IMT reduction is achievable in patients with at least one CV risk factor undertaking lifestyle/exercise interventions that last longer than six months. What is unclear however is whether or not patients with a diagnosis of CHD will experience C-IMT reduction after shorter exercise regimes such as that prescribed by Tanaka et al. (2002) or that provided in a UK CR exercise programme.

3.13 Aims of the thesis

The aim of this thesis was to assess the efficacy of routine practice in a UK CR programme by measuring VO_{2peak} and C-IMT change following an eight week (16 session) low to moderate intensity (40-70% HRR) exercise training regime. In response to these findings we determined whether higher exercise training doses could enhance the VO_{2peak} improvements experienced by patients during the short 'window' of opportunity that UK CR programmes have to improve patients CRF.

3.14   References

AACVPR. (2006). *AACVPR Cardiac Rehabilitation Resource Manual*. Leeds, UK: Human Kinetics.

ACPICR. (2015). Standards for physical activity and exercise in the cardiovascular population. In P. Heather, B. Helen, B. Samantha, B. John, Laura Burgess, G. Keri, G. Fiona, Tim Grove, Sally Turner & W. Catrin (Eds.), (3rd ed.): Association of Chartered Physiotherapists in Cardiac Rehabilitation (ACPICR).

ACSM. (2013). *ACSM's Guidelines for exercise testing and prescription* (9th ed.). Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health.

Ades, P. A., Savage, P. D., Toth, M. J., Harvey-Berino, J., Schneider, D. J., Bunn, J. Y., . . . Ludlow, M. (2009). High-calorie-expenditure exercise: a new approach to cardiac rehabilitation for overweight coronary patients. *Circulation, 119*(20), 2671-2678. doi: 10.1161/circulationaha.108.834184

Ades, P. A., Waldmann, M. L., Meyer, W. L., Brown, K. A., Poehlman, E. T., Pendlebury, W. W., . . . LeWinter, M. M. (1996). Skeletal Muscle and Cardiovascular Adaptations to Exercise Conditioning in Older Coronary Patients. *Circulation, 94*(3), 323-330. doi: 10.1161/01.cir.94.3.323

Agostoni, P., Corra, U., Cattadori, G., Veglia, F., Battaia, E., La Gioia, R., . . . Piepoli, M. F. (2013). Prognostic value of indeterminable anaerobic threshold in heart failure. *Circulation: Heart Failure, 6*(5), 977-987. doi: 10.1161/circheartfailure.113.000471

Amato, M., Montorsi, P., Ravani, A., Oldani, E., Galli, S., Ravagnani, P. M., . . . Baldassarre, D. (2007). Carotid intima-media thickness by B-mode ultrasound as surrogate of coronary atherosclerosis: correlation with quantitative coronary angiography and coronary intravascular ultrasound findings. *European Heart Journal, 28*(17), 2094-2101. doi: 10.1093/eurheartj/ehm244

American Thoracic Society/American College of Chest Physicians. (2003). ATS/ACCP Statement on cardiopulmonary exercise testing. *American Journal of Respiratory and Critical Care Medicine, 167*(2), 211. doi: 10.1164/rccm.167.2.211

Anand, S. S., Islam, S., Rosengren, A., Franzosi, M. G., Steyn, K., Yusufali, A. H., . . . Yusuf, S. (2008). Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. *European Heart Journal, 29*(7), 932-940. doi: 10.1093/eurheartj/ehn018

Anthonisen, N. R., Skeans, M. A., Wise, R. A., Manfreda, J., Kanner, R. E., & Connett, J. E. (2005). The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Annals of internal medicine, 142*(4), 233-239. doi: 10.7326/0003-4819-142-4-200502150-00005

Antoine-Jonville, S., Pichon, A., Vazir, A., Polkey, M. I., & Dayer, M. J. (2012). Oxygen uptake efficiency slope, aerobic fitness, and V (E)-VCO2 slope in heart failure. *Medicine and Science in Sports and Exercise, 44*(3), 428-434. doi: 10.1249/MSS.0b013e31822f8427.

Appel, L. J., Moore, T. J., Obarzanek, E., Vollmer, W. M., Svetkey, L. P., Sacks, F. M., . . . Windhauser, M. M. (1997). A clinical trial of the effects of dietary patterns on blood

pressure. DASH Collaborative Research Group. *New England Journal of Medicine, 336*(16), 1117-1124. doi:10.1056/NEJM199704173361601

Arena, R., Humphrey, R., & Peberdy, M. A. (2003). Prognostic ability of VE/VCO2 slope calculations using different exercise test time intervals in subjects with heart failure. *European Journal of Cardiovascular Prevention & Rehabilitation, 10*(6), 463-468. doi: 10.1097/01.hjr.0000102817.74402.5b

Arena, R., Myers, J., Abella, J., Peberdy, M. A., Bensimhon, D., Chase, P., & Guazzi, M. (2007). Development of a ventilatory classification system in patients with heart failure. *Circulation, 115*(18), 2410-2417. doi:10.1161/CIRCULATIONAHA.107.686576

Arena, R., Myers, J., Aslam, S. S., Varughese, E. B., & Peberdy, M. A. (2004). Peak VO2 and VE/VCO2 slope in patients with heart failure: a prognostic comparison. *American Heart Journal, 147*(2), 354-360. doi:10.1016/j.ahj.2003.07.014

Arena, R., Myers, J., Hsu, L., Peberdy, M. A., Pinkstaff, S., Bensimhon, D., . . . Guazzi, M. (2007). The Minute Ventilation/Carbon Dioxide Production Slope is Prognostically Superior to the Oxygen Uptake Efficiency Slope. *Journal of Cardiac Failure, 13*(6), 462-469. doi: 10.1016/j.cardfail.2007.03.004

Arrigo, I., Brunner-LaRocca, H., Lefkovits, M., Pfisterer, M., & Hoffmann, A. (2008). Comparative outcome one year after formal cardiac rehabilitation: the effects of a randomized intervention to improve exercise adherence. *European Journal of Cardiovascular Prevention & Rehabilitation, 15*(3), 306-311. doi: 10.1097/HJR.0b013e3282f40e01

Baba, R., Nagashima, M., Goto, M., Nagano, Y., Yokota, M., Tauchi, N., & Nishibata, K. (1996). Oxygen uptake efficiency slope: A new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. *Journal of the American College of Cardiology, 28*(6), 1567-1572. doi: 10.1016/S0735-1097(96)00412-3

BACPR. (2012a). RAMIT presents an outdated version of cardiac rehabilitation. *Heart, 98*(8), 672. doi: 10.1136/heartjnl-2012-301766

BACPR. (2012b). Standards and Core Components for Cardiovascular Disease Prevention and Rehabilitation. http://www.bacpr.com/resources/

BACR. (2006). *British Association For Cardiac Rehabilitation: Exercise instructor training module* (4th ed.). Leeds: Human Kinetics.

Balady, G. J., Arena, R., Sietsema, K., Myers, J., Coke, L., Fletcher, G. F., . . . Milani, R. V. (2010). Clinician's Guide to Cardiopulmonary Exercise Testing in Adults: A Scientific Statement From the American Heart Association. *Circulation, 122*(2), 191-225. doi: 10.1161/CIR.0b013e3181e52e69

Balady, G. J., Jette, D., Scheer, J., Downing, J., The Massachusetts Association of Cardiovascular, & Pulmonary Rehabilitation Database Co-investigators. (1996). Changes in Exercise Capacity Following Cardiac Rehabilitation in Patients Stratified According to Age and Gender: Results of the Massachusetts Association of Cardiovascular and Pulmonary Rehabilitation Multicenter Database. *Journal of Cardiopulmonary Rehabilitation and Prevention, 16*(1), 38-46.

Baldassarre, D., Veglia, F., Hamsten, A., Humphries, S. E., Rauramaa, R., de Faire, U., . . . Mannarino, E. (2013). Progression of carotid intima-media thickness as predictor of vascular events results from the IMPROVE study. *Arteriosclerosis, Thrombosis, and Vascular Biology, 33*(9), 2273-2279. doi:10.1161/ATVBAHA.113.301844

Balke, B., & Ware, R. W. (1959). An experimental study of physical fitness of Air Force personnel. *US Armed Forces Medical Journal, 10*, 675-688.

Bassett, D., & Howley, E. (2000). Limiting factors for maximum oxygen uptake and determinants of endurance performance. *Medicine and Science in Sports and Exercise, 32*(1), 70-84.

Beauchamp, A., Worcester, M., Ng, A., Murphy, B., Tatoulis, J., Grigg, L., . . . Goble, A. (2013). Attendance at cardiac rehabilitation is associated with lower all-cause mortality after 14 years of follow-up. *Heart, 99*(9), 620-625. doi:10.1136/heartjnl-2012-303022

Beaver, W. L., Wasserman, K., & Whipp, B. J. (1986). Bicarbonate buffering of lactic acid generated during exercise. *Journal of Applied Physiology, 60*(2), 472-478.

Beere, P. A., Russell, S. D., Morey, M. C., Kitzman, D. W., & Higginbotham, M. B. (1999). Aerobic Exercise Training Can Reverse Age-Related Peripheral Circulatory Changes in Healthy Older Men. *Circulation, 100*(10), 1085-1094. doi: 10.1161/01.cir.100.10.1085

Belardinelli, R., Lacalaprice, F., Carle, F., Minnucci, A., Cianci, G., Perna, G., & D'Eusanio, G. (2003). Exercise-induced myocardial ischaemia detected by cardiopulmonary exercise testing. *Eur Heart J, 24*(14), 1304-1313. doi:10.1016/S0195-668X(03)00210-0

Bellotto, F., Compostella, L., Agostoni, P., Torregrossa, G., Setzu, T., Gambino, A., . . . Gerosa, G. (2011). Peripheral Adaptation Mechanisms in Physical Training and Cardiac Rehabilitation: The Case of a Patient Supported by a Cardiowest Total Artificial Heart. *Journal of Cardiac Failure, 17*(8), 670-675. doi: 10.1016/j.cardfail.2011.04.006

Bethell, H., Lewin, R., & Dalal, H. (2009). Cardiac rehabilitation in the United Kingdom. *Heart, 95*(4), 271-275. doi:doi:10.1136/hrt.2007.134338

Blackie, S. P., Fairbarn, M. S., McElvaney, N. G., Wilcox, P. G., Morrison, N. J., & Pardy, R. L. (1991). Normal values and ranges for ventilation and breathing pattern at maximal exercise. *Chest, 100*(1), 136-142. doi:10.1378/chest.100.1.136

Bode, C., & Zirlik, A. (2007). STEMI and NSTEMI: the dangerous brothers. *European Heart Journal, 28*(12), 1403-1404. doi:10.1093/eurheartj/ehm159

Boden, W. E., O'Rourke, R. A., Teo, K. K., Hartigan, P. M., Maron, D. J., Kostuk, W. J., . . . Weintraub, W. S. (2007). Optimal Medical Therapy with or without PCI for Stable Coronary Disease. *New England Journal of Medicine, 356*(15), 1503-1516. doi: doi:10.1056/NEJMoa070829

Borg, G. A. (1982). Psychophysical bases of perceived exertion. *Medicine and Science in Sports and Exercise, 14*(5), 377-381.

Braunwald, E. (1989). Unstable angina: a classification. *Circulation, 80*, 410-414. doi: 10.1161/01.CIR.80.2.410

British Heart Foundation. (2014). The National Audit for Cardiac Rehabilitation Annual Statisitics Report 2014. http://www.cardiacrehabilitation.org.uk/docs/2014.pdf

Brodie, D., Bethell, H., & Breen, S. (2006). Cardiac rehabilitation in England: a detailed national survey. *European Journal of Cardiovascular Prevention & Rehabilitation, 13*(1), 122- 128. doi: 10.1097/01.hjr.0000192741.04103.d3

Brubaker, P. H., & Kitzman, D. W. (2011). Chronotropic Incompetence: Causes, Consequences, and Management. *Circulation, 123*(9), 1010-1020. doi: 10.1161/circulationaha.110.940577

Buttitta, F., Limbruno, U., Petronio, A. S., Baglini, R., Strata, G., Mariotti, R., . . . Balbarini, A. (2000). Usefulness of Carotid Intima-Media Thickness Measurement and Peripheral B-Mode Ultrasound Scan in the Clinical Screening of Patients with Coronary Artery Disease. *Angiology, 51*(4), 269-279. doi: 10.1177/000331970005100401

Byrne, N. M., Hills, A. P., Hunter, G. R., Weinsier, R. L., & Schutz, Y. (2005). Metabolic equivalent: one size does not fit all. *Journal of Applied Physiology, 99*(3), 1112-1119. doi: 10.1152/japplphysiol.00023.2004

Campeau, L. (1976). Letter: Grading of angina pectoris. *Circulation, 54*(3), 522-523. doi: 10.1161/01.CIR.54.3.522.b

Cardozo, G. G., Oliveira, R. B., & Farinatti, P. T. (2015). Effects of High Intensity Interval versus Moderate Continuous Training on Markers of Ventilatory and Cardiac Efficiency in Coronary Heart Disease Patients. *The Scientific World Journal, 2015*. doi: 10.1155/2015/192479

Carroll, S., Tsakirides, C., Hobkirk, J., Moxon, J. W. A., Moxon, J. W. D., Dudfield, M., & Ingle, L. (2011). Differential Improvements in Lipid Profiles and Framingham Recurrent Risk Score in Patients With and Without Diabetes Mellitus Undergoing Long-Term Cardiac Rehabilitation. *Archives of Physical Medicine and Rehabilitation, 92*(9), 1382-1387. doi: 10.1016/j.apmr.2011.04.013

Carson, P., Phillips, R., Lloyd, M., Tucker, H., Neophytou, M., Buch, N. J., . . . Simpson, T. (1982). Exercise after myocardial infarction: a controlled trial. *Journal of the Royal College of Physicians of London, 16*(3), 147-151.

Chaturvedi, N. (2003). Ethnic differences in cardiovascular disease. *Heart, 89*(6), 681-686. doi: 10.1136/heart.89.6.681

Chatzizisis, Y. S., Coskun, A. U., Jonas, M., Edelman, E. R., Feldman, C. L., & Stone, P. H. (2007). Role of Endothelial Shear Stress in the Natural History of Coronary Atherosclerosis and Vascular RemodelingMolecular, Cellular, and Vascular Behavior. *Journal of the American College of Cardiology, 49*(25), 2379-2393. doi: 10.1016/j.jacc.2007.02.059

Chaudhry, S., Arena, R., Wasserman, K., Hansen, J. E., Lewis, G. D., Myers, J., . . . Boden, W. E. (2009). Exercise-Induced Myocardial Ischemia Detected by Cardiopulmonary Exercise Testing. *The American Journal of Cardiology, 103*(5), 615-619. doi: 10.1016/j.amjcard.2008.10.034

Chow, C. K., Islam, S., Bautista, L., Rumboldt, Z., Yusufali, A., Xie, C., . . . Yusuf, S. (2011). Parental history and myocardial infarction risk across the world: the INTERHEART

Study. *Journal of the American College of Cardiology, 57*(5), 619-627. doi: 10.1016/j.jacc.2010.07.054.

Chua, T. P., Ponikowski, P., Harrington, D., Anker, S. D., Webb-Peploe, K., Clark, A. L., . . . Coats, A. J. S. (1997). Clinical Correlates and Prognostic Significance of the Ventilatory Response to Exercise in Chronic Heart Failure. *Journal of the American College of Cardiology, 29*(7), 1585-1590. doi: 10.1016/S0735-1097(97)00078-8

Cicoira, M., Davos, C. H., Florea, V., Shamim, W., Doehner, W., Coats, A. J., & Anker, S. D. (2001). Chronic heart failure in the very elderly: clinical status, survival, and prognostic factors in 188 patients more than 70 years old. *American Heart Journal, 142*(1), 174- 180.

Clark, A. L., Poole-Wilson, P. A., & Coats, A. J. S. (1996). Exercise limitation in chronic heart failure: Central role of the periphery. *Journal of the American College of Cardiology, 28*(5), 1092-1102. doi: 10.1016/S0735-1097(96)00323-3

Clément, K., Viguerie, N., Poitou, C., Carette, C., Pelloux, V., Curat, C. A., . . . Langin, D. (2004). Weight loss regulates inflammation-related genes in white adipose tissue of obese subjects. *The FASEB Journal, 18*(14), 1657-1669. doi: 10.1096/fj.04-2204com

Coats, A. J., Adamopoulos, S., Radaelli, A., McCance, A., Meyer, T. E., Bernardi, L., . . . Forfar, C. (1992). Controlled trial of physical training in chronic heart failure. Exercise performance, hemodynamics, ventilation, and autonomic function. *Circulation, 85*(6), 2119-2131. doi: 10.1161/01.cir.85.6.2119

Cohen-Solal, A., Barnier, P., Pessione, F., Seknadji, P., Logeart, D., Laperche, T., & Gourgon, R. (1997). Comparison of the long term prognostic value of peak exercise oxygen pulse and peak oxygen uptake in patients with chronic heart failure. *Heart, 78*(6), 572-576.

Conraads, V. M., Denollet, J., De Maeyer, C., Van Craenenbroeck, E., Verheyen, J., & Beckers, P. (2012). Exercise training as an essential component of cardiac rehabilitation. *Heart, 98*(8), 674-675. doi: DOI 10.1136/heartjnl-2012-301912

Cooper, A., Timmis, A., & Skinner, J. (2010). Assessment of recent onset chest pain or discomfort of suspected cardiac origin: summary of NICE guidance. *BMJ, 340*.

Corrà, U., Mezzani, A., Bosimini, E., Scapellato, F., Imparato, A., & Giannuzzi, P. (2002). Ventilatory response to exercise improves risk stratification in patients with chronic heart failure and intermediate functional capacity. *American Heart Journal, 143*(3), 418- 426. doi: http://dx.doi.org/10.1067/mhj.2002.120772

Critchley, J. A., & Capewell, S. (2003). Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: A systematic review. *Journal of the American Medical Association, 290*(1), 86-97. doi: 10.1001/jama.290.1.86

Critoph, C. H., Patel, V., Mist, B., & Elliott, P. M. (2014). Cardiac output response and peripheral oxygen extraction during exercise among symptomatic hypertrophic cardiomyopathy patients with and without left ventricular outflow tract obstruction. *Heart, 100*(8), 639-646. doi: doi:10.1136/heartjnl-2013-304914

Dalal, H. M., Zawada, A., Jolly, K., Moxham, T., & Taylor, R. S. (2010). Home based versus centre based cardiac rehabilitation: Cochrane systematic review and meta-analysis. *BMJ, 340*, b5631.

Davies, E. J., Moxham, T., Rees, K., Singh, S., Coats, A. J. S., Ebrahim, S., . . . Taylor, R. S. (2010). Exercise based rehabilitation for heart failure. *Cochrane Database of Systematic Reviews*(4). Doi 10.1002/14651858.Cd003331.Pub3

Davies, L. C., Wensel, R., Georgiadou, P., Cicoira, M., Coats, A. J. S., Piepoli, M. F., & Francis, D. P. (2006). Enhanced prognostic value from cardiopulmonary exercise testing in chronic heart failure by non-linear analysis: oxygen uptake efficiency slope. *European Heart Journal, 27*(6), 684-690. doi: 10.1093/eurheartj/ehi672

Defoor, J., Schepers, D., Reybrouck, T., Fagard, R., & Vanhees, L. (2006). Oxygen uptake efficiency slope in coronary artery disease: clinical use and response to training. *International journal of sports medicine, 27*(9), 730-737.

Dekleva, M. N., Mazic, S. D., Suzic-Lazic, J. M., Marković-Nikolić, N. S., Beleslin, B. D., Stevanović, A. M., . . . Arandjelović, A. M. (2014). Left ventricular diastolic performance at rest is essential for exercise capacity in patients with non-complicated myocardial infarction. *Heart & Lung: The Journal of Acute and Critical Care, 43*(6), 500-505.

Department of Health. (2010). *Department of Health's commissioning pack on cardiac rehabilitation*

Department of Health. (2011). *Physical activity guidelines for Adults (19–64 years)*. Retrieved from https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213 740/dh_128145.pdf.

DETRY, J.-M. R., ROUSSEAU, M., VANDENBROUCKE, G., KUSUMI, F., BRASSEUR, L. A., & BRUCE, R. A. (1971). Increased Arteriovenous Oxygen Difference After Physical Training in Coronary Heart Disease. *Circulation, 44*(1), 109-118. doi: 10.1161/01.cir.44.1.109

Doherty, P., & Lewin, R. (2012). The RAMIT trial, a pragmatic RCT of cardiac rehabilitation versus usual care: what does it tell us? *Heart, 98*(8), 605-606. doi: 10.1136/heartjnl- 2012-301728

Duncan, G. E., Anton, S. D., Sydeman, S. J., Newton, R. L., Corsica, J. A., Durning, P. E., . . . Perri, M. G. (2005). Prescribing exercise at varied levels of intensity and frequency: a randomized trial. *Archives of Internal Medicine, 165*(20), 2362-2369.

Duscha, B. D., Schulze, P. C., Robbins, J. L., & Forman, D. E. (2008). Implications of chronic heart failure on peripheral vasculature and skeletal muscle before and after exercise training. *Heart failure reviews, 13*(1), 21-37.

Dzau, V. J., Antman, E. M., Black, H. R., Hayes, D. L., Manson, J. E., Plutzky, J., . . . Stevenson, W. (2006). The Cardiovascular Disease Continuum Validated: Clinical Evidence of Improved Patient Outcomes: Part II: Clinical Trial Evidence (Acute Coronary Syndromes Through Renal Disease) and Future Directions. *Circulation, 114*(25), 2871-2891. doi: 10.1161/circulationaha.106.655761

Ehrman, J. K., Gordon, P. M., Visich, P. S., & Keteyian, S. J. (2013). *Clinical exercise physiology*: Human Kinetics.

Ehsani, A. A., Heath, G. W., Hagberg, J. M., Sobel, B. E., & Holloszy, J. O. (1981). Effects of 12 months of intense exercise training on ischemic ST-segment depression in patients with coronary artery disease. *Circulation, 64*(6), 1116-1124. doi: 10.1161/01.cir.64.6.1116

Ellestad, M. H. (1996). Chronotropic Incompetence The Implications of Heart Rate Response to Exercise (Compensatory Parasympathetic Hyperactivity?). *Circulation, 93*(8), 1485-1487.

Erdman, R. A. M., Duivenvoorden, H. J., Verhage, F., Kazemier, M., & Hugenholtz, P. G. (1986). Predictability of Beneficial Effects in Cardiac Rehabilitation: A Randomized Clinical Trial of Psychosocial Variables. *Journal of Cardiopulmonary Rehabilitation and Prevention, 6*(6), 206-213.

Feairheller, D. L., Diaz, K. M., Kashem, M. A., Thakkar, S. R., Veerabhadrappa, P., Sturgeon, K. M., . . . Lee, H. (2014). Effects of moderate aerobic exercise training on vascular health and blood pressure in african americans. *The Journal of Clinical Hypertension, 16*(7), 504-510.

Fletcher, G. F., Balady, G. J., Amsterdam, E. A., Chaitman, B., Eckel, R., Fleg, J., . . . Rodney, R. (2001). Exercise standards for testing and training a statement for healthcare professionals from the American Heart Association. *Circulation, 104*(14), 1694-1740.

Franciosa, J. A., Park, M., & Barry Levine, T. (1981). Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. *The American Journal of Cardiology, 47*(1), 33-39. doi: http://dx.doi.org/10.1016/0002-9149(81)90286-1

Fukuda, T., Kurano, M., Fukumura, K., Yasuda, T., Iida, H., Morita, T., . . . Nakajima, T. (2013). Cardiac Rehabilitation Increases Exercise Capacity with a Reduction of Oxidative Stress. *Korean circulation journal, 43*(7), 481-487.

Gademan, M. G. J., Swenne, C. A., Verwey, H. F., van de Vooren, H., Haest, J. C. W., van Exel, H. J., . . . van der Wall, E. E. (2008). Exercise training increases oxygen uptake efficiency slope in chronic heart failure. *European Journal of Cardiovascular Prevention & Rehabilitation, 15*(2), 140-144. doi: 10.1097/HJR.0b013e3282ef19986

Gardin, J. M., Leifer, E. S., Fleg, J. L., Whellan, D., Kokkinos, P., LeBlanc, M.-H., . . . Kitzman, D. W. (2009). Relationship of Doppler-Echocardiographic left ventricular diastolic function to exercise performance in systolic heart failure: The HF-ACTION study. *American Heart Journal, 158*(4, Supplement), S45-S52. doi: http://dx.doi.org/10.1016/j.ahj.2009.07.015

Gayda, M., Brun, C., Juneau, M., Levesque, S., & Nigam, A. (2008). Long-term cardiac rehabilitation and exercise training programs improve metabolic parameters in metabolic syndrome patients with and without coronary heart disease. *Nutrition, Metabolism and Cardiovascular Diseases, 18*(2), 142-151.

Gianrossi, R., Detrano, R., Mulvihill, D., Lehmann, K., Dubach, P., Colombo, A., . . . Froelicher, V. (1989). Exercise-induced ST depression in the diagnosis of coronary artery disease. A meta-analysis. *Circulation, 80*(1), 87-98.

Gitt, A. K., Wasserman, K., Kilkowski, C., Kleemann, T., Kilkowski, A., Bangert, M., . . . Senges, J. (2002). Exercise Anaerobic Threshold and Ventilatory Efficiency Identify Heart Failure Patients for High Risk of Early Death. *Circulation, 106*(24), 3079-3084. doi: 10.1161/01.cir.0000041428.99427.06

Goodman, J. M., Pallandi, D. V., Reading, J. R., Plyley, M. J., Liu, P. P., & Kavanagh, T. (1999). Central and peripheral adaptations after 12 weeks of exercise training in post-coronary artery bypass surgery patients. *J Cardiopulm Rehabil, 19*(3), 144-150.

Grabowski, T., & Tortora, G. (2003). *Principles of anatomy and physiology*: John Wiley & Sons.

Guazzi, M., Adams, V., Conraads, V., Halle, M., Mezzani, A., Vanhees, L., . . . Myers, J. (2012). Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *European Heart Journal, 33*(23), 2917-2927. doi: 10.1093/eurheartj/ehs221

Hage, C., Mattsson, E., & Ståhle, A. (2003). Long term effects of exercise training on physical activity level and quality of life in elderly coronary patients — A three- to six-year follow-up. *Physiotherapy Research International, 8*(1), 13-22. doi: 10.1002/pri.268

Hambrecht, R., Adams, V., Erbs, S., Linke, A., Kränkel, N., Shu, Y., . . . Schuler, G. (2003). Regular Physical Activity Improves Endothelial Function in Patients With Coronary Artery Disease by Increasing Phosphorylation of Endothelial Nitric Oxide Synthase. *Circulation, 107*(25), 3152-3158. doi: 10.1161/01.cir.0000074229.93804.5c

Hambrecht, R., Fiehn, E., Weigl, C., Gielen, S., Hamann, C., Kaiser, R., . . . Schuler, G. (1998). Regular Physical Exercise Corrects Endothelial Dysfunction and Improves Exercise Capacity in Patients With Chronic Heart Failure. *Circulation, 98*(24), 2709-2715. doi: 10.1161/01.cir.98.24.2709

Hambrecht, R., Niebauer, J., Fiehn, E., Kälberer, B., Offner, B., Hauer, K., . . . Schuler, G. (1995). Physical training in patients with stable chronic heart failure: Effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. *Journal of the American College of Cardiology, 25*(6), 1239-1249. doi: 10.1016/0735- 1097(94)00568-B

Hambrecht, R., Walther, C., Möbius-Winkler, S., Gielen, S., Linke, A., Conradi, K., . . . Schuler, G. (2004). Percutaneous Coronary Angioplasty Compared With Exercise Training in Patients With Stable Coronary Artery Disease: A Randomized Trial. *Circulation, 109*(11), 1371-1378. doi: 10.1161/01.cir.0000121360.31954.1f

Hansen, J., Sue, D., & Wasserman, K. (1984). Predicted values for clinical exercise testing. *The American review of respiratory disease, 129*(2 Pt 2), S49-55.

Haskell, W. L. (2001). What to look for in assessing responsiveness to exercise in a health context. *Medicine and Science in Sports and Exercise, 33*(6 Suppl), S454-458; discussion S493-454.

Heller, R. F., Knapp, J. C., Valenti, L. A., & Dobson, A. J. (1993). Secondary prevention after acute myocardial infarction. *The American Journal of Cardiology, 72*(11), 759-762.

Heran, B. S., Chen, J., Ebrahim, S., Moxham, T., Oldridge, N., Rees, K., . . . Taylor, R. S. (2011). Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database of Systematic Reviews, 7*.

Hoffman, S. N., TenBrook, J. J. A., Wolf, M. P., Pauker, S. G., Salem, D. N., & Wong, J. B. (2003). A meta-analysis of randomized controlled trials comparing coronary artery bypass graft with percutaneous transluminal coronary angioplasty: one- to eight-year outcomes. *Journal of the American College of Cardiology, 41*(8), 1293-1304. doi: 10.1016/S0735-1097(03)00157-8

Hofman-Bang, C., Lisspers, J., Nordlander, R., Nygren, Å., Sundin, Ö., Öhman, A., & Rydén, L. (1999). Two-year results of a controlled study of residential rehabilitation for patients treated with percutaneous transluminal coronary angioplasty. A randomized study of a multifactorial programme. *European Heart Journal, 20*(20), 1465-1474. doi: 10.1053/euhj.1999.1544

Hugh, J., & Mullee, M. A. (1990). A controlled trial of community based coronary rehabilitation. *British Heart Journal, 64*(6), 370-375. doi: 10.1136/hrt.64.6.370

Hulthe, J., Wikstrand, J., Emanuelsson, H., Wiklund, O., de Feyter, P. J., & Wendelhag, I. (1997). Atherosclerotic Changes in the Carotid Artery Bulb as Measured by B-Mode Ultrasound Are Associated With the Extent of Coronary Atherosclerosis. *Stroke, 28*(6), 1189-1194. doi: 10.1161/01.str.28.6.1189

Ingle, L., & Carroll, S. (2013). Cardiac rehabilitation and exercise training. *Heart*. doi: 10.1136/heartjnl-2013-304015

Ingle, L., Goode, K., Carroll, S., Sloan, R., Boyes, C., Cleland, J. G. F., & Clark, A. L. (2007). Prognostic value of the VE/VCO2 slope calculated from different time intervals in patients with suspected heart failure. *International Journal of Cardiology, 118*(3), 350-355. doi: 10.1016/j.ijcard.2006.07.105

Ingle, L., Rigby, A. S., Carroll, S., Butterly, R., King, R. F., Cooke, C. B., . . . Clark, A. L. (2007). *Prognostic value of the 6 min walk test and self-perceived symptom severity in older patients with chronic heart failure* (Vol. 28).

Ingle, L., Rigby, A. S., Sloan, R., Carroll, S., Goode, K. M., Cleland, J. G., & Clark, A. L. (2014). Development of a composite model derived from cardiopulmonary exercise tests to predict mortality risk in patients with mild-to-moderate heart failure. *Heart, 100*(10), 781-786. doi: 10.1136/heartjnl-2013-304614

Ingle, L., Witte, K. K., Cleland, J. G. J. F., & Clark, A. L. (2008). The prognostic value of cardiopulmonary exercise testing with a peak respiratory exchange ratio of <1.0 in patients with chronic heart failure. *International Journal of Cardiology, 127*(1), 88-92. doi: 10.1016/j.ijcard.2007.04.075

Jairath, N. (1999). *Coronary Heart Disease & Risk Factor Management: A Nursing Perspective*. Philadelphia, Pennsylvania, USA: W.B Saunders Company.

Jolliffe, J., Rees, K., Taylor, R. R., Thompson, D. R., Oldridge, N., & Ebrahim, S. (2001). Exercise-based rehabilitation for coronary heart disease. *The Cochrane Library*.

Jolly, K., Taylor, R. S., Lip, G. Y., & Stevens, A. (2006). Home-based cardiac rehabilitation compared with centre-based rehabilitation and usual care: a systematic review and meta-analysis. *International Journal of Cardiology, 111*(3), 343-351.

Juutilainen, A., Lehto, S., Rönnemaa, T., Pyörälä, K., & Laakso, M. (2005). Type 2 Diabetes as a "Coronary Heart Disease Equivalent": An 18-year prospective population-based study in Finnish subjects. *Diabetes Care, 28*(12), 2901-2907. doi: 10.2337/diacare.28.12.2901

Kadoglou, N., Iliadis, F., & Liapis, C. (2008). Exercise and carotid atherosclerosis. *European Journal of Vascular and Endovascular Surgery, 35*(3), 264-272.

Kannel, W. B., Feinleib, M., McNamara, P. M., Garrison, R. J., & Castelli, W. P. (1979). AN INVESTIGATION OF CORONARY HEART DISEASE IN FAMILIES: THE FRAMINGHAM OFFSPRING STUDY. *American Journal of Epidemiology, 110*(3), 281-290.

Kavanagh, T., Mertens, D. J., Hamm, L. F., Beyene, J., Kennedy, J., Corey, P., & Shephard, R. J. (2002). Prediction of Long-Term Prognosis in 12 169 Men Referred for Cardiac Rehabilitation. *Circulation, 106*(6), 666-671. doi: 10.1161/01.cir.0000024413.15949.ed

Kavanagh, T., Mertens, D. J., Hamm, L. F., Beyene, J., Kennedy, J., Corey, P., & Shephard, R. J. (2003). Peak oxygen intake and cardiac mortality in women referred for cardiac rehabilitation. *Journal of the American College of Cardiology, 42*(12), 2139-2143. doi: 10.1016/j.jacc.2003.07.028

Kavanagh, T., Myers, M. G., Baigrie, R. S., Mertens, D., Sawyer, P., & Shephard, R. (1996). Quality of life and cardiorespiratory function in chronic heart failure: effects of 12 months' aerobic training. *Heart, 76*(1), 42-49.

Keeley, E. C., Boura, J. A., & Grines, C. L. (2003). Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *The Lancet, 361*(9351), 13-20. doi: http://dx.doi.org/10.1016/S0140-6736(03)12113-7

Keith, S., Jacobs, I., & McLellan, T. (1992). Adaptations to training at the individual anaerobic threshold. *European Journal of Applied Physiology and Occupational Physiology, 65*(4), 316-323. doi: 10.1007/BF00868134

Kesaniemi, Y. K., Danforth, E., Jr., Jensen, M. D., Kopelman, P. G., Lefebvre, P., & Reeder, B. A. (2001). Dose-response issues concerning physical activity and health: an evidence-based symposium. *Medicine and Science in Sports and Exercise, 33*(6 Suppl), S351-358.

Keteyian, S. J., Brawner, C. A., Savage, P. D., Ehrman, J. K., Schairer, J., Divine, G., . . . Ades, P. A. (2008). Peak aerobic capacity predicts prognosis in patients with coronary heart disease. *American Heart Journal, 156*(2), 292-300.

Kodama, S., Saito, K., Tanaka, S., & et al. (2009). Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: A meta-analysis. *Journal of the American Medical Association, 301*(19), 2024-2035. doi: 10.1001/jama.2009.681

Kregel, K. C., & Zhang, H. J. (2007). An integrated view of oxidative stress in aging: basic mechanisms, functional effects, and pathological considerations. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 292*(1), R18-R36.

Kurz, M., Mattu, A., & Brady, W. (2014). Acute coronary Syndrome. *Rosen's Emergency Medicine. Elsevier, Philadelphia*.

Laukkanen, J. A., Kurl, S., Salonen, J. T., Lakka, T. A., & Rauramaa, R. (2006). Peak oxygen pulse during exercise as a predictor for coronary heart disease and all cause death. *Heart, 92*(9), 1219-1224.

Lavie, C. J., Milani, R. V., & Mehra, M. R. (2004). Peak exercise oxygen pulse and prognosis in chronic heart failure. *The American Journal of Cardiology, 93*(5), 588-593. doi: http://dx.doi.org/10.1016/j.amjcard.2003.11.023

Lavie, C. J., Milani, R. V., & Ventura, H. O. (2009). Obesity and Cardiovascular DiseaseRisk Factor, Paradox, and Impact of Weight Loss. *Journal of the American College of Cardiology, 53*(21), 1925-1932. doi: 10.1016/j.jacc.2008.12.068

Libby, P., Ridker, P. M., & Hansson, G. K. (2011). Progress and challenges in translating the biology ofatherosclerosis. *Nature, 473*(7347), 317-325. doi: doi:10.1038/nature10146

Libby, P., & Theroux, P. (2005). Pathophysiology of Coronary Artery Disease. *Circulation, 111*(25), 3481-3488. doi: 10.1161/CIRCULATIONAHA.105.537878

Lindsay, G. M., & Gaw, A. (Eds.). (2004). *Coronary Heart Disease Prevention: A Handbook for the Health-Care Team* (2nd ed.). London, UK: Churchill Livingstone.

Little, W. C., & Oh, J. K. (2009). Echocardiographic Evaluation of Diastolic Function Can Be Used to Guide Clinical Care. *Circulation, 120*(9), 802-809. doi: 10.1161/circulationaha.109.869602

Lloyd-Jones, D. M., Larson, M. G., Beiser, A., & Levy, D. (1999). Lifetime risk of developing coronary heart disease. *The Lancet, 353*(9147), 89-92. doi: http://dx.doi.org/10.1016/S0140-6736(98)10279-9

Lorenz, M. W., Markus, H. S., Bots, M. L., Rosvall, M., & Sitzer, M. (2007). Prediction of Clinical Cardiovascular Events With Carotid Intima-Media Thickness: A Systematic Review and Meta-Analysis. *Circulation, 115*(4), 459-467. doi: 10.1161/circulationaha.106.628875

Lorenz, M. W., Polak, J. F., Kavousi, M., Mathiesen, E. B., Völzke, H., Tuomainen, T.-P., . . . Thompson, S. G. (2012). Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. *The Lancet, 379*(9831), 2053-2062. doi: http://dx.doi.org/10.1016/S0140-6736(12)60441-3

Lymperopoulos, A., Rengo, G., & Koch, W. J. (2013). Adrenergic Nervous System in Heart Failure: Pathophysiology and Therapy. *Circulation Research, 113*(6), 739-753. doi: 10.1161/circresaha.113.300308

Mancini, D. M., Eisen, H., Kussmaul, W., Mull, R., Edmunds, L. H., & Wilson, J. R. (1991). Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation, 83*(3), 778-786. doi: 10.1161/01.cir.83.3.778

Mann, D. L., & Bristow, M. R. (2005). Mechanisms and Models in Heart Failure: The Biomechanical Model and Beyond. *Circulation, 111*(21), 2837-2849. doi: 10.1161/circulationaha.104.500546

McConnell, T. R., Menapace, F. J., Hartley, L. H., & Pfeffer, M. A. (1998). Captopril reduces the VE/VCO2 ratio in myocardial infarction patients with low ejection fraction. *CHEST Journal, 114*(5), 1289-1294.

McMurray J, J., V, Adamopoulos, S., Anker, S. D., Auricchio, A., Böhm, M., Dickstein, K., . . . Zeiher, A. (2012). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *European Heart Journal, 33*(14), 1787-1847. doi:10.1093/eurheartj/ehs104

McQueen, M. J., Hawken, S., Wang, X., Ounpuu, S., Sniderman, A., Probstfield, J., . . . Yusuf, S. (2008). Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. *The Lancet, 372*(9634), 224-233. doi:http://dx.doi.org/10.1016/S0140-6736(08)61076-4

Mendis, S., Puska, P., & Norrving, B. (2011). Global Atlas on Cardiovascular Disease Prevention and Control.

Mezzani, A., Agostoni, P., Cohen-Solal, A., Corrà, U., Jegier, A., Kouidi, E., . . . Vanhees, L. (2009). Standards for the use of cardiopulmonary exercise testing for the functional evaluation of cardiac patients: a report from the Exercise Physiology Section of the European Association for Cardiovascular Prevention and Rehabilitation. *European Journal of Cardiovascular Prevention & Rehabilitation, 16*(3), 249-267. doi: 10.1097/HJR.0b013e32832914c8

Milani, R. V., & Lavie, C. J. (2007). Impact of Cardiac Rehabilitation on Depression and Its Associated Mortality. *The American Journal of Medicine, 120*(9), 799-806. doi: http://dx.doi.org/10.1016/j.amjmed.2007.03.026

Motohiro, M., Yuasa, F., Hattori, T., Sumimoto, T., Takeuchi, M., Kaida, M., . . . Iwasaka, T. (2005). Cardiovascular adaptations to exercise training after uncomplicated acute myocardial infarction. *Am J Phys Med Rehabil, 84*(9), 684-691.

Murias, J. M., Kowalchuk, J. M., & Paterson, D. H. (2010a). Mechanisms for increases in VO2max with endurance training in older and young women. *Medicine and Science in Sports and Exercise, 42*(10), 1891-1898.

Murias, J. M., Kowalchuk, J. M., & Paterson, D. H. (2010b). Time course and mechanisms of adaptations in cardiorespiratory fitness with endurance training in older and young men. *Journal of Applied Physiology, 108*(3), 621-627.

Myers, J., Goldsmith, R. L., Keteyian, S. J., Brawner, C. A., Brazil, D. A., Aldred, H., . . . Burkhoff, D. (2010). The ventilatory anaerobic threshold in heart failure: a multicenter evaluation of reliability. *Journal of Cardiac Failure, 16*(1), 76-83.

Myers, J., Prakash, M., Froelicher, V., Do, D., Partington, S., & Atwood, J. E. (2002). Exercise Capacity and Mortality among Men Referred for Exercise Testing. *New England Journal of Medicine, 346*(11), 793-801. doi:doi:10.1056/NEJMoa011858

Naci, H., & Ioannidis, J. (2013). Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study. *BMJ: British Medical Journal, 347*.

Najjar, S. S., Scuteri, A., & Lakatta, E. G. (2005). Arterial Aging: Is It an Immutable Cardiovascular Risk Factor? *Hypertension, 46*(3), 454-462. doi: 10.1161/01.hyp.0000177474.06749.98

Nambi, V., Chambless, L., Folsom, A. R., He, M., Hu, Y., Mosley, T., . . . Ballantyne, C. M. (2010). Carotid Intima-Media Thickness and Presence or Absence of Plaque Improves Prediction of Coronary Heart Disease Risk: The ARIC (Atherosclerosis Risk In Communities) Study. *Journal of the American College of Cardiology, 55*(15), 1600-1607. doi: http://dx.doi.org/10.1016/j.jacc.2009.11.075

National Insitute for Health and Care Excellence. (2011). *Hypertension: Clinical management of primary hypertension in adults*. Retrieved from https://www.nice.org.uk/guidance/CG127/chapter/Introduction.

National Insitute for Health and Care Excellence. (2014). *Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease*. Retrieved from https://www.nice.org.uk/guidance/cg181/chapter/Introduction.

Naughton, J., Sevelius, G., & Balke, B. (1963). PHYSIOLOGICAL RESPONSES OF NORMAL AND PATHOLOGICAL SUBJECTS TO A MODIFIED WORK CAPACITY TEST. *The Journal of sports medicine and physical fitness, 3*, 201.

Nesto, R. W., & Kowalchuk, G. J. (1987). The ischemic cascade: Temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia. *The American Journal of Cardiology, 59*(7), C23-C30. doi: http://dx.doi.org/10.1016/0002-9149(87)90192-5

New York Heart Association. (1964). *Diseases of the heart and blood vessels: nomenclature and criteria for diagnosis*: Little, Brown.

NICE (Producer). (2013, 12/08/2014). Cardiac Rehabilitation Services. [National Health Care Guidance] Retrieved from http://www.nice.org.uk/guidance/cmg40/chapter/1-Commissioning-cardiac-rehabilitation-services

Nichols, S., Milner, M., Meijer, R., Carroll, S., & Ingle, L. (2014). Variability of automated carotid intima-media thickness measurements by novice operators. *Clinical Physiology and Functional Imaging*.

Nieuwland, W., Berkhuysen, M. A., van Veldhuisen, D. J., Brügemann, J., Landsman, M. L., van Sonderen, E., . . . Rispens, P. (2000). Differential effects of high-frequency versus low-frequency exercise training in rehabilitation of patients with coronary artery disease. *Journal of the American College of Cardiology, 36*(1), 202-207.

Noonan, V., & Dean, E. (2000). Submaximal Exercise Testing: Clinical Application and Interpretation. *Physical Therapy, 80*(8), 782-807.

O'Donovan, G., Owen, A., Bird, S. R., Kearney, E. M., Nevill, A. M., Jones, D. W., & Woolf-May, K. (2005). Changes in cardiorespiratory fitness and coronary heart disease risk factors following 24 wk of moderate-or high-intensity exercise of equal energy cost. *Journal of Applied Physiology, 98*(5), 1619-1625.

O'Leary, D. H., & Bots, M. L. (2010). Imaging of atherosclerosis: carotid intima–media thickness. *European Heart Journal, 31*(14), 1682-1689. doi:10.1093/eurheartj/ehq185

O'Connor, C. M., Whellan, D. J., Lee, K. L., Keteyian, S. J., Cooper, L. S., Ellis, S. J., . . . Blumenthal, J. A. (2009). Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *Journal of the American Medical Association, 301*(14), 1439-1450.

Okada, K., Maeda, N., Tatsukawa, M., Shimizu, C., Sawayama, Y., & Hayashi, J. (2004). The influence of lifestyle modification on carotid artery intima-media thickness in a suburban Japanese population. *Atherosclerosis, 173*(2), 327-335.

Oliveira, R. B., Myers, J., Araujo, C. G. S., Abella, J., Mandic, S., & Froelicher, V. (2009). Maximal exercise oxygen pulse as a predictor of mortality among male veterans referred for exercise testing. *European Journal of Cardiovascular Prevention & Rehabilitation, 16*(3), 358-364.

Ornish, D., Scherwitz, L. W., Billings, J. H., & et al. (1998). INtensive lifestyle changes for reversal of coronary heart disease. *Journal of the American Medical Association, 280*(23), 2001-2007. doi:10.1001/jama.280.23.2001

Passino, C., Poletti, R., Bramanti, F., Prontera, C., Clerico, A., & Emdin, M. (2006). Neuro-hormonal activation predicts ventilatory response to exercise and functional capacity in patients with heart failure. *European Journal of Heart Failure, 8*(1), 46-53.

Piepoli, M. F., Clark, A. L., & Coats, A. J. (1995). *Muscle metaboreceptors in hemodynamic, autonomic, and ventilatory responses to exercise in men* (Vol. 269).

Piepoli, M. F., Davos, C., Francis, D. P., & Coats, A. J. (2004). Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ, 328*(7433), 189. doi: 10.1136/bmj.37938.645220.EE

Pignoli, P., Tremoli, E., Poli, A., Oreste, P., & Paoletti, R. (1986). Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. *Circulation, 74*(6), 1399-1406. doi:10.1161/01.cir.74.6.1399

Piña, I. L., Apstein, C. S., Balady, G. J., Belardinelli, R., Chaitman, B. R., Duscha, B. D., . . . Sullivan, M. J. (2003). Exercise and Heart Failure: A Statement From the American Heart Association Committee on Exercise, Rehabilitation, and Prevention. *Circulation, 107*(8), 1210-1225. doi:10.1161/01.cir.0000055013.92097.40

Polak, J. F., Pencina, M. J., Pencina, K. M., O'Donnell, C. J., Wolf, P. A., & D'Agostino, R. B. (2011). Carotid-Wall Intima–Media Thickness and Cardiovascular Events. *New England Journal of Medicine, 365*(3), 213-221. doi:doi:10.1056/NEJMoa1012592

Poole, D. C., Hirai, D. M., Copp, S. W., & Musch, T. I. (2012). Muscle oxygen transport and utilization in heart failure: implications for exercise (in) tolerance. *American Journal of Physiology-Heart and Circulatory Physiology, 302*(5), H1050-H1063.

Rees, K., Taylor, R. R., Singh, S., Coats, A. J., & Ebrahim, S. (2004). Exercise based rehabilitation for heart failure. *The Cochrane Library*.

Roca, J., Agusti, A. G., Alonso, A., Poole, D. C., Viegas, C., Barbera, J. A., . . . Wagner, P. D. (1992). *Effects of training on muscle O2 transport at VO2max* (Vol. 73).

Rohani, M., Jogestrand, T., Ekberg, M., van der Linden, J., Källner, G., Jussila, R., & Agewall, S. (2005). Interrelation between the extent of atherosclerosis in the thoracic aorta, carotid intima-media thickness and the extent of coronary artery disease. *Atherosclerosis, 179*(2), 311-316.

Rubins, H. B., & Robins, S. J. (2000). Conclusions from the VA-HIT study. *Am J Cardiol, 86*(5), 543-544.

Rubins, H. B., Robins, S. J., Collins, D., Fye, C. L., Anderson, J. W., Elam, M. B., . . . Wittes, J. (1999). Gemfibrozil for the Secondary Prevention of Coronary Heart Disease in Men with Low Levels of High-Density Lipoprotein Cholesterol. *New England Journal of Medicine, 341*(6), 410-418. doi: doi:10.1056/NEJM199908053410604

Sacks, F. M., Svetkey, L. P., Vollmer, W. M., Appel, L. J., Bray, G. A., Harsha, D., . . . Cutler, J. A. (2001). Effects on Blood Pressure of Reduced Dietary Sodium and the Dietary Approaches to Stop Hypertension (DASH) Diet. *New England Journal of Medicine, 344*(1), 3-10. doi: doi:10.1056/NEJM200101043440101

Sandercock, G., Cardoso, F., & Almodhy, M. (2013). Cardiorespiratory fitness changes in patients receiving comprehensive outpatient cardiac rehabilitation in the UK: a multicentre study. *Heart, 99*(17), 1298-1299. doi: 10.1136/heartjnl-2013-304085

Sandercock, G., Cardoso, F., Almodhy, M., & Pepera, G. (2013). Cardiorespiratory fitness changes in patients receiving comprehensive outpatient cardiac rehabilitation in the UK: a multicentre study. *Heart, 99*(11), 785-790. doi: 10.1136/heartjnl-2012-303055

Sandercock, G., Hurtado, V., & Cardoso, F. (2011). Changes in cardiorespiratory fitness in cardiac rehabilitation patients: A meta-analysis. *International Journal of Cardiology*(0). doi: 10.1016/j.ijcard.2011.11.068

Sato, S., Makita, S., Uchida, R., Ishihara, S., & Majima, M. (2008). Physical activity and progression of carotid intima-media thickness in patients with coronary heart disease. *Journal of Cardiology, 51*(3), 157-162. doi: http://dx.doi.org/10.1016/j.jjcc.2008.02.005

Scholl, J., Bots, M. L., & Peters, S. A. E. (2015). Contribution of cardiorespiratory fitness, relative to traditional cardiovascular disease risk factors, to common carotid intima–media thickness. *Journal of Internal Medicine, 277*(4), 439-446. doi: 10.1111/joim.12271

Scott, A. C., Francis, D. P., Davies, L. C., Ponikowski, P., Coats, A. J. S., & Piepoli, M. F. (2000). Contribution of skeletal muscle 'ergoreceptors' in the human leg to respiratory control in chronic heart failure. *The Journal of Physiology, 529*(Pt 3), 863-870. doi: 10.1111/j.1469-7793.2000.00863.x

Scottish Intercollegiate Guidelines Network. Scottish Intercollegiate Guidelines Network. Cardiac rehabilitation: a National Guideline No57.

Seals, D. R., DeSouza, C. A., Donato, A. J., & Tanaka, H. (2008). Habitual exercise and arterial aging. *Journal of Applied Physiology, 105*(4), 1323-1332. doi: 10.1152/japplphysiol.90553.2008

Shelton, R. J., Ingle, L., Rigby, A. S., Witte, K. K., Cleland, J. G., & Clark, A. L. (2010). Cardiac output does not limit submaximal exercise capacity in patients with chronic heart failure. *European Journal of Heart Failure, 12*(9), 983-989.

Skalski, J., Allison, T. G., & Miller, T. D. (2012). The Safety of Cardiopulmonary Exercise Testing in a Population With High-Risk Cardiovascular Diseases. *Circulation, 126*(21), 2465- 2472. doi: 10.1161/circulationaha.112.110460

Sonoda, M., Yonekura, K., Yokoyama, I., Takenaka, K., Nagai, R., & Aoyagi, T. (2004). Common carotid intima–media thickness is correlated with myocardial flow reserve in patients with coronary artery disease: a useful non-invasive indicator of coronary atherosclerosis. *International Journal of Cardiology, 93*(2), 131-136.

Spina, R. J., Ogawa, T., Kohrt, W. M., Martin, W. H., Holloszy, J. O., & Ehsani, A. A. (1993). *Differences in cardiovascular adaptations to endurance exercise training between older men and women* (Vol. 75).

Stanner, S. (2008). *Cardiovascular Disease: Diet, Nutrition and Emerging Risk Factors (The Report of the British Nutrition Foundation Task Force)*: John Wiley & Sons.

Stein, J. H., Korcarz, C. E., Hurst, R. T., Lonn, E., Kendall, C. B., Mohler, E. R., . . . Post, W. S. (2008). Use of Carotid Ultrasound to Identify Subclinical Vascular Disease and Evaluate Cardiovascular Disease Risk: A Consensus Statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *Journal of the American Society of Echocardiography, 21*(2), 93-111.

Stenestrand, U., Lindbäck, J., & Wallentin, L. (2006). Long-term outcome of primary percutaneous coronary intervention vs prehospital and in-hospital thrombolysis for patients with ST-elevation myocardial infarction. *Journal of the American Medical Association, 296*(14), 1749-1756.

Sullivan, M., Higginbotham, M., & Cobb, F. (1989). Exercise training in patients with chronic heart failure delays ventilatory anaerobic threshold and improves submaximal exercise performance. *Circulation, 79*(2), 324-329.

Sullivan, M. J., Higginbotham, M. B., & Cobb, F. R. (1988). Increased exercise ventilation in patients with chronic heart failure: intact ventilatory control despite hemodynamic and pulmonary abnormalities. *Circulation, 77*(3), 552-559. doi: 10.1161/01.cir.77.3.552

Sullivan, M. J., Higginbotham, M. B., & Cobb, F. R. (1989). Exercise training in patients with chronic heart failure delays ventilatory anaerobic threshold and improves submaximal exercise performance. *Circulation, 79*(2), 324-329. doi: 10.1161/01.cir.79.2.324

Swain, D. P., & Franklin, B. A. (2002). VO~ 2 reserve and the minimal intensity for improving cardiorespiratory fitness. *Medicine and Science in Sports and Exercise, 34*(1), 152-157.

Swanton, R. H. (2003). *Pocket Consultant: Cardiology* (5th ed.). Massachusetts, USA: Blackwell Publishing.

Tajik, P., Meijer, R., Duivenvoorden, R., Peters, S. A., Kastelein, J. J., Visseren, F. J., . . . Grobbee, D. E. (2012). Asymmetrical distribution of atherosclerosis in the carotid   artery:

identical patterns across age, race, and gender. *European Journal of Preventive Cardiology, 19*(4), 687-697.

Takashi, W., Tsutomu, F., & Kentaro, F. (2002). Ultrasonic Correlates of Common Carotid Atherosclerosis in Patients with Coronary Artery Disease. *Angiology, 53*(2), 177-183. doi: 10.1177/000331970205300208

Tanaka, H., Seals, D. R., Monahan, K. D., Clevenger, C. M., DeSouza, C. A., & Dinenno, F. A. (2002). Regular aerobic exercise and the age-related increase in carotid artery intima-media thickness in healthy men. *Journal of Applied Physiology, 92*(4), 1458-1464.

Taylor, C., Nichols, S., & Ingle, L. (2015). A clinician's guide to cardiopulmonary exercise testing 1: an introduction. *Br J Hosp Med (Lond), 76*(4), 192-195. doi: 10.12968/hmed.2015.76.4.192

Taylor, R. S. (2012). The RAMIT trial: its results in the context of 2012 Cochrane review. *Heart, 98*(8), 672-673. doi: 10.1136/heartjnl-2012-301709

Taylor, R. S., Brown, A., Ebrahim, S., Jolliffe, J., Noorani, H., Rees, K., . . . Oldridge, N. (2004). Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *The American Journal of Medicine, 116*(10), 682-692. doi: http://dx.doi.org/10.1016/j.amjmed.2004.01.009

Taylor, R. S., Unal, B., Critchley, J. A., & Capewell, S. (2006). Mortality reductions in patients receiving exercise-based cardiac rehabilitation: how much can be attributed to cardiovascular risk factor improvements? *European Journal of Cardiovascular Prevention & Rehabilitation, 13*(3), 369-374. doi: 10.1097/01.hjr.0000199492.00967.11

Timin, M. T., Shores, K. V., & Reicks, M. (2002). Behavior change outcomes in an outpatient cardiac rehabilitation program. *Journal of the American Dietetic Association, 102*(5), 664-671. doi: http://dx.doi.org/10.1016/S0002-8223(02)90152-5

Touboul, P. J., Hennerici, M. G., Meairs, S., Adams, H., Amarenco, P., Bornstein, N., . . . Woo, K. S. (2012). Mannheim Carotid Intima-Media Thickness and Plaque Consensus (2004–2006–2011). *Cerebrovascular Diseases, 34*(4), 290-296.

Townsend N, Williams J, Bhatnagar P, Wickramasinghe K, & M, R. (2014). Cardiovascular Disease Statisitics 2014. *British Heart Foundation. London*.

Tsurugaya, H., Adachi, H., Kurabayashi, M., Ohshima, S., & Taniguchi, K. (2006). Prognostic Impact of Ventilatory Efficiency in Heart Disease Patients With Preserved Exercise Tolerance. *Circulation Journal, 70*(10), 1332-1336. doi: 10.1253/circj.70.1332

Unal, B., Critchley, J. A., & Capewell, S. (2004). Explaining the decline in coronary heart disease mortality in England and Wales between 1981 and 2000. *Circulation, 109*(9), 1101-1107. doi: 10.1161/01.CIR.0000118498.35499.B2

Van de Veire, N. R., Van Laethem, C., Philippé, J., De Winter, O., De Backer, G., Vanderheyden, M., & De Sutter, J. (2006). VE/Vco2 slope and oxygen uptake efficiency slope in patients with coronary artery disease and intermediate peakVo2. *European Journal of Cardiovascular Prevention & Rehabilitation, 13*(6), 916-923. doi: 10.1097/01.hjr.0000238400.35094.72

Van Laethem, C., Bartunek, J., Goethals, M., Nellens, P., Andries, E., & Vanderheyden, M. (2005). Oxygen uptake efficiency slope, a new submaximal parameter in evaluating exercise capacity in chronic heart failure patients. *American Heart Journal, 149*(1), 175- 180.

Van Laethem, C., De Sutter, J., Peersman, W., & Calders, P. (2009). Intratest reliability and test–retest reproducibility of the oxygen uptake efficiency slope in healthy participants. *European Journal of Cardiovascular Prevention & Rehabilitation, 16*(4), 493-498. doi: 10.1097/HJR.0b013e32832c88a8.

Van Laethem, C., Goethals, M., Verstreken, S., Walravens, M., Wellens, F., De Proft, M., . . . Vanderheyden, M. (2007). Response of the oxygen uptake efficiency slope to orthotopic heart transplantation: lack of correlation with changes in central hemodynamic parameters and resting lung function. *The Journal of Heart and Lung Transplantation, 26*(9), 921-926.

van Lennep, J. E. R., Westerveld, H. T., Erkelens, D. W., & van der Wall, E. E. (2002). Risk factors for coronary heart disease: implications of gender. *Cardiovascular research, 53*(3), 538-549.

Vanhees, L., Fagard, R., Thijs, L., & Amery, A. (1995). Prognostic value of training-induced change in peak exercise capacity in patients with myocardial infarcts and patients with coronary bypass surgery. *The American Journal of Cardiology, 76*(14), 1014-1019.

Vanoli, D., Lindqvist, P., Wiklund, U., Henein, M., & Näslund, U. (2013). Fully automated on-screen carotid intima-media thickness measurement: A screening tool for subclinical atherosclerosis. *Journal of Clinical Ultrasound, 41*(6), 333-339. doi: 10.1002/jcu.22041

Vanoli, D., Wiklund, U., Lindqvist, P., Henein, M., & Näslund, U. (2013). Successful novice's training in obtaining accurate assessment of carotid IMT using an automated ultrasound system. *European Heart Journal – Cardiovascular Imaging, 15*(6), 637-642. doi: 10.1093/ehjci/jet254

Vasiliauskas, D., Benetis, R., Jasiukeviciene, L., Grizas, V., Marcinkeviciene, J., Navickas, R., & Leimoniene, L. (2007). Exercise training after coronary angioplasty improves cardiorespiratory function. *Scandinavian Cardiovascular Journal, 41*(3), 142-148.

Vescovo, G., Serafini, F., Facchin, L., Tenderini, P., Carraro, U., Dalla Libera, L., . . . Ambrosio, G. (1996). Specific changes in skeletal muscle myosin heavy chain composition in cardiac failure: differences compared with disuse atrophy as assessed on microbiopsies by high resolution electrophoresis. *Heart, 76*(4), 337-343.

Warburton, D. E., McKenzie, D. C., Haykowsky, M. J., Taylor, A., Shoemaker, P., Ignaszewski, A. P., & Chan, S. Y. (2005). Effectiveness of high-intensity interval training for the rehabilitation of patients with coronary artery disease. *The American Journal of Cardiology, 95*(9), 1080-1084.

Wasserman, K., Hansen, J., Sue, D., Stringer, W., Sietsema, K., Sun, X.-G., & Whipp, B. (2011). *Principles of exercise testing and interpretation: Including pathophysiology and clinical applications* (Fifth ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins.

Weber, K. T., Kinasewitz, G. T., Janicki, J. S., & Fishman, A. P. (1982). Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. *Circulation, 65*(6), 1213-1223. doi: 10.1161/01.CIR.65.6.1213

West, R. R. (2012). 'The future of cardiac rehabilitation in the UK' and 'Exercise training as an essential component of cardiac rehabilitation': the response. *Heart, 98*(8), 675-675. doi: DOI 10.1136/heartjnl-2012-302125

West, R. R., & Henderson, A. H. (2013). Cardiac rehabilitation and exercise training. *Heart, 99*(11), 753-754. doi: DOI 10.1136/heartjnl-2012-303341

West, R. R., Jones, D. A., & Henderson, A. H. (2012). Rehabilitation after myocardial infarction trial (RAMIT): multi-centre randomised controlled trial of comprehensive cardiac rehabilitation in patients following acute myocardial infarction. *Heart, 98*(8), 637-644. doi: 10.1136/heartjnl-2011-300302

Whipp, B. J. (1983). Ventilatory Control During Exercise in Humans. *Annual Review of Physiology, 45*(1), 393-413. doi: doi:10.1146/annurev.ph.45.030183.002141

Whipp, B. J., Higgenbotham, M. B., & Cobb, F. C. (1996). Estimating exercise stroke volume from asymptotic oxygen pulse in humans. *Journal of Applied Physiology, 81*(6), 2674- 2679.

Wilson, K., Gibson, N., Willan, A., & Cook, D. (2000). Effect of smoking cessation on mortality after myocardial infarction: Meta-analysis of cohort studies. *Archives of Internal Medicine, 160*(7), 939-944. doi: 10.1001/archinte.160.7.939

Wisløff, U., Støylen, A., Loennechen, J. P., Bruvold, M., Rognmo, Ø., Haram, P. M., . . . Skjærpe, T. (2007). Superior Cardiovascular Effect of Aerobic Interval Training Versus Moderate Continuous Training in Heart Failure Patients: A Randomized Study. *Circulation, 115*(24), 3086-3094. doi: 10.1161/circulationaha.106.675041

World Health Organisation. (1983). Rehabilitation and Secondary Prevention After Acute Myocardial Infarction (Euro report 84). Copenhagen.

World Health Organisation. (1993). Rehabilitation after cardiovascular diseases, with special emphasis on developing countries: a report of a WHO Committee *World Health Organisation Technical Report Series* (pp. 1-122).

World Health Organisation. (2006). Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia *Report of a WHO/IDF Consultation*.

Yusuf, S., Hawken, S., Ôunpuu, S., Dans, T., Avezum, A., Lanas, F., . . . Varigos, J. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *The Lancet, 364*(9438), 937-952.

Zafrir, N., Fink, G., Klainman, E., Sulkes, J., & Spitzer, S. (1999). Relation between aerobic capacity and extent of myocardial ischemia in patients with normal cardiac function. *American Heart Journal, 138*(6), 1088-1092.

Chapter 3: The short and longer-term cardiorespiratory fitness changes following a routine eight week, 16 session, low to moderate intensity UK cardiac rehabilitation exercise training programme.

4.1   Abstract

Objective: UK cardiac rehabilitation (CR) exercise training guidelines appear conservative. Recent data indicates that the dose of exercise prescribed to UK CR patients result in modest cardiorespiratory fitness (CRF) improvements. However, in this investigation no control group was available for comparison. Moreover, CRF changes were estimated using metabolic equivalents (METs). It is not known whether the CRF change reported in this study accurately depicts VO_{2peak} change following routine CR or, if patients who decline CR experience a reduction in VO_{2peak}. Using maximal cardiopulmonary exercise testing (CPET), the aim of this study was to determine changes in directly- determined VO_{2peak} and supplementary CRF variables in patients completing and declining routine CR exercise training.

Methods: Patients with a recent diagnosis of coronary heart disease (CHD) were recruited. Patients choosing to take part in routine CR exercise training formed the treatment group (TG). Patients declining CR acted as a control group (CG). Patients in the TG undertook an eight week, (16 session) low to moderate intensity (40-70% heart rate reserve) exercise training programme. Controls were able to access all other recommended components of a 'comprehensive' CR programme and instructed to follow the advice of their healthcare professional. All patients undertook a baseline maximal CPET using the modified Bruce treadmill protocol (visit 1). For patients in the TG, reassessment was conducted upon completion of CR. Controls were reassessed approximately ten weeks after visit 1 (visit 2). To determine the longer-term effects of routine CR, a CPET reassessment was conducted 12 months after patients' initial visit (visit 3).

Results: n=34 patients (85.3% male; age 62.1 ± 8.8 years; body mass index [BMI] 29.5 ± 4.5 Kg·m^{-2}) met the study inclusion criteria. At the end of the intervention period (visit 2), there was no significant main effect (0.13 ml·kg^{-1}·min^{-1}; 95% CI -1.08 to 0.81 ml·kg^{-1}·min^{-1}; p=0.774) or group effect (1.62 ml·kg^{-1}·min^{-1}; 95% CI -1.21 to 5.33 ml·kg^{-1}·min^{-1}; p=0.380) for changes in VO_{2peak}. Likewise, there was no interaction effect (p=0.978) between VO_{2peak} change in the TG (mean change: 0.12 ml·kg^{-1}·min^{-1}; 95% CI -1.00 to 1.24 ml·kg^{-1}·min^{-1}) and CG VO_{2peak} change (mean change: 0.15 ml·kg^{-1}·min^{-1}; 95% CI -1.37 to 1.66 ml·kg^{-1}·min^{-1}). There was no significant main effect (0.22 ml·kg^{-1}·min^{-1}; 95% CI -0.33 to 0.77 ml·kg^{-1}·min^{-1}; p=0.431) or group effect (1.61 ml·kg^{-1}·min^{-1}; 95% CI -0.83 to 4.05 ml·kg^{-1}·min^{-1}; p=0.157) for the ventilatory anaerobic threshold (VAT). There was no interaction effect (p=0.176) between the TG (mean change: 0.55 ml·kg^{-1}·min^{-1}; 95% CI -0.11 to 1.21 ml·kg^{-1}·min^{-1}) and the CG for VAT either (mean change: -0.11 ml·kg^{-1}·min^{-1}; 95% CI -0.98 to 0.77 ml·kg^{-1}·min^{-1}). 31.8% of patients in the TG and 33.3% of patients in the CG experienced a VO_{2peak} increase during the intervention period, however this difference did not reach statistical significance.

Conclusion: Eight weeks (16 session) of low to moderate intensity routine CR exercise training is insufficient to increase VO_{2peak}. The proportion of patients who improved their VO_{2peak} by a magnitude at least as large as the minimal clinically important difference did not appear to differ between groups. Higher exercise doses within structured CR programmes may be required to significantly improve VO_{2peak} amongst patients with CHD. Close monitoring of patients exercise intensity and other programme characteristics are required to ensure that exercise prescriptions are consistent with those employed within clinical trial data.

4.2 Introduction

Exercise training in cardiac rehabilitation (CR) has been shown to reduce mortality (Jolliffe et al., 2001) most likely as a result of the physiological adaptations associated with improved VO_{2peak} and other cardiorespiratory fitness (CRF) characteristics. An inverse relationship between increased VO_{2peak} and mortality has been documented (Vanhees et al., 1995) making it one of the primary therapeutic targets of CR exercise training. The magnitude of VO_{2peak} change following completion of CR may therefore characterise programme efficacy. The ''gold-standard'' method of quantifying VO_{2peak} change is through cardiopulmonary exercise testing (CPET).

Higher exercise doses are typically responsible for enhanced CRF improvements (Sandercock et al., 2011, Nieuwland et al., 2000, Swain and Franklin, 2002). In the UK, the recommended exercise dose for CR patients appears to be substantially less than that prescribed in international CR programmes (Association of Chartered Physiotherapists in Cardiac Rehabilitation [ACPICR], 2015). UK CR patients can expect to receive approximately one third of the total number of exercise sessions (11.6 vs. 36) reported in international studies (Brodie et al., 2006). It is therefore unsurprising that UK patients' CRF improvements are also roughly one third of those reported in international studies [0.52 metabolic equivalents (METs) vs. 1.55 METs] (Sandercock et al., 2013b, Sandercock et al., 2011).

Recent RCT findings reported by West et al. (2012) showed that UK CR has little impact on all-cause mortality (*n*=1813 patients from 14 hospitals; weekly or bi-weekly exercise training; six to eight weeks; one, two and seven to nine year follow-up). Considered in conjunction with the findings of Sandercock et al. (2013b), there is compelling evidence that UK CR exercise training doses are insufficient to meaningfully affect CRF and long-term prognosis. However, Sandercock and colleagues' study (2013b) remains the *only* contemporary, large scale, multi-centre data to suggest that exercise training in UK CR programmes may be ineffective.

The potential importance of these findings cannot be disputed. However as discussed in Chapter 2, the use of METs to estimate VO_2 is imprecise and reporting estimated peak MET change may not reflect VO_{2peak} change. Factors such as myocardial ischaemia, chronotropic incompetence, Beta-Blockade and anaerobic metabolism may serve to attenuate the normal linear VO_2 to work rate relationship (Hughson, 1984, Belardinelli et al., 2003, Chaudhry et al., 2009, Brubaker and Kitzman, 2011,). Consequently, MET estimations may over estimate true VO_2. In addition, inter-individual variability of resting VO_2 [62% variability attributable to body composition; 14% attributable to age; (Byrne et al., 2005)] makes reliably estimating VO_{2peak} by multiplying estimated peak METs by the traditional 3.5 $ml^{.}kg^{-1.}min^{-1}$ unreliable. The only way to accurately determine VO_{2peak} is to use metabolic gas exchange during maximal CPET. To the author's knowledge, the only study to comprehensively investigate the application of peak MET change in coronary heart disease (CHD) found no association between VO_{2peak} and peak MET change following exercise training (Milani et al., 1995). Accordingly, the small MET change (0.52 METs) attributable to exercise training in CR (Sandercock et al., 2013b) may not be a valid measure of changes in VO_{2peak}. Evidence indicating that exercise prescription within UK CR is ineffective in improving VO_{2peak} requires substantiating through the application of 'gold standard' CPET.

To address the paucity of CPET data, we aimed to assess VO_{2peak} changes following a standard eight week, 16 session, low to moderate intensity UK CR exercise programme. Secondary CRF outcome measures adopted were ventilatory anaerobic threshold (VAT), VE/VCO_2 slope, peak O_2 pulse (O_2/HR) and O_2 uptake efficiency slope (OUES) change (Nichols et al., 2015, Guazzi et al., 2012). Analysis of patients' exercise prescriptions was conducted to quantify exercise dose. Agreement between VO_{2peak} and peak METs achieved during CPET; as well as METs calculated from submaximal cycle ergometry (conducted by the CR team) was performed. Analysis was performed on data obtained from an ongoing a priori study investigating the cardiovascular (CV) and respiratory adaptations in response to standard UK exercise based CR (Appendix 1).

4.3   Methods

4.3.1   Ethical Approval

Ethical approval for the overarching study was obtained from the Humber Bridge NHS Research Ethics Committee - Yorkshire and the Humber on the 27th September 2013, (12/YH/0278). All aspects of this study conform to the declaration of Helsinki 1964 and its subsequent revisions. Patient recruitment commenced on March 12th 2014 and remains ongoing. For the purpose of this thesis, data was censored on 15th July 2015 to facilitate timely analysis.

4.3.2   Cardiac Rehabilitation Referral Pathway in Hull

Hull's CR service follows national recommendations outlined by the National Institute for Health and Care Excellence (2013a) and operates using a 7 stage (0 to 6) CR process as follows:

1. Identify and refer patient

2. Manage patient and refer to CR programme

3. Assess patient for CR programme

4. Develop patient care plan

5. Deliver comprehensive CR programme

6. Conduct final assessment

7. Discharge and transition to long-term management

Stage zero and one take place within Castle Hill Hospital and includes referral to the community CR service. Stage two and three involves patients' attendance at a cardiac nurse-led clinic and the development of a comprehensive care plan which may include referral to a CR exercise training programme (physiotherapy-led). Following the delivery of CR, patients are invited back to the cardiac nurse-led clinic for final assessment prior to discharge (stage five and six). There are currently no long-term CR provisions in the regional NHS area (Hull).

4.3.3 Study Outline

Patients with a primary diagnosis of coronary heart disease (CHD) were eligible for this study. Patients were recruited within one week of sustaining a cardiac event at a nurse-led clinic offered to 'in-scope' patients referred to CR. At their appointment, patients were able to access all CR secondary prevention components recommended by the British Association of Cardiac Prevention and Rehabilitation (BACPR) including exercise training (BACPR, 2012b). Those choosing to take part in CR exercise training formed the treatment group (TG) and those declining CR comprised the control group (CG). Access to other components of CR was not restricted. Randomisation was not performed as this was deemed unethical given the current evidence base demonstrating the benefits of CR.

Following recruitment, patients received a group specific (TG/CG) patient information sheet (PIS) explaining the study aims, objectives and testing methods. Approximately one week after receiving the PIS, patients were contacted to determine if they were still interested in participating in the study. Any outstanding questions were answered at this point. Patients were then invited to attend the Academic Cardiology Research Laboratory at Castle Hill Hospital on three occasions. For TG patients, initial appointments (visit 1) were planned to coincide with the start date of their exercise class. In most cases this was approximately 28 days post cardiac event with the exception of coronary artery bypass graft patients who typically attended visit 1 more than six weeks post-surgery. CG patients were invited to attend visit 1 at similar times following their cardiac event (approximately 28 days). Following visit 1 all patients were instructed to follow the advice of their healthcare team including any physical activity or exercise recommendations. TG follow-up appointments (visit 2) were arranged to coincide with the completion of the CR exercise training regime (approximately 8 to 12 weeks later). CG visit 2 was planned at approximately equal time points. A third visit (visit 3) was arranged for both groups 12 months after visit 1. All patients were clinically stable at the time of recruitment. Inclusion and exclusion criteria are detailed in Table 1.

Table 1 – Study inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Clinically stable patients	Clinically unstable patients
Recent MI, CABG, PCI, CHF or hospital admission for newly diagnosed exertional angina	Valvular heart disease
Aged 30 to 85 years	Patients with congenital heart conditions, significant co-morbidities including severe CHF, advanced cancer and conditions preventing the patient from providing informed consent
Willing to undetake all tests described in the PIS	Current drug abusers, excessive alcohol drinkers and patients currently serving a sentence with HM prison
Absence of contraindications to exercise	Patients unwilling or unable to participate in key aspects of the study
Contractually capable and mentally able to understand and follow the instructions of the health professional team	Ongoing clinical complications, open wounds or systemic infections
Able to provide signed informed consent	Women who are pregnant or breastfeeding

MI = Myocardial Infarction; CABG = Coronary Artery Bypass Graft; PCI = Percutaneous Coronary Intervention; CHF = Chronic Heart Failure; PIS = Participant Information Sheet;

4.3.4 Exercise Training Group

Hull's exercise based CR programme comprises two exercise sessions per week conducted over eight weeks (16 sessions). Each patient received a one-to-one assessment with a physiotherapist prior to commencing exercise training. A personal exercise prescription was developed. Functional capacity was estimated using submaximal, incremental cycle ergometry using two minute stages with 30 or 25 W stage increments. Exercise testing was terminated at 70% of patients' heart rate reserve (HRR; formula detailed below), a Borg score (Borg, 1982) of 14 to 15 or the development of angina symptoms. Data obtained from the exercise test included heart rate (HR), Borg's rating of perceived exertion [RPE] (Borg, 1982); and O_2 saturation (SPO_2) where available. MET's achieved and predicted maximal METs were estimated from BACPR's reference tables (unpublished). Data were used for CR risk stratification according to guidance from the ACPICR (2015) and BACPR (BACR, 2006) as well as to evaluate patients' response to submaximal exercise.

HR training zones during exercise training were estimated according to local protocol. Karvonen method (Karvonen and Vuorimaa, 1988) was used for patients aged <45 years:

$$(220 \text{ bpm} - \text{age} - \text{RHR} [-30\text{bpm where } \beta\text{-Blocked}]) \times \text{desired HR\%} + \text{RHR}$$

Tanaka and colleagues (2001) method was used for those ≥45 years:

$$(206 \text{ bpm} \times 0.7\text{age} - \text{RHR} [-30\text{bpm where } \beta\text{-Blocked}]) \times \text{desired HR\%} + \text{RHR}$$

A training intensity of 40-60% of patients' predicted HRR was typically used during a standard exercise circuit with some patients permitted to exercise up to 70% HRR. An eight or nine station circuit (depending on perceived ability of the patient) incorporating CV and active recovery (AR) exercises was used (Figure 1; Table 2). Patients usually started their CR programme with alternating CV and AR exercises. Patients perceived to be fitter had AR exercises replaced with CV exercises to increase total CV exercise time. Each CV exercise was initially prescribed for short durations of one to two minutes and was up-titrated at each session depending on their HR RPE and any clinical response to exercise. Total CV time was not standardised and was selected based on the clinical judgement of the physiotherapist. A minimum CV exercise duration of 20 minutes was the target for most patients (ACPICR, 2015). Patients were also advised to exercise at an intensity corresponding to an RPE of 11-14 during each CV exercise and, to record their RPE at the end of each CV station. This helped the physiotherapist to keep track of exercise intensity. Patients were required to record their exercise HR's prior to and following each CV exercise using HR monitors of different makes (dependent on venue).

4.3.5   Informed Consent

At visit 1 a member of the research team discussed the study protocol with the patient and answered any questions. Consent was then taken by a cardiologist. A consent form was filed in the patient medical notes, a second retained for the study site file and a third copy was given to the patient.

4.3.6   Standardisation

Patients were instructed to attend Academic Cardiology's testing laboratory at Castle Hill Hospital in a euhydrated state, with their GTN spray (where prescribed), an up-to-date medication list and having not taken part in strenuous exercise within the previous 24 hours. Patients were not required to fast prior to attendance due to the long appointment duration (three to four hours). Patients were instructed to eat a light breakfast or lunch depending on whether their appointment was scheduled for morning or afternoon. Where possible patients' second and third appointments were scheduled for the same time of day as their first to control for circadian variation however in many cases patient availability made this impractical.
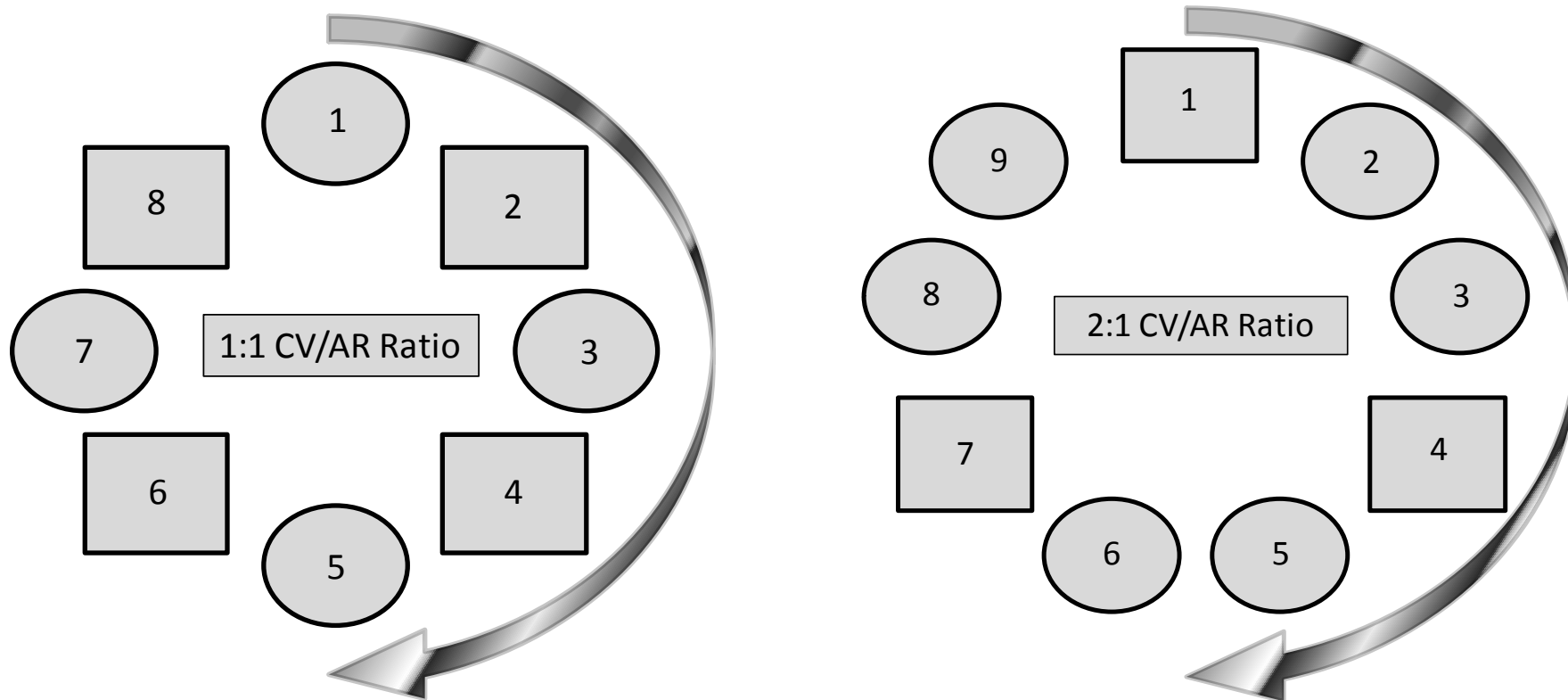
Figure 1 – Diagram depicts two examples of a typical exercise circuit. The standard 1:1 circuit (left) shows alternating cardiovascular (circles) and active recovery (squares) whilst the progression (right) shows two cardiovascular exercises for every active recovery exercise. Arrows show the order in which patients complete their exercises.

Table 2 – Examples of cardiovascular and active recovery exercises prescribed as part of a cardiac rehabilitation class

CV Exercises	Active Recovery Exercises
Box Stepping	Arm Curls
Static Cycling	Sit to Stand
Treadmill Walking	Wall Press-up
Concept II Rower	Leg Curls
Marching on the Spot	Lateral Arm Raises
Knee Raises	Trunk Rotation
Half Stars	

4.3.7 Physical Assessment

At each visit, medical records were reviewed prior to a physical examination and assessment of patients' current and past health status. Information on presenting cardiac diagnosis, past medical history, current symptoms and medications were documented. TG and CG patients were asked to recall the number of additional exercise sessions conducted between visit 1 and 2. Resting HR and blood pressure (BP) were taken after 15 minutes of rest (seated with legs elevated on examination bed) using a 12-lead ECG (GE Healthcare, Buckinghamshire, UK) and an ECG-gated automated BP cuff placed on the patient's left arm over the brachial artery (Tango, SunTech Medical, Eynsham, United Kingdom).

4.3.8 Anthropometric Measurements

Body mass (Kg) was measured using a Tanita Body Composition Analyser MC – 180MA (Tanita, Amsterdam, The Netherlands). Patients were instructed to remove footwear, jackets and items from their pockets before standing in the centre of the scales. When the measurement device had stabilised, body mass was recorded to one decimal place. Height (cm) was measured using a Leicester Height Measure (SECA, Birmingham, United Kingdom) with patients standing, without footwear, in the Frankfort plane with their heels and head positioned to the back of the stadiometer. The highest measurement recorded during the in-breath was taken as the individual's height. Body mass index (BMI) was calculated by dividing the patient's body mass by the square of their height (metres^2) and recorded as $Kg \cdot m^{-2}$ (Pescatello et al., 2009). As recommended by the National Obesity Task Force, [cited by the ACSM's Guidelines for Exercise Testing and Prescription (ACSM, 2013)], waist measurements were taken 1 cm above the iliac crest. Hip measurements were taken from the widest aspect of the hip (maximal protrusion of the buttocks) using an inflexible tape measure. Both were recorded in cm and a ratio of the two was calculated to obtain waist to hip ratio.

4.3.9   Duel X-Ray Absorptiometry Scan

Body composition was analysed using Duel X-Ray Absorptiometry [DXA] (Lunar iDXA, GE Healthcare, Buckinghamshire, UK). An automated calibration was performed daily using a control block of known composition. Prior to each scan, patients received a full explanation of the investigation including risks of radiation. Patients were asked to remove any metallic objects such as weddings rings and watches before lying supine on the scanner. Patients were aligned within a rectangular positioning grid with their head positioned at the top of the scanning field. Shoulders and arms were positioned symmetrically. Fingers were placed away from the body where possible. The torso and legs were aligned to follow the uniform sagittal line of the body. A velcro belt was loosely placed around both legs at the anterior tibial crest to prevent movement during the scan. Patients were asked not to talk to avoid movement artefact. Patient height and body mass were entered into the DXA computer so that an appropriate radiation dosage could be automatically calculated. Composition analysis was performed by integrated software. For the purpose of this chapter, total mass (Kg), total body fat (%) and lean body mass (Kg) were reported.

4.3.10   Metabolic Cart Calibration

Respiratory gas exchange data were collected using an Oxycon Pro (Jaeger, Hoechburg, Germany) breath-by-breath metabolic cart. Computer-automated calibration of ambient temperature, humidity, altitude and barometric pressure was conducted. Known gas flow-volumes were calibrated using a 3L syringe. Volume calibrations were repeated on at least two occasions. Offset values were automatically calculated to allow accurate measurement of ventilatory volumes. Two point calibration, using known gas concentrations, was conducted to allow accurate quantification of inspired O_2 and expired CO_2 concentrations (control gas: O_2 16.4%; CO_2 4.5%).

4.3.11 Spirometry

Respiratory function was evaluated from resting spirometry and conducted using an Oxycon Pro. The ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) are reported in this chapter. Details of the full spirometry protocol are available in Appendix 2. Patients were asked to attach a nose clip to restrict nasal gas exchange before breathing into a mouth piece attached to the metabolic cart's gas flow turbine. Flow volume loops were conducted to obtain forced spirometry measurements. Prior to the manoeuvre being attempted, a demonstration and clear instructions were given. The following terms were used as instruction points:

- Maintaining a 'neutral' head position

- Sitting upright/good posture

- Taking a forced (rapid) deep breath in until their lungs were fully expanded

- Making a forced breath out to breathe out as much air as possible in the first second

- To continue breathing out until they could no longer do so

Up to eight flow-volume loops were conducted to obtain three high quality manoeuvres. Acceptable reproducibility was defined as ≤0.150 L difference between the largest and second largest FEV_1 and FVC measurements (American Thoracic Society/European Respiratory Society, 2005).

4.3.12 Cardiopulmonary Exercise Testing

CPET was conducted according to guidelines outlined by the American Thoracic Society (American Thoracic Society/American College of Chest Physicians, 2003) and others (Balady et al., 2010) in a temperature controlled room (21°C). An explanation of CPET was given to all participants, including description of the test protocol, RPE, potential adverse symptoms and CPET stop procedures. Any questions were answered prior to attaching equipment and

beginning the test.

Table 3– Test termination criteria

Indications for exercise termination
Chest pain suggestive of ischemia
Ischemic ECG
changes Complex
ectopy
Second or third degree heart block
Fall in systolic pressure 20 mm Hg from the highest value during the test
Hypertension (250mmHg systolic; 120mmHg diastolic)
Severe desaturation: SpO$_2$ less than 80% when accompanied by symptoms and signs of severe hypoxemia
Sudden pallor
Loss of coordination
Mental confusion
Dizziness or faintness
Signs of respiratory failure

ECG = Electrocardiogram; mmHg = Millimetres of Mercury; SPO$_2$ = Peripheral Capillary O$_2$ saturation

4.3.13 Cardiopulmonary Exercise Testing Preparation

A 12 lead ECG was placed in the Mason-Likar configuration. Body hair was removed with a disposable razor where necessary. Skin surface was prepared with emery paper and alcohol swabs for ECG electrode placement. To reduce movement artefact during CPET, ECG cables were secured to the patient's skin with body tape. ECG was measured continuously throughout CPET. An ECG-gated automated BP cuff with inbuilt microphone-stethoscope was placed on the subject's left arm over the brachial artery. BP was monitored from the start of CPET and at the second minute of each stage until the end of the test. ECG and BP were monitored throughout exercise, and thereafter until HR was <100 bpm and ECG or BP changes had normalised.

4.3.14 Exercise Protocol

A CPET face mask was attached to the patient using a harness. The exercise testing protocol was conducted according to the Modified Bruce Protocol (Bruce et al., 1973). All exercise tests were preceded by a seated three minute rest period to record pre-test gas exchange, BP and HR

100

values. Following the rest period, patients undertook CPET on a treadmill (General Electric [GR]) driven by a GE Case system (GE Healthcare, Buckinghamshire, UK). CPET data from expired gas analysis were collected continuously during the three minute rest period, during exercise and a six minute recovery period. Patients were advised not to talk during the exercise test with the exception of instructing the test administrator to stop exercise and to provide RPE scores. RPE was obtained after two and a half minutes of each three minute exercise stage, at peak exercise and, during recovery. For safety reasons patients were also periodically asked to confirm that they were asymptomatic. CPET was terminated when patients advised the investigator that they could no longer sustain exercise, or if symptoms/ECG signs of myocardial ischaemia (ST segment depression >2mm/Table 3 criteria), confusion or any other test termination criteria presented (Table 3). At the end of the test, data were saved and exported for offline analysis as 15 second, breath-by-breath averages. This interval minimises breath-by-breath signal noise whilst avoiding unnecessary 'data smoothing'.

4.3.15 CPET Variable Calculation

Patients were deemed to have achieved peak exercise performance if two or more of the criteria outlined in Table 4 were achieved (American Thoracic Society/American College of Chest Physicians, 2003). A VO_2 plateau or VO_2 change <150 $ml^{-1} \cdot min^{-1}$ despite increasing work rate was not used as peak exercise performance criteria because the stage-increments of the modified Bruce protocol are large and often result in test termination within the first few seconds of a new stage. This was thought to increase the likelihood of erroneously identifying a VO_2 change <150 $ml^{-1} \cdot min^{-1}$. VO_{2peak} was defined as the mean VO_2 over the last 30 seconds of CPET (mean of two 15 second data averaging periods). VO_{2peak} was reported relative to patients' body mass ($ml \cdot kg^{-1} \cdot min^{-1}$) and lean body mass ($ml \cdot kg^{-1} \cdot min^{-1}$) recorded during the DXA scan. Peak respiratory exchange ratio (RER) was also defined as the mean VCO_2/VO_2 data averages over the last 30 seconds of CPET.

Table 4 – Peak Exercise Test Criteria

Criteria
Failure to achieve 90% of age predicted HR maximum
A Peak RER $\geq$ 1.10
An RPE > 17 on the 6-20 Borg scale

HR = Heart Rate; RER = Respiratory Exchange Ratio; RPE =Rating of Perceived Exertion

VAT was determined using the V-slope method (Beaver et al., 1986b) and verified using the ventilatory equivalents method (Mezzani et al., 2009). VAT was reported as VO_2 standardised to patients body mass, lean body mass recorded during the DXA scan ($ml·kg^{-1}·min^{-1}$) and, proportional to patients' VO_{2peak} (%).

The slope of the relationship between minute ventilation (VE) and expired CO_2 (VCO_2) was calculated to determine ventilatory efficiency with respect to CO_2 elimination (VE/VCO_2 slope). A VE/VCO_2 slope gradient >34 was considered indicative of poor ventilatory efficiency (Arena et al., 2004). Ventilatory efficiency with respect to VO_2 (O_2 uptake efficiency slope; OUES) was calculated by plotting VO_2 (litres) against VE_{log10} (Baba et al., 1996). A higher slope indicates superior ventilatory efficiency whereas a lower slope suggests reduced ventilatory efficiency.

Peak oxygen pulse (O_2/HR) was calculated by dividing VO_{2peak} by peak HR (HR_{peak}) as an estimate of peak exercise SV. Data was presented as uncorrected values (ml/beat) and following the application of the correction equation suggested by Mezzani et al. (2009). Mezzani and colleagues (2009) equation can be applied to attempt to remove the muscle O_2 extraction component of O_2/HR:

$$SV = (peak\ oxygen\ pulse/15) \times 100$$

The equation recommended by Mezzani and colleagues (2009) assumes a fixed haemoglobin concentration. This equation may not be valid in patients who are anaemic or have abnormal haemoglobin values.

HR$_{peak}$ was recorded as the highest HR achieved during CPET and was characterised as a percentage of the patients predicted HR max using either the Karvonen or Tanaka formulas (Karvonen and Vuorimaa, 1988, Tanaka et al., 2001) in line with local CR protocol. Attainment of >90% age predicted maximum HR indicted maximal CPET criteria (American Thoracic Society/American College of Chest Physicians, 2003). CPET HRR was calculated by subtracting the resting HR from HR$_{peak}$. Peak rate pressure product (RPP) was calculated as an indirect measure of myocardial workload using the formula:

$$RPP = \frac{HR_{peak} \times peak\ Systolic\ BP}{100}$$

METs were automatically calculated by a GE Case system, using American College of Sports Medicine metabolic equation for walking (2013):

$$METs = \frac{(Speed \times 0.1) + (grade/100 \times 1.8 \times speed) + 3.5}{3.5}$$

Where speed is recorded in metres per minute and grade is the treadmill gradient (%). METs calculated by the CR team were done so using unpublished reference tables provided by the BACPR on their 'Assessing Functional Capacity' training course.

4.3.16 Cardiac Rehabilitation Exercise Prescription Analysis

All exercise programmes were transcribed into a spreadsheet prior to analysis. CV exercise duration achieved at each of the 16 CR sessions was calculated for all patients. Patients' CV exercise duration at each session was pooled for analysis. Median, interquartile range (IQR) and range of each session's CV exercise duration was plotted as box-plots. Patients' total exercise time was calculated by summing the duration of all CV exercises conducted during the 16 sessions. Median and range were calculated for total CV exercise time. Because HR was only

documented prior to, and following completion of a CV exercise station, no dynamic HR data were available to quantify time in training zone. To provide *some* insight into exercise intensity at each exercise session, the mean of patients' HR following completion of all CV exercises for a particular session was calculated (mean peak HR). Patients' 'mean peak HR' for each exercise session was then pooled for analysis where the median 'mean peak HR' was calculated (median peak HR) and plotted as a box-plot. 'Median peak HR' was expressed as a percentage of the VAT determined from visit 1 CPET, relative to the CR teams estimated HRR and, relative to HRR obtained from visit 1 CPET. A composite score of intensity and CV exercise duration for each training session was calculated and summed to give an overall exercise dose for every patient. The composite score was defined as:

$$\frac{\text{Mean peak HR}}{\text{Patients' CPET HRR}} \text{ x CV exercise duration}$$

As an additional marker of exercise intensity the mean of a patient's RPE following completion of an exercise session was calculated (mean RPE). Patient's RPE scores for each exercise session were pooled for analysis and plotted as box-plots.

Median, rather than means were chosen for exercise prescription analysis due to the large variation in exercise duration and intensity. This attempted to minimise the impact of outlying data points and provide a better representation of the data.

4.3.17 Statistical Analysis

At the time of analysis the number of patients returning for visit 2 was substantially greater than those who had returned for visit 3. Consequently analysis was initially performed on the shorter-term effects of CR (visit 1 to 2) only. Separate analysis was performed on the smaller sample size of patients returning for visit 3.

Statistical analysis was conducted using SPSS version 22 (IBM, New York, USA). Patients were

excluded from analysis if they failed to attend any follow up visit. Normal distribution was assessed using histograms and the Shapiro-Wilk test. The Shapiro-Wilk test is the preferred test for normality in instances where samples sizes are <50 (Ghasemi and Zahediasl, 2012). Where the assumption of normal distribution was not met, Log_{10} and square root transformation was attempted. Where data transformation was successful, arithmetic means were reported for meaningful interpretation. Statistically significant differences ($\alpha < 0.05$) were calculated through repeated measures and one-way analysis of variance (ANOVA) with Bonferroni correction. Where parametric assumptions were not met, non-parametric analysis was performed using a Wilcoxon or Friedman test. Potential covariates were determined through correlation analysis. Analysis of covariance (ANCOVA) and treatment interactions (time x group) were analysed where appropriate. Treatment effect was also considered using minimal clinically important differences (MCID). The definition of MCID was originally suggested by Jaeschke (1989) as:

"the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management"

There is no 'gold standard' method for determining the MCID, however, for the purpose of this study it was calculated as:

$$MCID = Pooled\ SD \times 0.2$$

Where pooled SD is the pooled standard deviation of a population's baseline score for a specified outcome variable and 0.2 is the fraction of that which any score change must exceed to be deemed clinically meaningful (Page, 2014, Lemieux et al., 2007).

$$Pooled\ SD = \sqrt{\frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2}}$$

Where n is group 1 or 2 and S_2^2 is the squared SD for that group. For example:

$$\sqrt{\frac{(22-1) \times 5.79^2 + (12-1) \times 4.78^2}{22+12-2}} =$$

$$\frac{704.01 + 251.33}{32} = 5.46$$

$$5.46 \times 0.2 = 1.09$$

In the absence of wide 95% CI that substantially cross 0, changes exceeding the MCID in either a positive or negative direction were classed as clinically meaningful. Because the MCID is open to interpretation, partial eta^2 (η_p^2) sizes were also calculated with 0.01, 0.06 and 0.14 representing small, medium and large effect sizes respectively (Richardson, 2011).

Continuous normally distributed variables are displayed as mean with 95% confidence intervals (95% CI) or standard deviation (± SD) where specified. Non-normally distributed data are displayed as median (range). Categorical data are reported as percentages and analysed using Chi-squared analysis where appropriate. Pearson (or Spearman for non-parametric data) correlations were conducted to determine the association between independent and dependent variables. An r value of <0.25, 0.26 to 0.50, 0.51 to 0.75, and, >0.75 were considered weak, moderate, fair and strong relationships respectively (Berg and Latin, 2008). Correlations were confirmed if the associated p-value was <0.05. MET and predicated maximal MET scores from submaximal exercise tests conducted at patients' pre and post CR physiotherapy assessments were correlated against their corresponding VO_{2peak} scores at visit 1 and 2. Change in submaximal and estimated maximal METs were correlated against changes in VO_{2peak} between study visit 1 and 2 respectively. Correlations between peak METs achieved during CPET and VO_{2peak}, as well as change in peak METs and VO_{2peak} change were also performed. Peak METs were transformed into estimated VO_{2peak} by multiplying peak METs by 3.5 ml·kg^{-1}·min^{-1}. The process was repeated using the recommended 2.6 ml·kg^{-1}·min^{-1} 'average' resting MET of Byrne et al. (2005). Measurement variability of both values was determined through mean bias and

limits of agreement [LoA] (Bland and Altman, 1999). A Breusch-Pagen test was performed to check assumptions of homoscedasticity. Receiver operating characteristics (ROC) were used to identify any dose response for VO_{2peak} and VAT improvement in relation to total exercise duration, number of additional exercise sessions conducted and the dose composite score. Participants were binned into two groups based on whether they had achieved the MCID for VO_{2peak} and VAT (state variables). Where appropriate, area under the curve (AUC) and the test variable with the highest sensitivity and specificity was calculated.

4.4   Results

4.4.1   Group Characteristics

At the time of data censorship; n=38 patients had attended visit 1. One patient was readmitted for emergency CABG, one suffered a complex fracture of the patella (unrelated to the intervention) and two participants were lost to follow-up. In total n=3 TG patients and n=1 CG were excluded from analysis. n=34 patients (85.3% male; BMI 29.5 ± 4.5 $Kg·m^{-2}$) met the study inclusion criteria. The mean age (62.1 ± 8.8 years) was comparable to the national mean age (66 years) of patients accessing CR (British Heart Foundation, 2014). n=22 and n=12 patients formed the TG and CG respectively. Baseline characteristics of all patients are shown in Table 5. The majority of patients had sustained an MI (52.9%). 32.4% had received a PCI. There were no significant between group differences for age (0.2 years; 95% CI -6.3 to 6.7 years; p=0.946), BMI (0.2 $Kg·m^{-2}$; 95% CI -3.5 to 3.2 $Kg·m^{-2}$; p=0.946) or left ventricular EF (1.3 %; 95% CI -4.3 to 7.0 %; p=0.632). Only 5.9% of patients had undergone CABG. 23.5% of patients had sustained a previous MI. Type 2 diabetes mellitus (DM) was more prevalent within the CG than the TG (58.3% Vs 13.6%; p=0.006) as was the number of patients currently smoking (0.0% vs. 25.0%; p=0.024). As recommended by NICE (2013b) a high proportion of patients were prescribed relevant cardio-protective medications. Patient medications are listed in Table 6. There were no changes to patient medications between visit 1 and 2.

4.4.2 Exercise Training

There were no significant differences between the total number of exercise sessions completed by the TG and CG (p=0.462). The TG group attended a median of 16 (range: 6 to 16) structured CR exercise sessions and conducted 7.5 (range: 0 to 84) additional self-reported home-based exercise sessions. The CG group conducted a median of 21 (range: 0 to 78) non- prescribed home physical activity/exercise sessions. Friedman analysis showed that the TG group significantly increased their median exercise duration per from 11.5 minutes at session 1 (range: 6 to 27.5 minutes) to 20.5 minutes (range: 11.5 to 48 minutes) at session 16 [Figure 2; p<0.001). 68% of TG patients achieved a minimum of 20 minutes CV exercise per session upon programme completion. The majority of patients (55%) did not achieve 20 minutes of CV exercise until their eleventh exercise session. 23% of patients achieved 30 minutes of CV exercise per session upon completion of CR. 'Median peak HR' did not change significantly between session 1 (95 bpm; range: 72 to 116bpm) and session 16 (Figure 3; 98 bpm; range: 73 to 119bpm; p=0.920). The 'Median peak HR' was always above the mean HR at VAT. 'Median peak HR' corresponded to 40-60% HRR regardless of whether HRR was estimated or calculated from CPET data (Figure 4). Median RPE increased significantly from session 1 (RPE 11.5; range: 7.3 to 12.5) to session 16 (RPE 12; range: 8.3 to 14.3; p=0.020). Most patients did not exceed an RPE of 13 between session 1 (third quartile RPE: 12) and session 16 (third quartile RPE: 13; Figure 5).

Table 5 – Patient Baseline Characteristics (mean ± SD)

Variable	All	Treatment Group (*n* =22)	Control Group (*n* =12)
Participants (% male)	*n* =34 (85.3)	*n* =22 (81.8)	*n* =12 (91.7)
Age (years)	62.1 ± 8.8	62.1 ± 8.5	61.9 ± 9.6
BMI (Kg·m^{-2})	29.5 ± 4.5	29.4 ± 4.2	29.6 ± 5.1
W/H Ratio	0.95 ± 0.08	0.95 ± 0.09	0.97 ± 0.05
Resting SBP (mmHg)	129 ± 23	127 ± 20	134 ± 29
Resting DBP (mmHg)	81 ± 10	81 ± 12	60 ± 11
Resting HR (bpm)	58 ± 10	56 ± 6	54 ± 10
Resting EF (%)	55.1 ± 7.6	55.6 ± 6.4	54.3 ± 9.8
FEV$_1$/FVC Ratio	0.77 ± 0.8	0.78 ± 0.08	0.75 ± 0.06
STEMI + PPCI (%)	14.7 (*n* =5)	13.6 (*n* =3)	16.7 (*n* =2)
STEMI + Staged PCI	2.9 (*n* =1)	4.5 (*n* =1)	0.0 (*n* =0)
STEMI + POBA	2.9 (*n* =1)	4.5 (*n* =1)	0.0 (*n* =0)
NSTEMI + PCI	26.5 (*n* =9)	18.2 (*n* =4)	41.7 (*n* =5)
NSTEMI	5.9 (*n* =2)	9.1 (*n* =2)	0.0 (*n* =0)
Exertional Angina	8.8 (*n* =3)	9.1 (*n* =2)	8.3 (*n* =1)
PCI	32.4 (*n* =11)	36.4 (*n* =8)	25.0 (*n* =3)
CABG	5.9 (*n* =2)	4.5 (*n* =1)	8.3 (*n* =1)
Hypertension (%)	57.1 (*n* =16)	50.0 (*n* =11)	41.7 (*n* =5)
Hyperlipidaemia (%)	79.4 (*n* =27)	81.8 (*n* =18)	75.0 (*n* =9)
Previous MI (%)	23.5 (*n* =8)	18.1 (*n* =4)	33.3 (*n* =4)
Previous CABG (%)	5.9 (*n* =5.9)	4.5 (*n* =1)	8.3 (*n* =1)
Previous PCI (%)	14.7 (*n* =5)	9.1 (*n* =2)	25.0 (*n* =3)
Previous TIA (%)	5.9 (*n* =2)	4.5 (*n* =1)	8.3 (*n* =1)
Atrial Fibrillation (%)	5.9 (*n* =2)	4.5 (*n* =1)	8.3 (*n* =1)
Type 2 DM (%)	29.4 (*n* =10)	13.6 (*n* =3)	58.3 (*n* =7)
Asthma (%)	5.9 (*n* =2)	9.1 (*n* =2)	0.0 (*n* =0)
COPD (%)	5.9 (*n* =2)	4.5 (*n* =1)	8.3 (*n* =1)
Smoking Cessation (%)	5.9 (*n* =2)	4.5 (*n* =1)	8.3 (*n* =1)
Ex-Smoker (%)	52.9 (*n*= 18)	59.1 (*n* =13)	41.7 (*n* =5)
Smoker (%)	8.8 (*n* =3)	0.0 (*n* =0)	25.0 (*n* =3)
Cancer (%)	11.8 (*n* =4)	13.6 (*n* =3)	8.3 (*n* =1)

Kg·m^{-2} = Kilograms per Metres squared; W/H Ratio = Waist to Hip Ratio; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; mmHg = Millimetres of Mercury; HR = Heart Rate; bpm = Beats Per Minute; EF = Ejection Fraction; FEV$_1$ = Forced Expiratory Volume in One Second; FVC = Forced Vital Capacity; STEMI = ST Elevation Myocardial Infarction; PPCI = Primary Percutaneous Coronary Intervention; PCI = Percutaneous Coronary Intervention; POBA = Plain Old Balloon Angioplasty; NSTEMI = Non-ST Elevation Myocardial Infarction; CABG = Coronary Artery Bypass Graft; MI = Myocardial Infarction; TIA = Transient Ischaemic Attack; Type 2 DM; Type 2 Diabetes Mellitus; COPD = Chronic Obstructive Pulmonary Disease

Table 6 – Patient Medications

Medication	All (*n* =34)	Treatment Group (*n* =22)	Control Group (*n* =12)
Aspirin (%)	97.1 (*n* =33)	100.0 (*n* =22)	91.7 (*n* =11)
Clopidogrel (%)	26.5 (*n* =9)	36.4 (*n* =8)	8.3 (*n* =1)
Ticagrelor (%)	55.9 (*n* =19)	45.5 (*n* =10)	75.0 (*n* =9)
Beta-Blocker (%)	91.2 (*n* =31)	95.5 (*n* =21)	83.3 (*n* =10)
ACE-inhibitor (%)	52.9 (*n* =18)	50.0 (*n* =11)	58.3 (*n* =7)
AR Blocker (%)	11.8 (*n* =4)	13.6 (*n* =3)	8.3 (*n* =1)
Statin (%)	94.1 (*n* =32)	95.5 (*n* =21)	91.7 (*n* =11)
Fibrate (%)	2.9 (*n* =1)	0.0 (*n* =0)	8.3 (*n* =1)
Diuretic (%)	8.8 (*n* =8.8)	4.5 (*n* =1)	16.7 (*n* =2)
Nitrate (%)	23.5 (*n* =23.5)	22.7 (*n* =5)	25.0 (*n* =3)
GTN (%)	97.1 (*n* =33)	95.5 (*n* =21)	100.0 (*n* =12)

ACE = Angiotensin Converting Enzyme Inhibitor; AR = Angiotensin Receptor Blocker; GTN = Glyceryl Trinitrate

Figure 2 – Median CV exercise duration achieved per exercise session. Dashed line indicates recommended minimum 20 minute CV exercise duration.

CV = Cardiovascular; * = Significant Difference

110
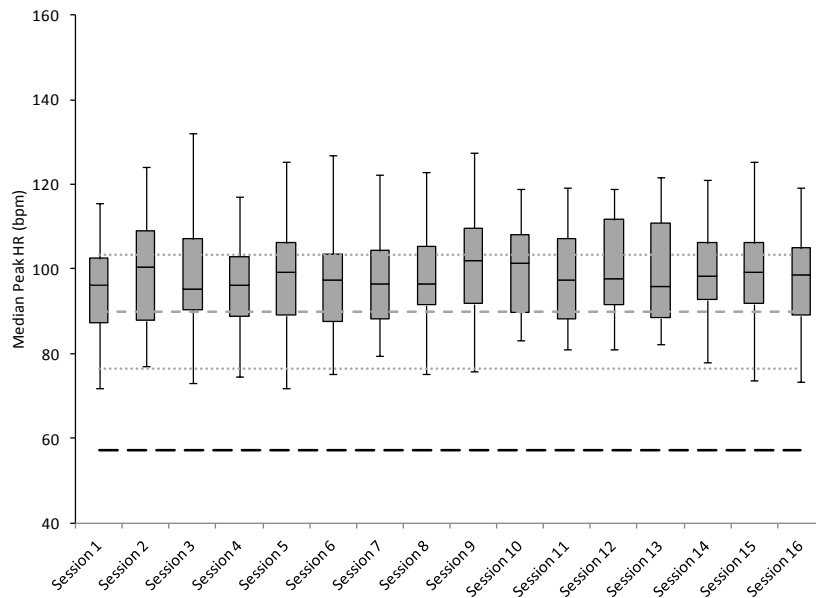
Figure 3 - Median peak heart rates achieved at each exercise session. Grey dashed line shows the mean HR at VAT during CPET. Grey upper and lower dotted lines represent 1 standard deviation of the HR at VAT. Lower black dashed lined represents patients resting HR.
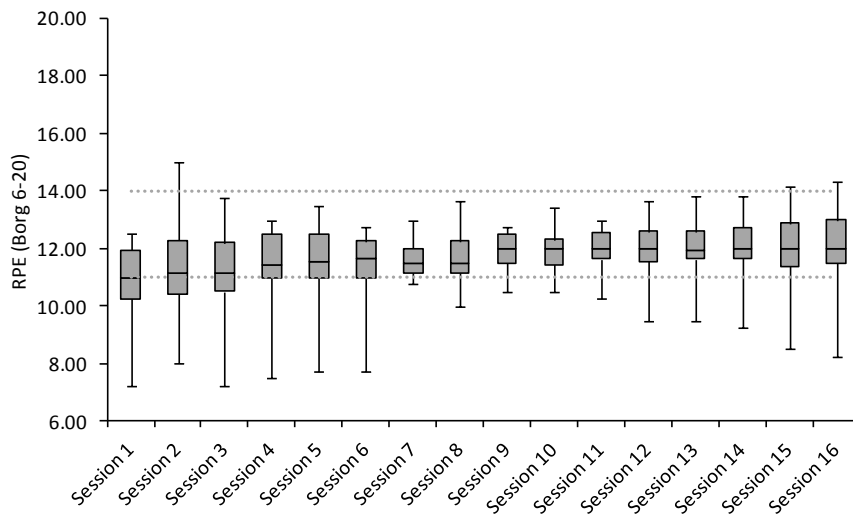
dotted line shows RPE 11, upper grey dotted line shows RPE 14.

RPE = Rating of Perceived Exertion; * = Significant Difference
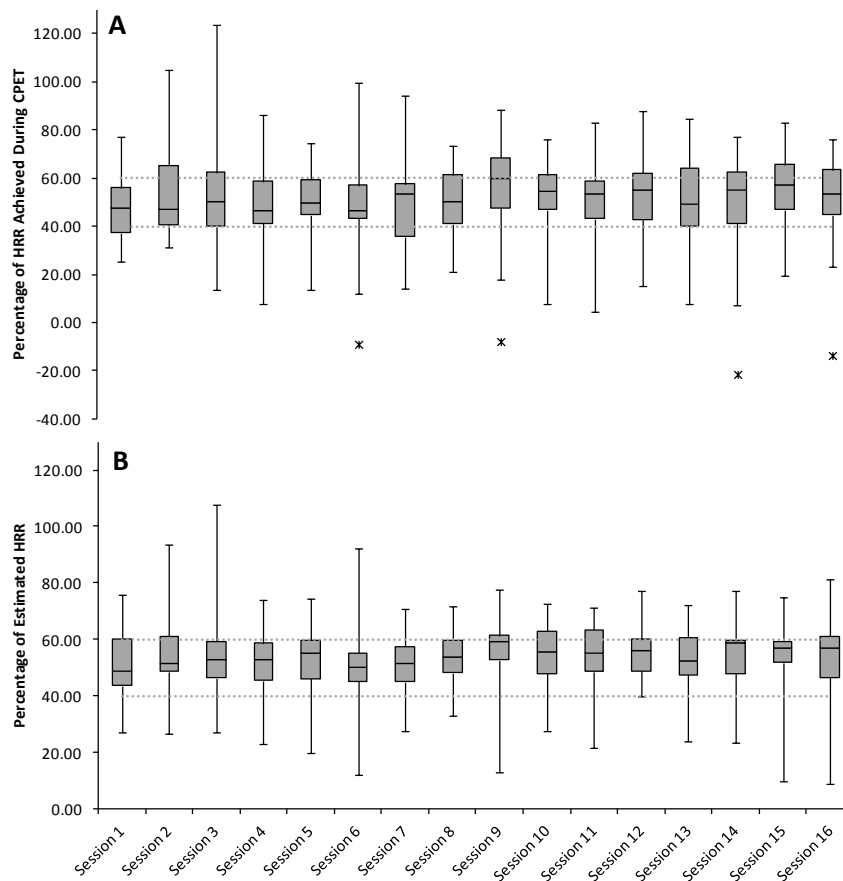
Figure 4 – Panel 'A' shows median peak HR at each exercise session relative to 40-60% HRR achieved during CPET. Panel 'B' shows median peak HR at each exercise session relative to 40-60% estimated HRR. Lower and upper grey dotted line shows 40 to 60% HRR reserve respectively.

HRR = Heart Rate Reserve; HR = Heart Rate; CPET = Cardiopulmonary Exercise Test; ✗ = Outlier

4.4.3   Cardiopulmonary Exercise Testing

4.4.4   Determining Covariate Inclusion

Changes in CRF variables were first analysed as the pre-post changes in body-mass adjusted VO_{2peak}. Covariate analysis was then conducted. Baseline VO_{2peak}, and changes in both HR_{peak} and peak RER between visit 1 and 2 were considered as covariates for VO_{2peak} changes. Similar, statistical adjustments were also undertaken for other supplementary measures of cardiorespiratory fitness/function derived from CPET. Covariates considered for VE/VCO_2 slope change were baseline VE/VCO_2 slope, change in peak RER and HR_{peak} change between visit 1 and 2. Baseline VAT was the only covariate considered for VAT change. There was a moderate

negative correlation between baseline VO_{2peak} and VO_{2peak} change (r=-0.405; p=0.018). VO_{2peak} change and RER (r=-0.047; p=0.792), as well as VO_{2peak} change and HR_{peak} (r=0.018; p=0.792) were not correlated. A fair, negative correlation between baseline VE/VCO_2 slope change was and VE/VCO_2 change was found (r=-0.554; p=0.001). VE/VCO_2 slope change and HR_{peak} change were positively, moderately correlated (r=0.405; p=0.018). Change in VE/VCO_2 slope and RER were not correlated (r=0.255; p=0.153). Baseline VAT was not correlated with VAT change (r=-0.252; p=0.158). Covariates included in analysis were baseline VO_{2peak} for VO_{2peak} change and, baseline VE/VCO_2 and, HR_{peak} change for VE/VCO_2 slope change. Table 7 summarises change in key CPET variables.

4.4.5   Change in VO_{2peak}

n=8 (66.6%) controls and n=19 (86.3%) patients in the TG achieved peak exercise criteria at visit 1. n=10 (83.3%) controls and n=18 (81.8%) patients in the TG achieved peak exercise criteria for visit 2. Data for VO_{2peak} change is displayed in Table 7. There was no significant main effect (0.13 ml·kg^{-1}·min^{-1}; 95% CI -1.08 to 0.81 ml·kg^{-1}·min^{-1}; p=0.774; η_p^2 = 0.003) or group effect (1.62 ml·kg^{-1}·min^{-1}; 95% CI -1.21 to 5.33 ml·kg^{-1}·min^{-1}; p=0.380; η_p^2=0.024) for VO_{2peak} when standardised to body mass during the intervention period. Figure 6A also illustrates that there was no interaction effect (p=0.978; η_p^2<0.001) between change in VO_{2peak} for the TG and CG (TG mean change: 0.12 ml·kg^{-1}·min^{-1}; 95% CI -1.00 to 1.24 ml·kg^{-1}·min^{-1}; CG VO_{2peak} mean change: 0.15 ml·kg^{-1}·min^{-1}; 95% CI -1.37 to 1.66 ml·kg^{-1}·min^{-1}). Neither group achieved the MCID (1.09 ml·kg^{-1}·min^{-1}) for VO_{2peak} improvement. No significant between group changes in VO_{2peak} were evident following adjustment for baseline VO_{2peak} (TG corrected mean change: 0.23 ml·kg^{-1}·min^{-1}; 95% CI -0.81 to 1.28 ml·kg^{-1}·min^{-1}; CG corrected mean change: -0.06 ml·kg^{-1}·min^{-1}; 95% CI -1.48 to 1.36 ml·kg^{-1}·min^{-1}; p=0.741; η_p^2= 0.004). n=7 (31.8%) patients in the TG and n=4 (33.3%) patient in the CG experienced a VO_{2peak} increase at least as large as the MCID. Chi Squared analysis was not performed due to violation of assumptions (valid entries>5). When VO_{2peak} was

standardised to patients' lean body mass, there was no main effect (0.00 ml·kg^{-1}·min^{-1}; 95% CI -1.54 to 1.53 ml·kg^{-1}·min^{-1}; p=0.997; η_p^2 <0.001), group effect (-3.46 ml·kg^{-1}·min^{-1}; 95% CI -8.14 to 1.22 ml·kg^{-1}·min^{-1}; p=0.142; η_p^2 = 0.066) or interaction effect (TG mean change; 0.20 ml·kg^{-1}·min^{-1}; 95% CI -1.63 to 2.03 ml·kg^{-1}·min^{-1}; CG mean change -0.21 ml·kg^{-1}·min^{-1}; 95% CI -2.68 to 2.27 ml·kg^{-1}·min^{-1}; p=0.790; η_p =<0.002).

4.4.6   Change in Ventilatory Anaerobic Threshold

VAT was not normally distributed. Log$_{10}$ data transformation successfully normalised data distribution. There was no significant main effect (0.22 ml·kg^{-1}·min^{-1}; 95% CI -0.33 to 0.77 ml·kg^{-1}·min^{-1}; p=0.431; η_p^2 = 0.020) or group effect (1.61 ml·kg ·min; 95% CI -0.83 to 4.05 ml·kg^{-1}·min^{-1}; p=0.157; η_p^2 = 0.064) for changes in the VAT. Figure 6B shows no significant interaction effect (p=0.176; η_p^2 = 0.058) between the TG (mean change: 0.55 ml·kg ·min; 95% CI -0.11 to 1.21 ml·kg^{-1}·min^{-1}) and the CG (mean change: -0.11 ml·kg^{-1}·min^{-1}; 95% CI -0.98 to 0.77 ml·kg^{-1}·min^{-1}). The TG failed to achieve the MCID (0.69 ml·kg^{-1}·min^{-1}) for VAT increase. *n*=10 (45.5%) patients in the TG achieved a VAT increase greater than the MCID. The CG also failed to achieve the MCID for VAT. Only *n*=3 (25.9%) patients in the CG achieved a VAT increase greater than the MCID. Individual changes expressed relative to patients' VAT at visit 1 are displayed in Figure 7. No significant between group changes in VAT were detected after the inclusion of baseline VAT as a covariate (TG corrected mean change: 0.61 ml·kg^{-1}·min 1; 95% CI -0.35 to 1.26 ml·kg^{-1}·min^{-1}; CG corrected mean change: -0.21 ml·kg^{-1}·min^{-1}; 95% CI -1.07 to 0.65 ml·kg^{-1}·min^{-1}; p=0.131; η_p^2 = 0.074). When VAT was standardised to patients' lean body mass, there was no main (0.32 ml·kg^{-1}·min^{-1}; 95% CI -0.58 to 1.21 ml·kg^{-1}·min^{-1}; p=0.474; η_p^2=0.016), group (-2.58 ml·kg^{-1}·min^{-1}; 95% CI -5.97 to 0.81 ml·kg^{-1}·min^{-1}; p=0.431; η_p^2=0.020) or interaction effect either (p=0.189; η_p^2=0.053).

Table 7 – Changes to key cardiopulmonary exercise test variables between visit 1 and 2 (mean ± SD; mean change with 95% CI)

Variable	Treatment Group		Mean Change (95% CI)	Control Group		Mean Change (95% CI)	P-Value		
	Visit 1	Visit 2		Visit 1	Visit 2		Time	Group	Time x Group
VO_{2peak} (L)	2.14 ± 0.64	2.15 ± 0.59	0.01 (-0.08 to 0.11)	1.99 ± 0.45	2.02 ± 0.51	0.03 (-0.10 to 0.16)	0.589	0.496	0.845
VO_{2peak} (ml·kg^{-1}·min^{-1})	24.75 ± 5.79	24.87 ± 4.73	0.12 (-1.00 to 1.24)	23.12 ± 4.78	23.26 ± 5.48	0.15 (-1.37 to 1.66)	0.774	0.380	0.978
VO_{2peak} Standardised to Lean Body Mass (ml·kg^{-1}·min^{-1})	40.09 ± 7.78	40.29 ± 6.42	0.20 (-1.63 to 2.03)	36.83 ± 5.55	36.63 ± 6.27	-0.21 (-2.68 to 2.27)	0.977	0.142	0.790
VO_2 at VAT (ml·kg^{-1}·min^{-1})	15.42 ± 3.73	15.97 ± 3.52	0.55 (-0.11 to 1.21)	14.14 ± 2.89	14.03 ± 2.92	-0.11 (-0.98 to 0.77)	0.431	0.157	0.176
VO_2 at VAT Standardised to Lean Body Mass (ml·kg^{-1}·min^{-1})	24.62 ± 5.38	25.52 ± 5.10	0.91 (-0.16 to 1.97)	22.62 ± 3.34	22.35 ± 4.22	-0.27 (-1.71 to 1.17)	0.474	0.131	0.189
VE/VCO$_2$ Slope	34.04 ± 5.35	33.26 ± 4.46	-0.78 (-2.31 to 0.75)	33.55 ± 6.52	34.48 ± 5.39	0.93 (-1.14 to 3.00)	0.723	0.880	0.143
OUES	2325.92 ± 594.67	2360.15 ± 561.87	34.22 (-81.88 to 150.33)	2253.81 ± 526.53	2233.98 ± 425.74	-19.83 (-177.04 to 137.37)	0.882	0.606	0.577
O$_2$/HR (ml/beat)	13.66 ± 3.43	14.02 ± 2.66	0.35 (-0.41 to 1.12)	13.53 ± 2.87	13.76 ± 2.98	0.24 (-0.75 to 1.23)	0.343	0.853	0.850
Estimated SV (ml/beat)	104.57 ± 27.09	105.50 ± 27.73	0.93 (-4.28 to 6.14)	102.49 ± 16.98	100.74 ± 20.67	-1.74 (-8.8 to 5.31)	0.852	0.695	0.539

SD = Standard Deviation; 95% CI = 95% Confidence Intervals; VO_{2peak} = Peak O_2 Uptake; L= Litres; VAT = Ventilatory Anaerobic Threshold; VE/VCO$_2$ slope = Ventilatory Efficiency with Respect to VCO$_2$; OUES = Oxygen Uptake Efficiency Slope; O$_2$/HR = O$_2$ pulse; SV = Stroke Volume

Table 8 – Changes to resting measurements and secondary exercise outcomes between visit 1 and 2 (mean ± SD; mean change with 95% CI)

Variable	Treatment Group		Mean Change (95% CI)	Control Group		Mean Change (95% CI)	P-Value		
	Visit 1	Visit 2		Visit 1	Visit 2		Time	Group	Time x Group
BMI (Kg·m^{-2})[b]	29.41 ± 4.24	29.52 ± 4.27	0.17 (-3.17 to 3.51)	29.58 ± 5.14	30.20 ± 5.58	0.69 (-2.80 to 4.17)	0.051	0.798	0.160
W/H Ratio[a]	0.96 (Range: 0.70 to 1.05)	0.97 (Range: 0.77 to 1.06)	0.00 (Range: -0.6 to 0.7; p=0.844)	0.96 (Range: 0.88 to 1.06)	0.97 (Range: 0.88 to 1.10)	0.01 (Range: -0.03 to 0.04; p=0.234)	-	-	-
Body Fat (%)[b]	36.19 ± 6.09	36.00 ± 6.13	-0.19 (-0.86 to 0.48)	34.93 ± 8.71	34.31 ± 9.07	-0.63 (-1.53 to 0.28)	0.152	0.570	0.433
Lean Body Mass (Kg)[b]	52.69 ± 9.64	53.04 ± 9.56	0.35 (-0.14 to 0.84)	53.76 ± 7.51	54.47 ± 6.74	0.71 (0.55 to 1.36)	0.012*	0.696	0.379
Resting SBP (mmHg)[b]	127 ± 20	118 ± 19	-9 (-15 to -3)	134 ± 29	125 ± 31	-9 (-17 to 0)	0.002*	0.445	0.976
Resting DBP (mmHg)[b]	81 ± 12	76 ± 13	-4 (-10 to 1)	82 ± 7	77 ± 14	-5 (-13 to 2)	0.050*	0.804	0.827
Resting HR (bpm)[b]	58 ± 9	56 ± 7	-1 (-4 to 1)	60 ± 11	63 ± 9	3 (0 to 6)	0.276	0.146	0.050
Peak RER[b]	1.10 ± 0.10	1.15 ± 0.10	0.05 (0.01 to 0.10)	1.08 ± 0.15	1.11 ± 0.15	0.04 (-0.02 to 0.10)	0.025*	0.462	0.758
Peak Borg Score[a]	18 (Range: 15 to 20)	19 (Range: 14 to 20)	0 (Range: -5 to 4; p=0.632)	17 (Range: 13 to 20)	17.5 (Range 15 to 19)	0 (Range: -1 to 5; p=0.078)	-	-	-
HR Max (bpm)[b]	135 ± 18	137 ± 16	2 (-2 to 7)	130 ± 19	132 ± 20	2 (-5 to 8)	0.349	0.420	0.925
Peak SBP (mmHg)[b]	178 ± 27	181 ± 26	2 (-17 to 20)	180 ± 21	181 ± 16	0 (-17 to 17)	0.550	0.904	0.823
Peak DBP (mmHg)[b]	88 ± 12	89 ± 13	1 (-7 to 8)	91 ± 14	89 ± 15	-2 (-12 to 8)	0.828	0.671	0.611
RPP[a]	238.46 ± 54.57	247.77 ± 51.99	-3.21 (-43.21 to 36.79)	235.25 ± 51.99	238.49 ± 35.72	-9.28 (-44.09 to 25.54)	0.462	0.721	0.705
Total Exercise Duration (Secs)[b]	860.00 (Range: 438 to 1175)	917.00 (Range: 588 to 1198)	36.00 (Range: -65 to 439; p=0.001*)	836.00 (Range: 470 to 1026)	936.00 (Range: 373 to 1094)	19.50 (Range: -149 to 281); p=0.433)	-	-	-

SD = Standard Deviation; 95% CI = 95% Confidence Intervals; BMI = Body Mass Index; Kg·m^{-2}; W/H Ratio = Waist to Hip Ratio; SBP =Systolic Blood Pressure; DBP = Diastolic Blood Pressure; mmHg = millimetres of Mercury; HR = Heart Rate; bpm = Beats per Minute; RER = Respiratory Exchange Ratio; RPP = Rate Pressure Product; Secs = Seconds
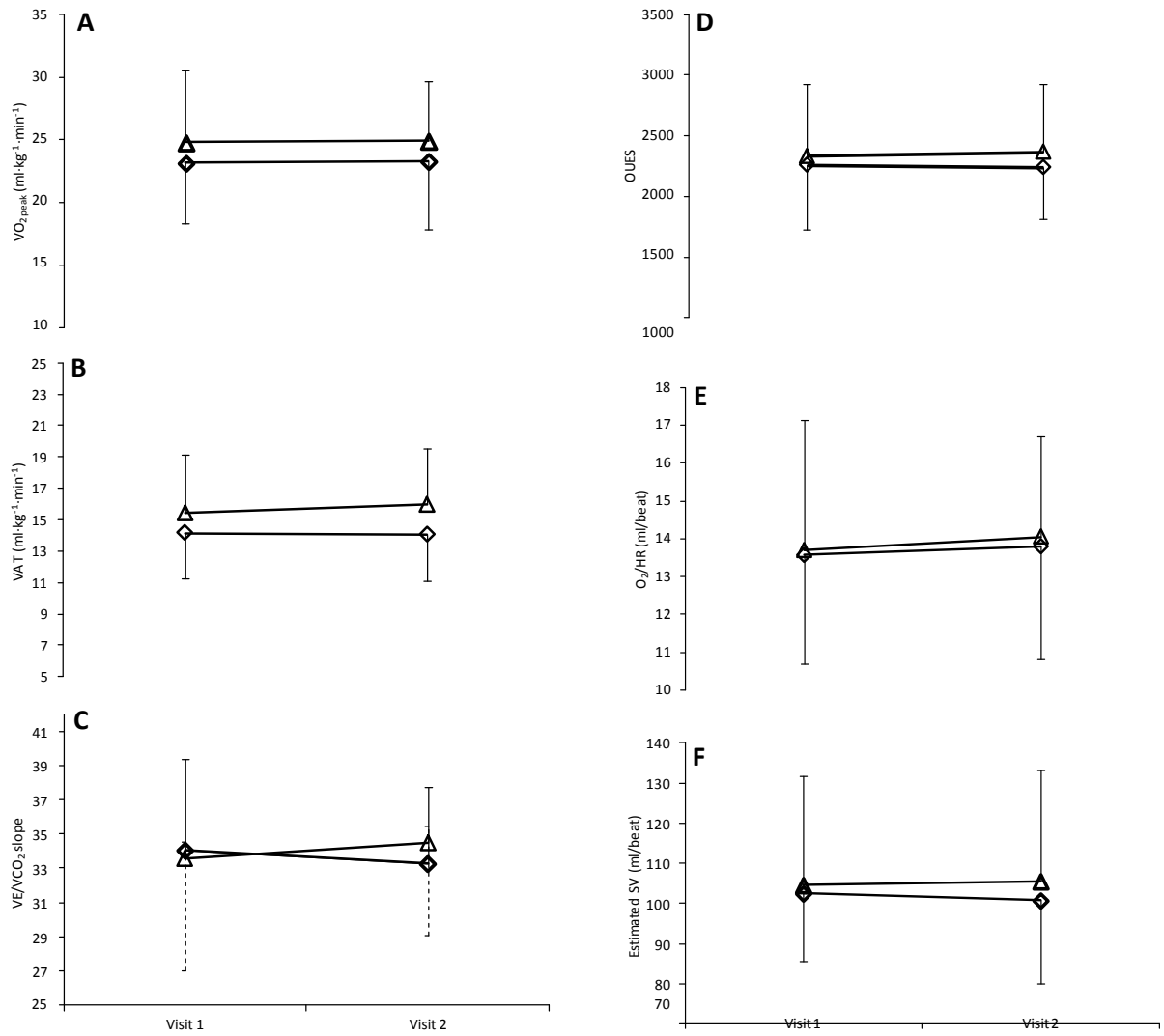
Figure 6 – Shows mean (±SD) differences in CPET derived variables following CR. Panel A, B, C D, E and F shows no significant changes in VO_{2peak}, VAT, VE/VCO_2 slope, OUES, O_2/HR and estimated SV respectively.

VO_{2peak} = Peak O_2 Uptake; VAT = Ventilatory Anaerobic Threshold; VE/VCO_2 slope = Ventilatory Efficiency with Respect to VCO_2; OUES = Oxygen Uptake Efficiency Slope; O_2/HR = O_2 pulse; SV = Stroke Volume; SD = Standard Deviation; CR = Cardiac Rehabilitation; Δ = Training Group; ◊ = Control Group

4.4.7 Change in VE/VCO_2 Slope

40.1% ($n=9$) of TG patients and 41.7% ($n=5$) of CG patients had a VE/VCO_2 slope >34, widely established cut-off value dichotomising those at greatest risk of premature death (Arena et al., 2007a). At visit 2, 45.5% ($n=10$) of TG patients and 41.7% ($n=5$) CG patients had a VE/VCO_2 slope >34. VE/VCO_2 slope values were not normally distributed and required Log_{10} data transformation. There was no significant main effect (0.08; 95% CI -1.21 to 1.36; p=0.723; η_p^2 = 0.004) or group effect (0.37; 95% CI -3.30 to 4.03; p=0.880; η_p^2 = 0.001). Figure 6C shows no interaction effect (p=0.143) for the TG (mean change: -0.78; 95% CI -2.31 to 0.75) or CG (mean change: 0.93; 95% CI -1.14 to 3.00). Although neither the TG nor CG achieved a VE/VCO_2 slope change[2] greater than the MCID (-1.16) the interaction effect was accompanied by a moderate effect size (η_p^2 = 0.066.) In addition $n=10$ (45.5%) of patients in the TG experienced a VE/VCO_2 slope reduction compared to $n=2$ (16.6%) in the CG. No significant between group changes were detected after the inclusion of baseline VE/VCO_2 slope as a covariate (TG corrected mean change: -0.72; 95% CI -2.01 to 0.57; CG corrected mean change: 0.82; 95% CI -0.93 to 2.57; p=0.158; η_p^2 = 0.063). The inclusion of HR_{peak} as a covariate also failed to significantly alter VE/VCO_2 slope (TG corrected mean change: -0.80; 95% CI -2.21 to 0.61; CG corrected mean change: 0.96; 95% CI -0.95 to 2.87; p=0.141; η_p^2= 0.068).

4.4.8 Change in OUES

There was no significant main (7.20; 95% CI -90.52 to 104.91; p=0.882; η_p^2 =0.001), group (-99.14; 95% CI -486.33 to 288.05; p=0.606; η_p^2 = 0.008) or interaction effect for OUES (p=0.577; η_p^2 = 0.010). Figure 6D shows mean change for the TG (34.22; 95% CI -81.88 to 150.33) and CG (-19.83; 95% CI -177.041 to 137.37). Neither group achieved a change greater than the MCID (114.43).
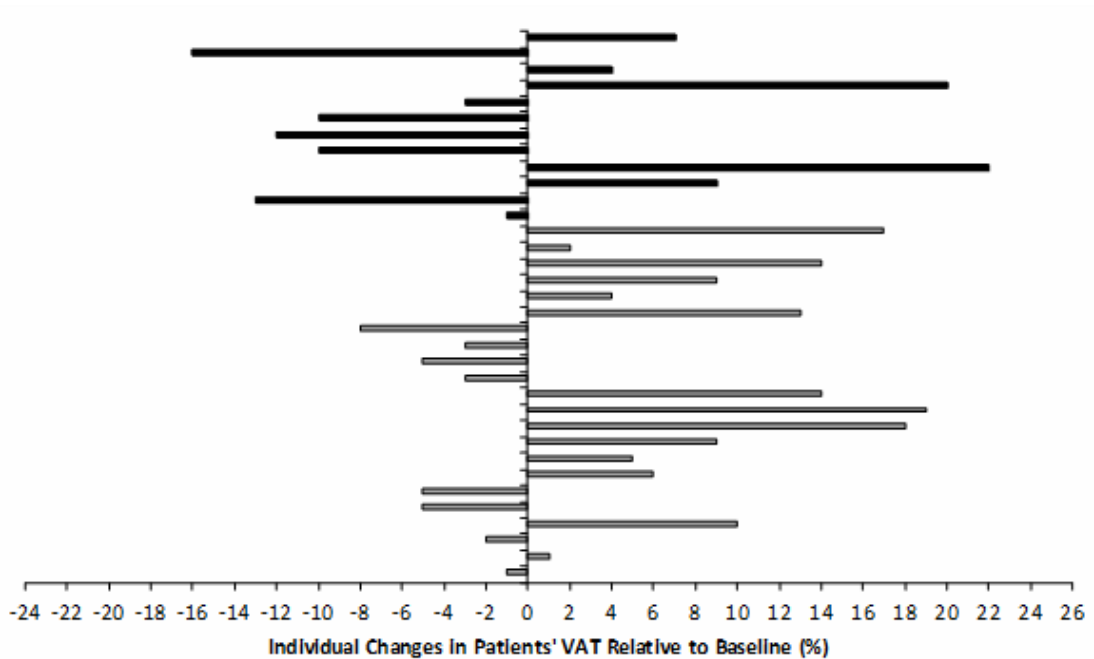
Figure 7 – Shows change in patients' VAT (%) expressed relative to VAT at visit 1. Black bars represent control patients. Grey bars represent training group patients.

VAT= Ventilatory Anaerobic Threshold

4.4.9 Change in Peak Oxygen Pulse

There was no significant main (0.30 ml/beat; 95% CI -0.33 to 0.92 ml/beat; p=0.343; η_p^2 =0.030) or group effect (0.20 ml/beat; 95% CI -1.96 to 2.36; p=0.853; η_p^2=0.001) for O_2/HR. Figure 6E shows no interaction effect (p=0.850; η_p^2= 0.001) between the TG (mean change: 0.35 ml/beat; 95% CI -0.41 to 1.12 ml/beat) and the CG (mean change: 0.24; 95% CI -0.75 to 1.23 ml/beat). Neither group achieved the MCID (0.65 ml/beat). When O_2/HR was converted in to estimated SV, main effect remained non-significant (-0.41 ml/beat; 95% CI -4.79 to 3.98; p=0.852; η_p^2=0.001) as did the group (3.42 ml/beat; 95% CI -14.18 to 21.03; p=0.695; η_p^2 =0.005) and interaction effect (Figure 6F; p=0.539; η_p^2=0.012). Estimated SV change in the TG (0.93 ml/beat) was approaching than the MCID (0.97 ml/beat) however the 95% CI (-4.28 to 6.14 ml/beat) were wide. Mean estimated SV change in the CG also exceeded the MCID (-1.74 ml/beat) however like the TG, 95% CI (-8.80 to 5.31) were wide. Neither group were classified as having achieved the MCID.

4.4.10 Change in Peak METS

Peak METs (ACSM equations; standardised resting MET value of 3.5 ml·kg^{-1}·min^{-1}) obtained during maximal CPET increased significantly from visit 1 to 2 (Figure 8; main effect: 1.08 METs; 95% CI 0.47 to 1.68 METs; p=0.001; η_p^2=0.287). There was no group (0.55 METs; 95% CI -2.67 to 1.57 METs; p=0.600; η_p^2=0.009) or interaction effect (TG mean change: 1.29; 95% CI 0.57 to 2.02; CG mean change: 0.86; 95% CI -0.12 to 1.84; p=0.475; η_p^2=0.016). Both groups exceeded the MCID for MET change (0.62 METs).

METs calculated from submaximal cycle ergometry as part of a routine CR assessment significantly increased from 5.87 to 7.51 METs between visit 1 and 2 within the TG group (main effect: 1.64 METs; 95% CI 1.20 to 2.09 METs; p<0.001; η_p^2=0.736). Estimated maximal METs increased from 9.31 to 11.26 METs between visit 1 and 2 (main effect: 1.95 METs; 95% CI 1.41 to 2.49 METs; p<0.001; η_p^2=0.725). Controls did not undertake submaximal cycle ergometry.
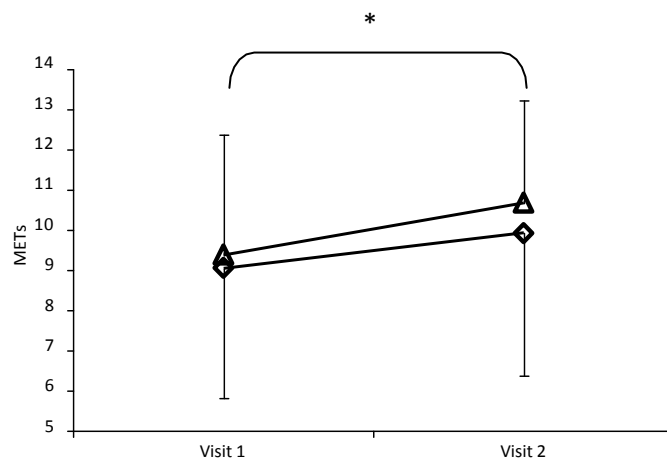
Figure 8 – Shows mean (±SD) significant improvement in METs achieved during CPET at visit 1 and visit 2

METs = Metabolic Equivalents; * = Significant Main Effect

4.4.11 Other Clinical and Exercise Test Variables

BMI and resting haemodynamics are shown in Table 8 with additional key CPET variables. Waist to hip ratio, peak Borg score and total exercise duration were not normally distributed despite attempting data transformation. Resting SBP and HR were also non-normally distributed but

were successfully normalised using Log_{10} transformation. The main effect for BMI fell short of statistical significance (0.36 kg·m⁻²; 95% CI 0.00 to 0.73 kg·m⁻²). There was no group (0.43 kg·m⁻²; 95% CI -2.96 to 3.82 kg·m⁻²) or interaction effect. Neither the TG nor GC (achieved the MCID (0.91 kg·m⁻²) for BMI change. There was a main effect for resting SBP but no group or interaction effect. There was also a main effect for resting DBP but no group or interaction effect. No significant main or group effect was recorded for resting HR. A significant interaction effect was documented. Post-hoc analysis showed that neither the TG or the CG maintained statistically significant changes.

There was a main effect for peak RER (0.05; 95% CI 0.01 to 0.08) but no group or interaction effect. No significant differences were detected between peak Borg scores at visit 1 and 2 for the TG or the CG. No main, group or interaction effects were recorded for HR, peak SBP, peak DBP, or RPP. There were no significant differences between groups for CPET exercise duration at visit 1 (p=0.817) or visit 2 (p=0.955). Median CPET exercise duration significantly increased between visit 1 and 2 for patients in the TG but not in the CG. The number of CPET stages completed by the TG significantly increased from visit 1 to visit 2 (TG median visit 1: 4; range: 2 to 6; median visit 2: 5; range: 3 to 6; p=0.008; CG median visit 1: 4.5; range: 2 to 5; median visit 2: 5; range: 2 to 6; p=0.317).

4.4.12 Exercise Dose Response

There was no significant correlation between VO_{2peak} change and the number of additional self-directed home-based exercise sessions conducted (r=0.204; p= 0.255) or, total CV exercise duration upon completion of the CR exercise training programme (r=0.117; p=0.605). A composite score of exercise intensity (% of HRR during training) x CV exercise duration for each CR exercise session was calculated and summed to create a total exercise dose for the 16 sessions. There was no significant correlation between this value and VO_{2peak} improvement either (r=0.005; p=0.981). Area under the curve (AUC) calculated from non-parametric ROC

curve analysis showed no association between VO_{2peak} improvement (state variable), and the total number of CV exercise minutes conducted (AUC: 0.571; 95% CI 0.309 to 0.834; p=0.585). Similar findings were demonstrated for the number of home exercise sessions conducted by the patient (AUC: 0.451; 95% CI 0.247 to 0.654; p=0.632). ROC curve analysis of the total exercise dose composite score maintained no association between exercise dose and VO_{2peak} improvement [state variable] (AUC: 0.500; 95% CI 0.233 to 0.767; p=1.000).

Similar to VO_{2peak}, there was no significant correlation between VAT change and the number of additional self-directed home-based exercise sessions conducted (r=-0.213; p= 0.341) or, total CV exercise duration upon completion of the CR exercise training programme (r=-0.093; p=0.681). There was no significant correlation between the total exercise dose composite score and VAT improvement (r=0.099; p=0.660). ROC curve analysis showed no association between VAT improvement (state variable) and the total number of CV exercise minutes conducted (AUC: 0.482; 95% CI 0.223 to 0.742; p=0.891) or, between VAT improvement (state variable) and additional home exercise sessions conducted (AUC: 0.479; 95% CI 0.275 to 0.684; p=0.836). ROC curve analysis of the dose composite score versus VAT improvement (state variable) demonstrated similar findings (AUC: 0.509; 95% 235 to 0.785; p=0.946).

4.4.13 One Year Follow-Up (Visit 3)

At the time of data censoring, *n*=10 patients from the overall study were eligible to attend visit 3. One TG patient died due to suffering a spontaneous intracranial haemorrhage. One CG patient was lost to follow-up. A further TG patient who attended visit 3 was unable to complete CPET due to suffering severe dizziness upon standing (suspected encephalitis). Therefore, a total of *n*=7 (n=1 CG patient) patients were included in 12 month follow up analysis. Sample size was low and the majority of data was not normally distributed, non- parametric analysis was used for data analysis at 12 months. Because MCID requires Gaussian distribution and visit 3 data was non-normally distributed, MCID analysis was not conducted. Changes to CPET variables at

visit 3 are shown in Table 9.

4.4.14 Cardiorespiratory Fitness Changes

Friedman analysis showed that there were no significant changes to VO_{2peak} between visit 1 and 3 in the TG (-0.94 $ml \cdot kg^{-1} \cdot min^{-1}$; range: -6.09 to 2.10 $ml \cdot kg^{-1} \cdot min^{-1}$). The single ($n$=1) control patient to have attended visit 3 experienced a decline in VO_{2peak} (-2.99 $ml \cdot kg^{-1} \cdot min^{-1}$). The VAT change at visit 3 was also not significant (TG mean change: 0.48 $ml \cdot kg^{-1} \cdot min^{-1}$; range: -5.90 to 3.88 $ml \cdot kg^{-1} \cdot min^{-1}$; p= 0.607). The VE/VCO_2 slope in the TG group change at visit 3 was not significant (-2.00; Range: -5.38 to -0.69; p= 0.070). The mean MET change in the TG between visit 1 and 3 (median 0.30 METs; range: -2.1 to 2.0 METs; p=0.094) was not significant. The patient in the CG group did not experience a MET change (visit 1: 4.4 METs; visit 3; 4.4 METs).

4.4.15 Association of METs with VO_{2peak}

VO_{2peak} and MET scores estimated from submaximal cycle ergometry were moderately correlated (Figure 9A; r=0.486; p<0.001). VO_{2peak} and predicted maximum METs were also moderately correlated (Figure 9B; r=0.424; p=0.002). There was no significant correlation between estimated VO_{2peak} change and submaximal MET change (Figure 9C; r=-0.089; p=0.692) or, estimated VO_{2peak} change and predicted maximal MET change (Figure 9D; r=-0.269; p=0.226).

Bland-Altman analysis showed that estimated VO_{2peak} calculated from submaximal cycle ergometry (estimated peak METs x 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$) significantly overestimated VO_{2peak} determined by gas analysis (Figure 10A; mean bias 10.98 $ml \cdot kg^{-1} \cdot min^{-1}$; p<0.001) and had wide LoA (-6.42 to 28.39 to $ml \cdot kg^{-1} \cdot min^{-1}$). The adjustment of the estimated peak METS formula according to the method of Byrne and colleagues (2005) [1 MET = 2.6 $ml \cdot kg^{-1} \cdot min^{-1}$] substantially improved mean bias (Figure 10B; -1.873 $ml \cdot kg^{-1} \cdot min^{-1}$; p=0.059) however LoA remained wide (-15.53 to 11.79 $ml \cdot kg^{-1} \cdot min^{-1}$). Multiplying peak METs by 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$ resulted in a significant overestimation of VO_{2peak} (Figure 10C; mean bias 10.13 $ml \cdot kg^{-1} \cdot min^{-1}$; p=<0.001) with high

measurement variability (LoA: -3.91 to 24.18 ml·kg^{-1}·min^{-1}). Multiplying peak METs achieved during CPET by 2.6 ml·kg^{-1}·min^{-1} resulted in a smaller mean bias (Figure 10D; 1.44 ml·kg^{-1}·min^{-1}; p=0.009) but retained wide LoA (-7.96 to 10.86 ml·kg^{-1}·min^{-1}). When Bland-Altman analysis of peak METs multiplied by 3.5 ml·kg^{-1}·min^{-1} (Figure 10C) was adjusted to account for heteroscedasticity [Figure 11A] (measurement variation in relation to magnitude LoA remained wide (-1.90 to 20.04 ml·kg^{-1}·min^{-1}). Likewise, when Bland-Altman analysis of peak METs multiplied by 2.6 ml·kg^{-1}·min^{-1} (Figure 10C) was adjusted to account heteroscedasticity, LoA also remained wide (Figure 11B -2.30 to 15.16 ml·kg^{-1}·min^{-1})

Directly-determined VO$_{2peak}$ was strongly correlated with estimated peak METs from the ACSM treadmill walking equation in all participants (Figure 12A; r=0.780; p<0.001). However, VO$_{2peak}$ and peak MET change were not significantly correlated (Figure 12B; r=0.309; p=0.076). Peak Estimated MET changes significantly overestimated VO$_{2peak}$ change (Figure 13; mean bias 3.85 ml·kg^{-1}·min^{-1}; LoA -6.91 to 14.62 ml·kg^{-1}·min^{-1}; p<0.001). When adjusted for heteroscedasticity, measurement variability of peak MET versus VO$_{2peak}$ change remained wide (Figure 14; LoA -6.79 to 8.01 ml·kg^{-1}·min^{-1}).

Table 9 – Changes to key cardiopulmonary exercise test variables at visit 3 ((median [range])

Variable	Treatment Group (n=6)			Median Post Intervention Change	Training Group P-Value	Control Group (n=1)			Median Post Intervention Change
VO$_{2peak}$ (ml·kg^{-1}·min^{-1})	26.02 (17.67 to 35.20)	25.18 (16.63 to 32.30)	23.57 (18.61 to 29.30)	-0.94 (: -6.09 to 2.10)	0.846	19.29	15.05	16.30	-2.99
VO$_2$ at VAT (ml·kg^{-1}·min^{-1})	17.14 (12.29 to 20.85)	16.20 (13.35 to 21.94)	14.57 (8.76 to 21.59)	-0.48 (: -5.90 to 3.88)	0.607	12.52	10.84	12.03	-0.49
VE/VCO$_2$ Slope	32.70 (27.14 to 48.44)	31.79 (26.19 to 42.17)	31.76 (27.35 to 43.06)	-2.00 (: -5.38 to -0.69)	0.070	46.74	50.26	44.58	-2.16

VO$_{2peak}$ = Peak O$_2$ Uptake; VAT = Ventilatory Anaerobic Threshold; VE/VCO$_2$ slope = Ventilatory Efficiency with Respect to VCO$_2$
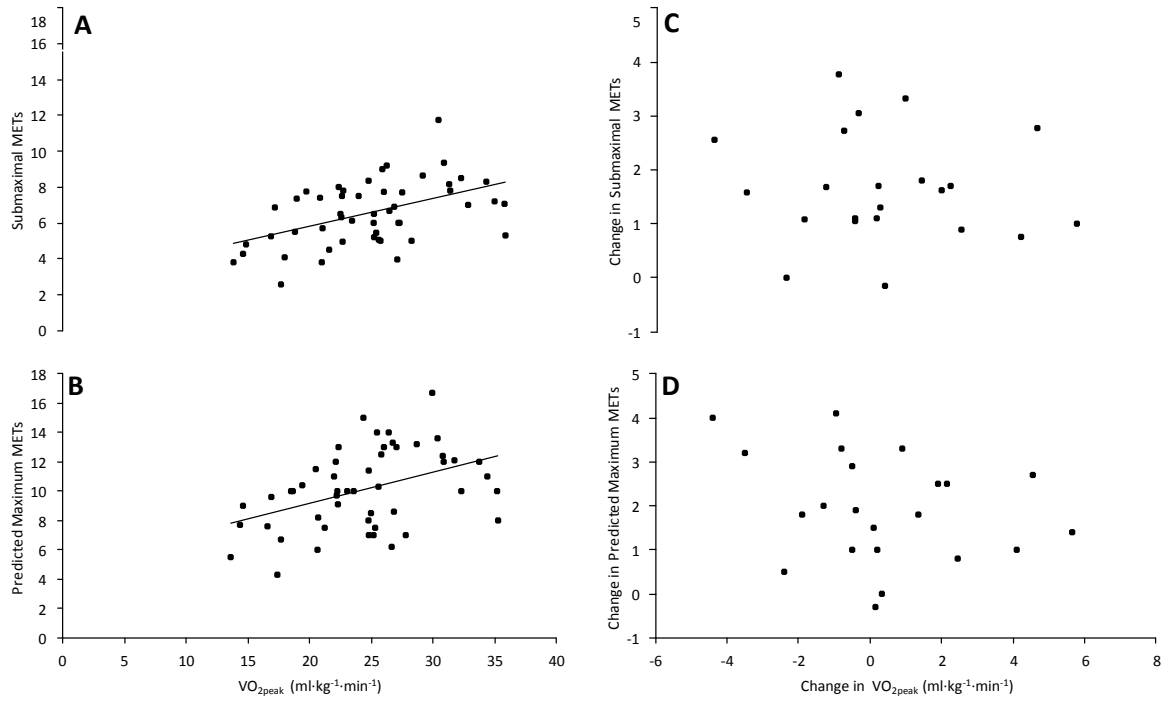
Figure 9 – Shows moderate correlation between VO_{2peak} and submaximal METs (A) and, VO_{2peak} and predicted maximum METs achieved during submaximal exercise testing (B). Panels C and D show no correlation between VO_{2peak} change and submaximal MET or predicted maximum MET change respectively.

METs = Metabolic Equivalents; VO_{2peak} = Peak O_2 Uptake
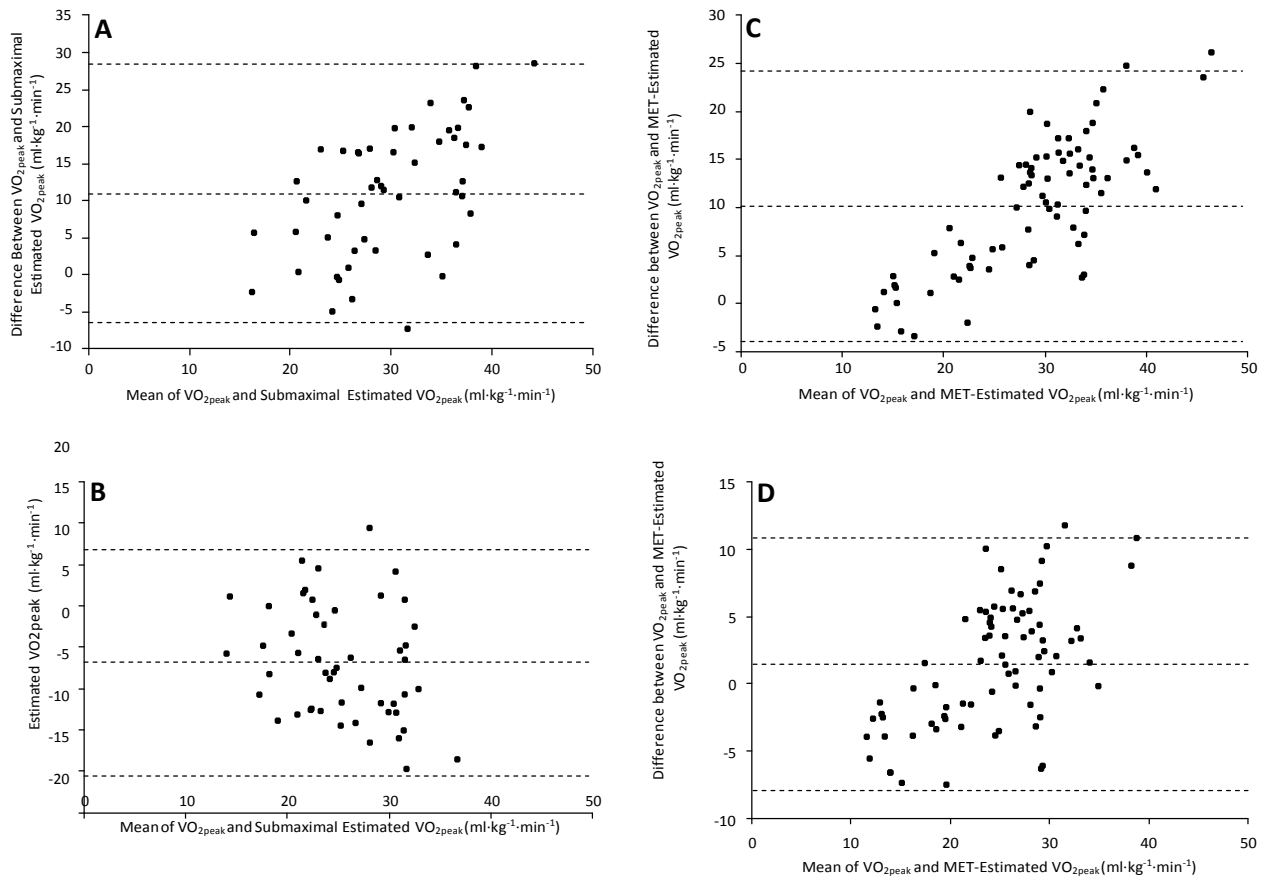
Figure 10 – Panel A shows that applying the multiplier (3.5 ml·kg^{-1}·min^{-1}) to estimate VO$_{2peak}$ from sub-maximally estimated METs led to a significant positive mean bias and wide limits of agreement. The multiplier suggested by Byrne and colleagues (2005) [2.6 ml·kg^{-1}·min^{-1}] reduced the mean bias but retained high measurement variability (B). Peak METs achieved during CPET showed similar findings for both 1 MET = 3.5 ml·kg^{-1}·min^{-1} (C) and 1 MET = 2.6 ml·kg^{-1}·min^{-1} (D).

VO$_{2peak}$ = Peak O$_2$ Uptake; METs = Metabolic Equivalents; CPET = Cardiopulmonary Exercise Testing
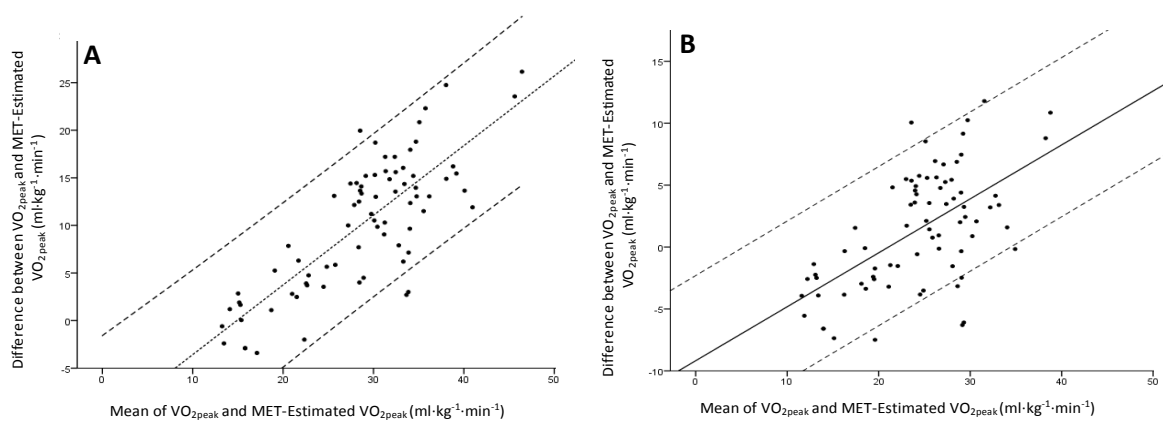
Figure 11 – Modification of the Bland-Altman analysis to allow for the non-uniformity in the relationship between estimated (Panel A, 1 MET = 3.5 ml·kg^{-1}·min^{-1}; Panel B, 1 MET = 3.5 ml·kg^{-1}·min^{-1}) and true VO$_{2peak}$. In panel A, limits of agreement were -1.90 to 20.04 ml·kg^{-1}·min^{-1}). In pane B, limits of agreement -2.30 to 15.15 ml·kg^{-1}·min^{-1})

METs = Metabolic Equivalents; VO$_{2peak}$ = Peak O$_2$ Uptake
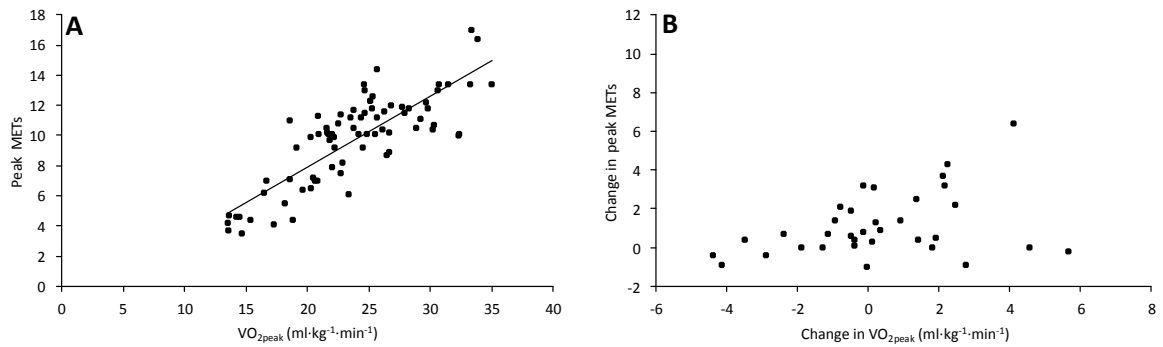
Figure 12 – Shows strong correlation between VO_{2peak} and peak METs (A) and, no significant correlation between VO_{2peak} change and peak MET change during CPET (B).

METs = Metabolic Equivalents; VO_{2peak} = Peak O_2 Uptake; CPET = Cardiopulmonary Exercise Testing
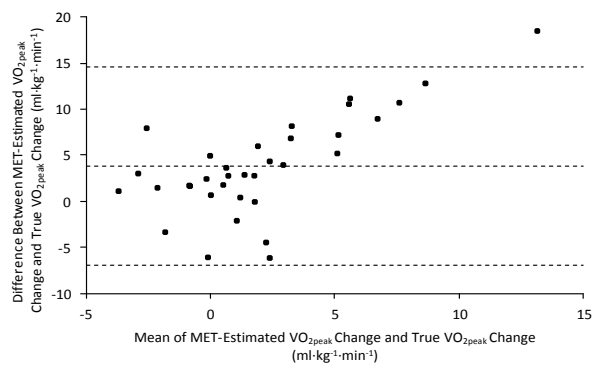
Figure 13 – The traditional multiplier applied to estimate VO_{2peak} change from peak MET change (3.5 ml·kg^{-1}·min^{-1}) led to a significant positive mean bias and wide limits of agreement during CPET.

MET = Metabolic Equivalent; VO_{2peak} = Peak O_2 Uptake; CPET = Cardiopulmonary Exercise Testing
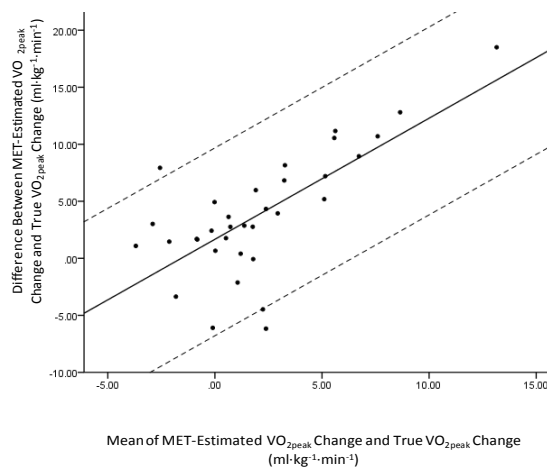
Figure 14 – Modification of the Bland-Altman analysis to allow for the non-uniformity in the relationship between estimated (1 MET = 3.5 ml·kg^{-1}·min^{-1}). Limits of agreement were -6.79 to 8.01 ml·kg^{-1}·min^{-1}

MET = Metabolic Equivalent; VO_{2peak} = Peak O_2 Uptake;

4.5 Discussion

4.5.1   Cardiorespiratory Fitness Change

This is the first contemporary UK study to use 'gold-standard' CPET techniques to evaluate a routine CR exercise training programme. The primary finding of this study was that an eight-week (16 sessions) low to moderate intensity (40-60% HRR) CR exercise training programme did not significantly improve VO_{2peak} when compared to patients not attending structured exercise training. The CR training programme also failed to significantly improve VAT, VE/VCO_2 slope, O_2/HR and OUES in the shorter (visit 1 to 2; 8 weeks) and longer-term (visit 3; 1 year). Patients' non-participation in CR exercise training did not appear to have a detrimental effect on CRF in the shorter-term. Similar to the findings of Madssen et al. (2014), the present study reported comparable levels of self-reported exercise training activity amongst TG and CG patients. This may explain why routine CR did not appear to provide TG patients with additional CPET-derived CRF benefits. ROC curve analysis suggested that higher exercise doses within routine CR did not increase the likelihood of attaining a VO_{2peak} increase amongst TG patients when compared to controls. However, this analysis was limited by the number of patients experiencing an actual VO_{2peak} increase following the intervention.

These findings go beyond those of Sandercock et al. (2013b) who reported modest CRF improvements (0.52 METs; 0.76 when following the modified Bruce protocol) equal to a 1.8 $ml·kg^{-1}·min^{-1}$ VO_{2peak} increase (1 MET = VO_2 of 3.5 $ml·kg^{-1}·min^{-1}$). In the present study, mean VO_{2peak} changes were 0.12 $ml·kg^{-1}·min^{-1}$ (95% CI -1.00 to 1.24 $ml·kg^{-1}·min^{-1}$) in the TG and 0.15 $ml·kg^{-1}·min^{-1}$ (95% CI -1.37 to 1.66 $ml·kg^{-1}·min^{-1}$) in the CG. Mean VO_{2peak} change did not exceed the MCID and associated effect sizes were small despite supplementary exercise test variables (peak RER, HR and RPE) indicating good compliance with the maximal effort criteria. Furthermore, OUES a CRF variable strongly associated with VO_{2peak} (even when maximal CPET criteria are not achieved), did not change following the intervention compared to controls (Van Laethem et al., 2005). This further verifies that no significant change in VO_{2peak} occurred as a result of the exercise training programme. The MCID for VAT improvement was also not

achieved by either group. However, proportionally fewer patients in the CG (25.9%) achieved the MCID for VAT compared to patients in the TG (45.5%). Whilst Chi Squared analysis was not conducted because too few patients in the CG ($n=2$) achieved the MCID for VAT increase, this data suggests that patients in the TG were more likely to experience a VAT increase than those in the CG. Even though VAT and VO_{2peak} improvements often occur concurrently (Myers et al., 1999, Warburton et al., 2005), it is possible for VAT improvements to occur independently of VO_{2peak} improvements through increased mitochondrial oxidative capacity or, increased capillarisation (Bassett and Howley, 2000, Holloszy and Coyle, 1984). If a VAT increase within the TG did in fact occur, the significant increase in CPET exercise duration observed in the TG may reflect this. Training adaptations associated with an enhanced VAT are strongly linked with maximal exercise duration (Ghosh, 2004). However, because no consistent effect of exercise training on VAT was observed and, other supplementary CPET variables were unchanged, it is likely that the exercise training doses during the CR exercise training programme were insufficient and/or inaccurately prescribed. CPET exercise duration may therefore have significantly improved due to test-retest familiarity and enhanced movement economy (Russell et al., 1998).

Whilst a reduction in VE/VCO_2 slope greater than the MCID was not achieved by either group, there was a tendency for the TG to experience a VE/VCO_2 slope reduction (mean change: -0.78; 95% CI -2.31 to 0.75) compared to the CG (mean change: 0.93; 95% CI -1.14 to 3.00) who tended to experience a VE/VCO_2 slope increase. In addition, proportionally fewer patients ($n=2$; 16.6%) in the CG experienced a VE/VCO_2 slope reduction when compared to the TG ($n=10$; 45.5%). However, whilst it is conceivable that ventilatory efficiency may have improved, the lack of statistical or clinically meaningful differences necessitate caution when interpreting these findings. Guazzi et al. (2004) and Myers et al. (1999) have demonstrated that exercise training can improve VE/VCO_2 slope, however changes in their study far surpassed those seen in ours. The most likely reason for this disagreement is that exercise intensity and frequency were higher (Guazzi et al: Cycling programme; 40 minutes, four days per week, 60-80% HRR; Myers et

al: Walking programme; Two hours, twice daily for eight weeks; Cycling programme: Four days per week, 45 mins per session; 60-80% HRR). The absence of any statistical or clinically meaningful improvements in VE/VCO_2 slope or other CPET derived indices of CRF in our study indicates that: 1) the recommended dose of UK CR exercise training (ACPICR, 2015) is inadequate, and/ or 2) the local CR programme was suboptimal.

The exercise training programme in the present study adhered to UK CR guidelines (ACPICR, 2015). In addition to home-based exercise sessions, patients undertook structured exercise on two days per week. However, few patients attained a consistent training HR of 70% HRR. Most attained a median peak training HR consistently above the VAT and between 40 to 60% HRR. Although median RPE increased significantly over the CR period, the finding that most patients exercised at an RPE of 12 indicates that training intensity may have been insufficient or progressed inadequately over the programme. Patients taking β-blockers may need to exercise at an RPE of at least 13, (12.7 ± 1.7) in order to achieve a training approximating the VAT (Tsai et al., 2015) an intensity range known to provoke CRF change (Keith et al., 1992). Furthermore, whilst most patients conducted more than 20 minutes of CV exercise per session prior to completing this CR training programme, this was not achieved until more than half of CR course had been completed. Early exercise training sessions during the rehabilitation period were under-prescribed which may have compromised the potential of some patients to improve VO_{2peak}. Although patients frequently present with numerous co-morbidities during the early stage of CR, many patients should be able to attain 20 minutes of CV exercise early on *if* exercise is prescribed appropriately. The ACPICR (2015) recommend progressing towards 60 minutes of CV exercise during the course of the CR programme. Consideration should be given to the rate that patients' exercise prescriptions are up titrated to the *minimum* recommended CV exercise duration. Despite this limitation, the present programme appeared to outperform other UK CR programmes when evaluated using METS, one of the most widely used metrics within UK CR.

When CRF change was estimated using METs calculated from maximal exercise testing, the present CR programme was approximately twice as effective as other UK CR programmes. Peak MET change between visit 1 and 2 (1.29 METs; 95% CI 0.57 to 2.02 METs) substantially exceeded the MET change (0.52/0.76 METs) documented by Sandercock et al. (2013b). It is therefore likely that VO_{2peak} did not improve because the nationally recommended dose of exercise is inadequate rather than the local CR programme failing to adequately optimise exercise training.

The available evidence-base for prescribing exercise in secondary prevention settings for mortality and other benefits, including exercise frequency and intensity/duration of individual training sessions is partly derived from the 2011 Cochrane systematic review on exercise based CR for CHD (Heran et al., 2011). Many studies included within this meta-analysis lasted longer than eight weeks (Seki et al., 2003, Seki et al., 2008, Hofman-Bang et al., 1999, Dugmore et al., 1999, Fletcher et al., 1994). Furthermore, unlike UK CR programmes which use estimated HR training zones, many studies included in this review prescribed exercise from maximal exercise tolerance tests (ETT) or CPET (Belardinelli et al., 2001, Bäck et al., 2008, Dugmore et al., 1999, Giallauria et al., 2008, Holmbäck et al., 1994, Leizoroviez et al., 1991, Seki et al., 2008). Such procedures substantially enhance the accuracy of exercise prescription. Our data shows that although the majority of patients were exercising between 40-60% HRR, approximately 25% of the cohort consistently trained below their VAT or, 40% HRR calculated from CPET. The likelihood of this exercise dose providing sufficient training stimulus to improve VO_{2peak} when exercise is conducted for 20-30 min, twice weekly is debatable. In addition, a significant number of studies included in the Heran et al. (2011) review were prescribed at or above the highest training intensities (>70%HRR) recommended in the UK.

In the UK, lower training intensities are advocated (ACPICR, 2015) because most patients do not undertake medically supervised maximal CPET or ETT. This is perceived to mitigate the risks of higher intensity exercise despite both moderate and high intensity exercise training being shown to have low fatal event rates (Rognmo et al., 2012). There appears to be a paucity

of evidence indicating that CR exercise training programmes delivered as interval circuit training, twice weekly (over eight weeks) for 20 to 30 minutes per session at 40-70% HRR can improve VO_{2peak}. Existing data tends to support short-term programmes of 8 to 12 weeks when intensities are higher, sessions exceed 30 minutes, or when weekly exercise sessions are more frequent (Duncan et al., 2005, Miller et al., 1984, Bethell et al., 1983, Marchionni et al., 2003, Milani et al., 1995). Fletcher et al. (2001) stated that training regimes within this intensity require longer-term adherence to meaningfully increase $VO_{2peak.}$ Duncan et al. (2005) reported that training sessions lasting a minimum of 30 minutes conducted on five days per week are needed to improve CRF at intensities of 45-55% HRR. It is therefore unsurprising that the CR programme in this study did not significantly improve $VO_{2peak,}$ VAT, VE/VCO_2 slope, O2/HR or OUES. Given that many CR programmes adhere to national UK guidelines (Brodie et al., 2006), our findings may represent the performance of the wider UK CR network, particularly within the context of other recent findings (Sandercock et al., 2013b). The suggestion that UK CR programmes may be 'under-dosed' appears to be worthy of further investigation. Larger studies that accurately quantify the exercise dose of CR patients' exercise are needed to confirm this assertion.

Our findings support recently published expert opinions (Sandercock et al., 2013a, Ingle and Carroll, 2013) suggesting that the exercise training component of CR may be insufficient to improve CRF. Despite this, existing data supports the view that CR programmes are effective, particularly those reporting a change in METs (Carroll et al., 2011, Gee et al., 2014, Sandercock et al., 2011). In agreement, our study showed that peak METs significantly increased following CR. However, the finding that VO_{2peak} remained unchanged suggests that peak MET change may overstate the effects of exercise training on CRF. This finding is of concern because the UK CR evidence base is strongly underpinned by studies reporting MET changes.

4.5.2 MET's Sensitivity to Cardiorespiratory Fitness Change

Our data indicates that patients significantly increased exercise duration and number of stages of the Bruce treadmill protocol completed at visit 2. Because the calculation of estimated peak METs assumes a linear relationship between work rate and VO_2, these changes manifested as a significant increase in estimated peak METs. Without maximal CPET, this extrapolation would have indicated that patients significantly increased their VO_{2peak}. Russell et al. (1998) demonstrated a 'placebo effect' in patients with chronic heart failure where CPET exercise duration significantly increased purely on the basis of test-retest familiarity. Fowler et al. (2005) documented similar findings using the incremental shuttle walk test (ISWT). In the present study, no significant change in VO_{2peak} occurred in spite of a total treadmill time duration increase during CPET. Change in peak work rate does not always indicate a change in VO_{2peak} and the assumption that VO_2 and work rate are linearly related to maximum is not generalisable, particularly in patients with CHD. Left ventricular systolic dysfunction (Poole et al., 2012), chronotropic incompetence (Brubaker and Kitzman, 2011) and beta-blockers are also known to slow VO_2 kinetics (Hughson, 1984). Subsequently, work rate increments may be sustained by anaerobic metabolism for longer periods. In addition, CHD pathology may affect VO_2 once patients reach an ischaemic threshold.

During incremental exercise, the onset of asymptomatic myocardial ischaemia can cause a reduction in SV due to regional myocardial wall motion abnormalities (Belardinelli et al., 2003, Chaudhry et al., 2009). This manifests as a VO_2 plateau (or inflection) despite increasing workloads (Figure 15). Lastly, the contributions of anaerobic metabolism near peak exercise are likely to be responsible for a greater proportion of workload increases than aerobic metabolism. For these reasons, a change in work rate (and estimated METs) alone cannot reliably detect underlying central CRF change. Changes in estimated METs are likely to over predict VO_{2peak} change. Our data shows no significant correlation between estimated peak MET change and VO_{2peak} change following eight weeks of structured exercise training in CHD patients. Bland-Altman analysis showed that as a predictor of VO_{2peak} change, estimated peak METs were

highly variable (LoA -6.91 to 14.62 ml·kg^{-1}·min^{-1}) with a mean bias of 3.85 ml·kg^{-1}·min^{-1} (approximately 1 MET. The discordance between estimated peak MET and VO$_{2peak}$ changes, are supported by the findings of Milani et al. (1995) who found no significant correlation between estimated MET change and VO$_{2peak}$ change (r=0.240; p=0.100) and, that MET estimation overestimated VO$_{2peak}$ before (38%) and after (92%) cardiac rehabilitation. The only change reliably detectable from exercise testing dependent on work rate increments alone is functional capacity i.e. the patient's ability to tolerate an increased workload.
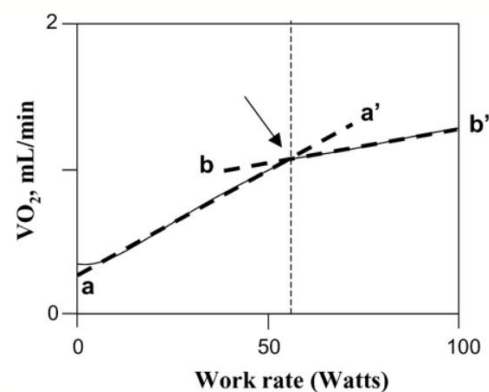
Figure 15 – Image reproduced from Belardinelli et al. (2003). VO$_2$ versus work rate during CPET in patients with CHD and reversible myocardial ischaemia is not linear from start to peak exercise. The transition from normal VO$_2$ increase as related to work rate (a-a) to a slow increase (b-b') is associated with myocardial ischaemia. Any existing linearity between VO$_2$ and work rate is lost. This occurrence precedes ECG changes and symptoms of angina.
VO$_2$ = O$_2$ uptake; CPET = Cardiopulmonary Exercise Test; CHD = Coronary Heart Disease

The serial use of estimated peak METs to assess the effect of a CR training intervention is not well validated. Fowler et al. (2005) and, Woolf-May et al. (2005) both indicate that distance walked during the ISWT is associated with VO$_{2peak}$. Correlations between distance walked and VO$_{2peak}$ were presented by Fowler et al. (2005). However, a clear observable measurement bias was present (but not reported on). Moreover participants included in the analysis by Woolf-May et al. (2005) do not appear to have completed maximal effort exercise test. Blood lactate levels were reported to be between 2 and 4 mmol at test termination. Although Fowler et al. (2005) claim that the ISWT had good test 'sensitivity' for documenting CRF change, their study is not

designed to quantify sensitivity with respect to aerobic fitness change. A plot of the residuals is inadequate for such analysis. Neither author investigated agreement between change in MET-estimated VO_{2peak} and true VO_{2peak} in a test-intervention-retest format. It is unknown whether change in walk distance reflects change in VO_{2peak}. Based on our finding that MET change overestimates VO_{2peak} change, it is possible that many CR studies utilising estimated METs as a primary outcome measure have overestimated the effect of their training intervention. However, whilst the estimated MET may be poor at detecting changes in VO_{2peak}, they may be considered a useful index of cross-sectional functional capacity.

The present study confirms a strong relationship between VO_{2peak} and estimated peak METs. At the individual level, however the estimated 'MET' may not be useful for assessing CRF, especially if precise quantification is needed. Our data suggest that estimated peak METs consistently over estimate VO_{2peak}, something that has been well documented (Milani et al., 1995, Wasserman et al., 2011, Byrne et al., 2005). Milani et al. (1995) found that whilst estimated METs were strongly correlated with VO_{2peak}, they typically overestimated VO_{2peak} by 38 to 92% irrespective of CPET protocol. The assumption that 1 MET is equal to 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$ is now highly questionable. The 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$ resting VO_2 was originally proposed based on a sample of n=1 male (age: 40 years; body mass 70 kg) more than 120 years ago (Byrne et al., 2005, Wasserman et al., 2011). Byrne et al. (2005) re-evaluated the use of 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$ and found that 2.6 ± 0.4 $ml \cdot kg^{-1} \cdot min^{-1}$ better reflected resting VO_2 (n=769; 16.5% male; age: 18-74 years; mass: 45 to 186kg). Our study agreed with this finding and found that when 1 MET was assumed to equal 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$, VO_{2peak} was overestimated by 35%. This translated in to a large positive mean bias for VO_{2peak} (mean bias 10.13 $ml \cdot kg^{-1} \cdot min^{-1}$) with wide LoA (-3.91 to 24.18 $ml \cdot kg^{-1} \cdot min^{-1}$). The mean bias associated with predicting VO_{2peak} from estimated peak METs in our study was considerably improved by using Byrne and colleagues (2005) 2.6 $ml \cdot kg^{-1} \cdot min^{-1}$ MET adjustment. However LoA were still large (mean bias 1.44 $ml \cdot kg^{-1} \cdot min^{-1}$; LoA -7.97 to 10.86 $ml \cdot kg^{-1} \cdot min^{-1}$). This most likely stems from inter-individual differences in resting VO_2 data. Body composition and age cumulatively contribute 76% of inter-individual variability in resting VO_2

(Byrne et al., 2005). One standard deviation of Byrne and colleague's (2005) 'average MET' is associated with a typical measurement error of 30% ($\pm$ 0.4 / 2.6 ml·kg^{-1}·min^{-1}). If a resting MET is incorrectly estimated, the act of multiplying the MET will over/underestimate VO_2 by a factor proportional to the error. Our data shows that it may not be possible to reliably estimate VO_{2peak} or, change in VO_{2peak} using estimated METs.

4.6   Conclusions

The dose of exercise recommended in UK CR programmes appears to be inadequate for the purposes of improving VO_{2peak}, or other supplementary CPET indices, including VAT, VE/VCO_2 slope, O_2/HR and OUES. Even though a high proportion of patients were taking beta-blockers [known to reduce VO_{2peak} by 5 to 15% via reductions in Q 15-20%] (Tesch, 1985), this is unlikely to reduce the patients' propensity to experiencing exercise mediated VO_{2peak} improvements (Vanhees et al., 1982). Taken in conjunction, with the results of a recent multicentre study (Sandercock et al., 2013b), our finding that CRF did not improve compared to controls adds further concerns relating to the clinical efficacy of UK CR exercise training programmes. Confirmatory evidence to the findings of (West et al., 2012) who reported that UK CR did not improve patient survival or CV risk factors. The recommended dose of exercise training, and the techniques used to prescribe exercise training appear to be inadequate (ACPICR, 2015). The application of CPET with more accurate exercise prescription methods and increasing the dose of exercise in line with the scientific literature is a simple step that will most likely increase the efficacy of the UK CR programmes. Current methods of assessing CRF changes following an intervention such as estimated MET change, may exaggerate the true benefits of the exercise programme. Further caution is required when interpreting exercise training studies within CHD cohorts reporting this outcome metric, particularly where sample sizes are small.

4.7 Limitations

One of the main limitations of this study is that patients' exercise training doses during the CR programme were self-reported. Furthermore, the training HR was based on a median of each patients' peak training HR for each exercise during a single exercise class. Without continuous monitoring of exercise it is difficult to accurately quantity a true training dose. It cannot be assumed that patients maintained an appropriate training HR (40-70% HRR) throughout the entirety of the exercise class on the basis that median peak training HR's were generally within the recommended training zones. It is conceivable that the training intensities during the exercise classes may have been less than those recommended by the ACPICR(2015).

A further consideration is that the number of participants who had received a PCI either electively or as the treatment for acute coronary syndrome was proportionally high. Such interventions may prevent permanent or, temporary myocardial damage and/or LV dysfunction (Fröhlich et al., 2013). This suggestion is supported by our finding that EF was well preserved (55.6 ± 6.4%) within the TG at the start of CR. VO_{2peak} improvement following exercise training may be more likely in patients with myocardial 'stunning' due to the natural time course (and potential) of myocardial recovery leading to improved determinants of Q such as diastolic function (Dekleva et al., 2014). However, given an appropriate exercise training dose, VO_{2peak} should improve amongst CHD patients (Swain and Franklin, 2002) irrespective of myocardial function. It is therefore likely that exercise prescription was inadequately individualised and, of insufficient overall dose to improve VO_{2peak}.

The use of the modified Bruce protocol (Bruce et al., 1973) also poses an additional study limitation. Whilst this protocol was chosen on the premise that it is widely understood and utilised within cardiological settings and CR, its large work rate increments are likely to result in rapid lactate accumulation and amplify the lag between the VO_2 and work rate increments (Myers et al., 1991). It is possible that the association between peak MET change and VO_{2peak} change may have been stronger had our study chosen to employ the use of a ramp protocol. A

ramp protocol would help maintain this relationship and, allow more accurate identification of the VAT. Notably however, our study demonstrated that patients with CHD were able to achieve an RER adequate to define most CPETs as 'peak' performance.

A further limitation is that data were extracted from an ongoing study. Although the study was developed for the purpose of evaluating UK CR exercise training, the sample size in this analysis is likely to be underpowered to detect significant changes using traditional hypothesis testing. To overcome this we chose to employ the MCID and η^2_p. However, the point-estimate in conjunction with these methods still indicated that VO_{2peak} remained unchanged. Moreover, there was no significant difference between the proportion of patients experiencing a VO_{2peak} increase at least as large as the MCID in the TG (31.8%) or CG (33.3). Consequently, although the study may be underpowered from a hypothesis testing perspective, the results of this study may still be considered an indication of the performance of UK CR.

Lastly, because the study was not randomised, there is a potential of selection bias. It is also possible that the changes in CRF in both groups followed the natural course of recovery of functional status in the time course following a cardiac event and hospitalisation. However, the purpose of this study was to assess whether those taking part in a routine CR exercise class significantly improved VO_{2peak}. Thus far, this does not appear to occur in this CR programme.

4.8   References

ACPICR. (2015). Standards for physical activity and exercise in the cardiovascular population. In P. Heather, B. Helen, B. Samantha, B. John, Laura Burgess, G. Keri, G. Fiona, Tim Grove, Sally Turner & W. Catrin (Eds.), (3rd ed.): Association of Chartered Physiotherapists in Cardiac Rehabilitation (ACPICR).

ACSM. (2013). *ACSM's Guidelines for exercise testing and prescription* (9th ed.). Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health.

American Thoracic Society/American College of Chest Physicians. (2003). ATS/ACCP Statement on cardiopulmonary exercise testing. *American Journal of Respiratory and Critical Care Medicine, 167*(2), 211. doi: 10.1164/rccm.167.2.211

American Thoracic Society/European Respiratory Society. (2005). Standardisation of spirometry. *Eur Respir J, 26*(2), 319-338. doi: 10.1183/09031936.05.00034805

Arena, R., Myers, J., Aslam, S. S., Varughese, E. B., & Peberdy, M. A. (2004). Peak VO2 and VE/VCO2 slope in patients with heart failure: a prognostic comparison. *American Heart Journal, 147*(2), 354-360. doi: 10.1016/j.ahj.2003.07.014

Baba, R., Nagashima, M., Goto, M., Nagano, Y., Yokota, M., Tauchi, N., & Nishibata, K. (1996). Oxygen uptake efficiency slope: A new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. *Journal of the American College of Cardiology, 28*(6), 1567-1572. doi: 10.1016/S0735-1097(96)00412-3

BACPR. (2012). Standards and Core Components for Cardiovascular Disease Prevention and Rehabilitation. http://www.bacpr.com/resources/

BACR. (2006). *British Association For Cardiac Rehabilitation: Exercise instructor training module* (4th ed.). Leeds: Human Kinetics.

Balady, G. J., Arena, R., Sietsema, K., Myers, J., Coke, L., Fletcher, G. F., . . . Milani, R. V. (2010). Clinician's Guide to Cardiopulmonary Exercise Testing in Adults: A Scientific Statement From the American Heart Association. *Circulation, 122*(2), 191-225. doi: 10.1161/CIR.0b013e3181e52e69

Beaver, W. L., Wasserman, K., & Whipp, B. J. (1986). A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol, 60*(6), 2020-2027.

Belardinelli, R., Lacalaprice, F., Carle, F., Minnucci, A., Cianci, G., Perna, G., & D'Eusanio, G. (2003). Exercise-induced myocardial ischaemia detected by cardiopulmonary exercise testing. *Eur Heart J, 24*(14), 1304-1313. doi: 10.1016/S0195-668X(03)00210-0

Berg, K. E., & Latin, R. W. (2008). *Essentials of research methods in health, physical education, exercise science, and recreation*: Lippincott Williams & Wilkins.

Blackie, S. P., Fairbarn, M. S., McElvaney, N. G., Wilcox, P. G., Morrison, N. J., & Pardy, R. L. (1991). Normal values and ranges for ventilation and breathing pattern at maximal exercise. *Chest, 100*(1), 136-142. doi: 10.1378/chest.100.1.136

Bland, J. M., & Altman, D. G. (1999). Measuring agreement in method comparison studies. *Statistical Methods in Medical Research, 8*(2), 135-160. doi: 10.1177/096228029900800204

Borg, G. A. (1982). Psychophysical bases of perceived exertion. *Medicine and Science in Sports and Exercise, 14*(5), 377-381.

Brodie, D., Bethell, H., & Breen, S. (2006). Cardiac rehabilitation in England: a detailed national survey. *European Journal of Cardiovascular Prevention & Rehabilitation, 13*(1), 122- 128. doi: 10.1097/01.hjr.0000192741.04103.d3

Brubaker, P. H., & Kitzman, D. W. (2011). Chronotropic Incompetence: Causes, Consequences, and Management. *Circulation, 123*(9), 1010-1020. doi: 10.1161/circulationaha.110.940577

Bruce, R. A., Kusumi, F., & Hosmer, D. (1973). Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *American Heart Journal, 85*(4), 546-562. doi: http://dx.doi.org/10.1016/0002-8703(73)90502-4

Byrne, N. M., Hills, A. P., Hunter, G. R., Weinsier, R. L., & Schutz, Y. (2005). Metabolic equivalent: one size does not fit all. *Journal of Applied Physiology, 99*(3), 1112-1119. doi: 10.1152/japplphysiol.00023.2004

Campbell, S. C. (1982). A comparison of the maximum voluntary ventilation with the forced expiratory volume in one second: an assessment of subject cooperation. *Journal of Occupational and Environmental Medicine, 24*(7), 531-533.

Cardozo, G. G., Oliveira, R. B., & Farinatti, P. T. (2015). Effects of High Intensity Interval versus Moderate Continuous Training on Markers of Ventilatory and Cardiac Efficiency in Coronary Heart Disease Patients. *The Scientific World Journal, 2015*. doi: 10.1155/2015/192479

Carroll, S., Tsakirides, C., Hobkirk, J., Moxon, J. W. A., Moxon, J. W. D., Dudfield, M., & Ingle, L. (2011). Differential Improvements in Lipid Profiles and Framingham Recurrent Risk Score in Patients With and Without Diabetes Mellitus Undergoing Long-Term Cardiac Rehabilitation. *Archives of Physical Medicine and Rehabilitation, 92*(9), 1382-1387. doi: 10.1016/j.apmr.2011.04.013

Chaudhry, S., Arena, R., Wasserman, K., Hansen, J. E., Lewis, G. D., Myers, J., . . . Boden, W. E. (2009). Exercise-Induced Myocardial Ischemia Detected by Cardiopulmonary Exercise Testing. *The American Journal of Cardiology, 103*(5), 615-619. doi: 10.1016/j.amjcard.2008.10.034

Duncan, G. E., Anton, S. D., Sydeman, S. J., Newton, R. L., Corsica, J. A., Durning, P. E., . . . Perri, M. G. (2005). Prescribing exercise at varied levels of intensity and frequency: a randomized trial. *Archives of Internal Medicine, 165*(20), 2362-2369.

Fletcher, G. F., Balady, G. J., Amsterdam, E. A., Chaitman, B., Eckel, R., Fleg, J., . . . Rodney, R. (2001). Exercise standards for testing and training a statement for healthcare professionals from the American Heart Association. *Circulation, 104*(14), 1694-1740.

Fowler, S. J., Singh, S. J., & Revill, S. (2005). Reproducibility and validity of the incremental shuttle walking test in patients following coronary artery bypass surgery. *Physiotherapy, 91*(1), 22-27. doi: http://dx.doi.org/10.1016/j.physio.2004.08.009

Frederix, I., Driessche, N. V., Hansen, D., Berger, J., Bonne, K., Alders, T., & Dendale, P. (2015). Increasing the medium-term clinical benefits of hospital-based cardiac rehabilitation by physical activity telemonitoring in coronary artery disease patients. *European Journal of Preventive Cardiology, 22*(2), 150-158. doi: 10.1177/2047487313514018

Gee, M. A., Viera, A. J., Miller, P. F., & Tolleson-Rinehart, S. (2014). Functional Capacity in Men and Women Following Cardiac Rehabilitation. *Journal of Cardiopulmonary Rehabilitation and Prevention, 34*(4), 255-262. doi: 10.1097/hcr.0000000000000066

Ghasemi, A., & Zahediasl, S. (2012). Normality tests for statistical analysis: a guide for non-statisticians. *International Journal of Endocrinology and Metabolism, 10*(2), 486.

Guazzi, M., Reina, G., Tumminello, G., & Guazzi, M. D. (2004). Improvement of alveolar- capillary membrane diffusing capacity with exercise training in chronic heart failure. *Journal of Applied Physiology, 97*(5), 1866-1873. doi: 10.1152/japplphysiol.00365.2004

Hansen, J., Sue, D., & Wasserman, K. (1984). Predicted values for clinical exercise testing. *The American review of respiratory disease, 129*(2 Pt 2), S49-55.

Heran, B. S., Chen, J., Ebrahim, S., Moxham, T., Oldridge, N., Rees, K., . . . Taylor, R. S. (2011). Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database of Systematic Reviews, 7*.

Hughson, R. L. (1984). Alterations in the oxygen deficit-oxygen debt relationships with beta-adrenergic receptor blockade in man. *The Journal of Physiology, 349*(1), 375-387. doi: 10.1113/jphysiol.1984.sp015161

Ingle, L., & Carroll, S. (2013). Cardiac rehabilitation and exercise training. *Heart*. doi: 10.1136/heartjnl-2013-304015

Ingle, L., Witte, K. K., Cleland, J. G. J. F., & Clark, A. L. (2008). The prognostic value of cardiopulmonary exercise testing with a peak respiratory exchange ratio of <1.0 in patients with chronic heart failure. *International Journal of Cardiology, 127*(1), 88-92. doi: 10.1016/j.ijcard.2007.04.075

Jolliffe, J., Rees, K., Taylor, R. R., Thompson, D. R., Oldridge, N., & Ebrahim, S. (2001). Exercise-based rehabilitation for coronary heart disease. *The Cochrane Library*.

Karvonen, J., & Vuorimaa, T. (1988). Heart rate and exercise intensity during sports activities. *Sports Medicine, 5*(5), 303-311.

Kavanagh, T., Mertens, D. J., Hamm, L. F., Beyene, J., Kennedy, J., Corey, P., & Shephard, R. J. (2002). Prediction of Long-Term Prognosis in 12 169 Men Referred for Cardiac Rehabilitation. *Circulation, 106*(6), 666-671. doi: 10.1161/01.cir.0000024413.15949.ed

Kavanagh, T., Mertens, D. J., Hamm, L. F., Beyene, J., Kennedy, J., Corey, P., & Shephard, R. J. (2003). Peak oxygen intake and cardiac mortality in women referred for cardiac rehabilitation. *Journal of the American College of Cardiology, 42*(12), 2139-2143. doi: 10.1016/j.jacc.2003.07.028

Keith, S., Jacobs, I., & McLellan, T. (1992). Adaptations to training at the individual anaerobic threshold. *European Journal of Applied Physiology and Occupational Physiology, 65*(4), 316-323. doi: 10.1007/BF00868134

Lemieux, J., Beaton, D. E., Hogg-Johnson, S., Bordeleau, L. J., & Goodwin, P. J. (2007). Three methods for minimally important difference: no relationship was found with the net proportion of patients improving. *Journal of Clinical Epidemiology, 60*(5), 448-455. doi: 10.1016/j.jclinepi.2006.08.006

Mezzani, A., Agostoni, P., Cohen-Solal, A., Corrà, U., Jegier, A., Kouidi, E., . . . Vanhees, L. (2009). Standards for the use of cardiopulmonary exercise testing for the functional evaluation of cardiac patients: a report from the Exercise Physiology Section of the European Association for Cardiovascular Prevention and Rehabilitation. *European Journal of Cardiovascular Prevention & Rehabilitation, 16*(3), 249-267. doi: 10.1097/HJR.0b013e32832914c8

Milani, R. V., Lavie, C. J., & Spiva, H. (1995). Limitations of estimating metabolic equivalents in exercise assessment in patients with coronary artery disease. *The American Journal of Cardiology, 75*(14), 940-942.

Myers, J., Buchanan, N., Walsh, D., Kraemer, M., McAuley, P., Hamilton-Wessler, M., & Froelicher, V. F. (1991). Comparison of the ramp versus standard exercise protocols. *Journal of the American College of Cardiology, 17*(6), 1334-1342. doi: 10.1016/S0735-1097(10)80144-5

Myers, J., Dziekan, G., Goebbels, U., & Dubach, P. (1999). Influence of high-intensity exercise training on the ventilatory response to exercise in patients with reduced ventricular function. *Medicine and Science in Sports and Exercise, 31*(7), 929-937.

Myers, J., Prakash, M., Froelicher, V., Do, D., Partington, S., & Atwood, J. E. (2002). Exercise Capacity and Mortality among Men Referred for Exercise Testing. *New England Journal of Medicine, 346*(11), 793-801. doi: doi:10.1056/NEJMoa011858

NICE (Producer). (2013, 12/08/2014). Cardiac Rehabilitation Services. [National Health Care Guidance] Retrieved from http://www.nice.org.uk/guidance/cmg40/chapter/1-Commissioning-cardiac-rehabilitation-services

Nieuwland, W., Berkhuysen, M. A., van Veldhuisen, D. J., Brügemann, J., Landsman, M. L., van Sonderen, E., . . . Rispens, P. (2000). Differential effects of high-frequency versus low-frequency exercise training in rehabilitation of patients with coronary artery disease. *Journal of the American College of Cardiology, 36*(1), 202-207.

Page, P. (2014). BEYOND STATISTICAL SIGNIFICANCE: CLINICAL INTERPRETATION OF REHABILITATION RESEARCH LITERATURE. *International Journal of Sports Physical Therapy, 9*(5), 726.

Pescatello, L. S., Thompson, W. R., & Gordon, N. F. (2009). A Preview of ACSM's Guidelines for Exercise Testing and Prescription. *ACSM's Health & Fitness Journal, 13*(4), 23-26.

Poole, D. C., Hirai, D. M., Copp, S. W., & Musch, T. I. (2012). Muscle oxygen transport and utilization in heart failure: implications for exercise (in) tolerance. *American Journal of Physiology-Heart and Circulatory Physiology, 302*(5), H1050-H1063.

Richardson, J. T. E. (2011). Eta squared and partial eta squared as measures of effect size in educational research. *Educational Research Review, 6*(2), 135-147. doi: 10.1016/j.edurev.2010.12.001

Rognmo, Ø., Moholdt, T., Bakken, H., Hole, T., Mølstad, P., Myhr, N. E., . . . Wisløff, U. (2012). Cardiovascular Risk of High- Versus Moderate-Intensity Aerobic Exercise in Coronary Heart Disease Patients. *Circulation, 126*(12), 1436-1440. doi: 10.1161/circulationaha.112.123117

Russell, S. D., McNeer, F. R., Beere, P. A., Logan, L. J., & Higginbotham, M. B. (1998). Improvement in the mechanical efficiency of walking: An explanation for the "placebo effect" seen during repeated exercise testing of patients with heart failure. *American Heart Journal, 135*(1), 107-114. doi: http://dx.doi.org/10.1016/S0002-8703(98)70350-3

Sandercock, G., Cardoso, F., & Almodhy, M. (2013). Cardiorespiratory fitness changes in patients receiving comprehensive outpatient cardiac rehabilitation in the UK: a multicentre study. *Heart, 99*(17), 1298-1299. doi: 10.1136/heartjnl-2013-304085

Sandercock, G., Cardoso, F., Almodhy, M., & Pepera, G. (2013). Cardiorespiratory fitness changes in patients receiving comprehensive outpatient cardiac rehabilitation in the UK: a multicentre study. *Heart, 99*(11), 785-790. doi: 10.1136/heartjnl-2012-303055

Sandercock, G., Hurtado, V., & Cardoso, F. (2011). Changes in cardiorespiratory fitness in cardiac rehabilitation patients: A meta-analysis. *International Journal of Cardiology*(0). doi: 10.1016/j.ijcard.2011.11.068

Swain, D. P., & Franklin, B. A. (2002). VO~ 2 reserve and the minimal intensity for improving cardiorespiratory fitness. *Medicine and Science in Sports and Exercise, 34*(1), 152-157.

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

Tsai, S.-W., Huang, Y.-H., Chen, Y.-W., & Ting, C.-T. (2015). Influence of β-blockers on heart rate recovery and ratings of perceived exertion when determining training intensity for cardiac rehabilitation. *Journal of the Chinese Medical Association*(0). doi: http://dx.doi.org/10.1016/j.jcma.2015.05.009

Van Laethem, C., Bartunek, J., Goethals, M., Nellens, P., Andries, E., & Vanderheyden, M. (2005). Oxygen uptake efficiency slope, a new submaximal parameter in evaluating exercise capacity in chronic heart failure patients. *American Heart Journal, 149*(1), 175- 180.

Vanhees, L., Fagard, R., Thijs, L., & Amery, A. (1995). Prognostic value of training-induced change in peak exercise capacity in patients with myocardial infarcts and patients with coronary bypass surgery. *The American Journal of Cardiology, 76*(14), 1014-1019.

Warburton, D. E., McKenzie, D. C., Haykowsky, M. J., Taylor, A., Shoemaker, P., Ignaszewski, A. P., & Chan, S. Y. (2005). Effectiveness of high-intensity interval training for the rehabilitation of patients with coronary artery disease. *The American Journal of Cardiology, 95*(9), 1080-1084.

Wasserman, K., Hansen, J., Sue, D., Stringer, W., Sietsema, K., Sun, X.-G., & Whipp, B. (2011). *Principles of exercise testing and interpretation: Including pathophysiology and clinical*

applications (Fifth ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins.

West, R. R., Jones, D. A., & Henderson, A. H. (2012). Rehabilitation after myocardial infarction trial (RAMIT): multi-centre randomised controlled trial of comprehensive cardiac rehabilitation in patients following acute myocardial infarction. *Heart, 98*(8), 637-644. doi: 10.1136/heartjnl-2011-300302

Woolf-May, K., Bird, S., & MacIntyre, P. (2005). Physical activity levels during phase IV cardiac rehabilitation in a group of male myocardial infarction patients. *British Journal of Sports Medicine, 39*(3), e12-e12. doi:10.1136/bjsm.2003.010983

Chapter 4: The short and longer-term changes to carotid intima-media thickness following a standard eight week, 16 session, low to moderate intensity UK cardiac rehabilitation exercise training programme

5.1   Abstract

Introduction: The long-term survival benefits associated with undertaking routine UK cardiac rehabilitation (CR) have been brought in to question. This may be because the dose of exercise prescribed as part of a routine CR exercise training regime only result in modest cardiorespiratory fitness (CRF) improvements. It is therefore likely that UK CR exercise training programmes do not attenuate coronary risk factors or inflammatory responses known to affect the progression of coronary atherosclerosis. The aim of this study was to determine whether the progression of carotid intima-media thickness (C-IMT), a surrogate marker of coronary arthrosclerosis is attenuated by undertaking a routine CR exercise training regime.

Methods: Patients with a recent diagnosis of coronary heart disease (CHD) were recruited to this study. Patients choosing to take part in routine CR exercise training formed a treatment group (TG) and completed an eight week, (16 session) low to moderate intensity exercise training regime. Patients declining CR formed the control group (CG). Control patients were able to access all other recommended components of a 'comprehensive' CR programme and instructed to follow the advice of their healthcare professional. All patients underwent an initial bilateral C-IMT assessment using B-mode ultrasound (visit 1). Mean and maximum C-IMT measurements were taken 1cm proximally from the bifurcation of the common carotid artery (CCA). For patients in the TG, reassessment was conducted upon completion of CR. Controls were reassessed approximately ten weeks following their initial visit (visit 2). To determine the longer-term effects of routine CR, a further reassessment was conducted 12 months after visit 1 (visit 3).

Results: n=34 patients (85.3% male; age 62.1 ± 8.8 years; BMI 29.5 ± 4.5 Kg·m^{-2}) met the study inclusion criteria. Controls (n=12) experienced a significant increase in mean C-IMT at the right lateral aspect of their CCA visit 2 (median change: 0.070 mm; range -0.060 to 0.200 mm; p=0.038). All other mean C-IMT measurements between visit 1 and 2 remained unchanged in both groups. There were no changes to maximum C-IMT at visit 2 in either group. The TG (n=22) significantly reduced mean C-IMT between visit 2 and 3 (median change: -0.054 mm; range -0.160 to 0.020 mm; p=0.015). All other changes to mean and max C-IMT at visit 3 were non-significant.

Conclusion: A 'standard' eight week (16 sessions) low to moderate intensity UK CR exercise training programme does not reduce C-IMT in the short term. C-IMT progression may advance at a faster rate when patients do not fully participate in a CR programme. In the longer-term (visit 3), patients undertaking routine CR exercise training may experience a reduction in C- IMT. Further testing is needed before firm conclusions regarding the longer-term effects of UK CR exercise training on C-IMT can be drawn.

5.2 Introduction

The progression of arthrosclerosis is associated with adverse cardiovascular (CV) outcomes (Taylor et al., 2005). Tools such as the Framingham risk score are useful for cross-sectional CV risk stratification, however, their use in serial testing is not well validated (Grundy et al., 1999). The use of pathologically relevant intermediary end-points has emerged as a way of determining CV disease progression.

Insonation of the common carotid artery (CCA) using B-mode ultrasound can quantify carotid intima-media thickness (C-IMT), a recognised indicator of subclinical atherosclerosis (Pignoli et al., 1986, O'Leary and Bots, 2010). CV risk factors including systolic blood pressure (BP) and physical inactivity are known to accelerate C-IMT progression (Sato et al., 2008). C-IMT is a reliable surrogate marker of coronary heart disease (CHD) severity (Amato et al., 2007) and, a 0.1 mm increase elevates MI risk by 15% amongst the 'general population' [i.e. not a CVD risk population (Lorenz et al., 2007)]. However, whilst C-IMT has been widely investigated as prognosticator, (Lorenz et al., 2012, Baldassarre et al., 2013) few studies have evaluated C-IMT change following exercise training.

It is known that an adequate dose of exercise training may slow the progression of coronary atherosclerosis in stable CHD patients (Hambrecht et al., 2004, Niebauer et al., 1997). More recently, an inverse relationship between VO_{2peak} and C-IMT severity has been described in middle-aged adults (Scholl et al., 2015). Research investigating the relationship between exercise training and C-IMT regression is limited. Existing literature has focused on 'leisure time' physical activity but does indicate that C-IMT progression is attenuated amongst physically active individuals. In a six month (walking) exercise regime, Sato et al. (2008) found that total walking distance was inversely associated with C-IMT progression (r=−0.510; p<0.01). A daily distance of at least 4.25 km was shown to inhibit C-IMT progression. Similar findings have been reported by Kim et al. (2006) in patients with type 2 diabetes mellitus (DM). One of the few studies to report the effect of *structured* exercise on C-IMT showed that six months of training (20 to 40 minutes;

three days per week; 40-65% VO_{2peak}) in hypertensive African- American males significantly reduced C-IMT (Feairheller et al., 2014). By contrast, three months of structured exercise training (40 minutes; five days per-week; ~70% HR max) in healthy individuals has been shown to have no effect on C-IMT despite a significant improvement in VO_{2peak} (Tanaka et al., 2002). Tanaka and colleagues' (2002) training period was substantially shorter than that conducted by others (Sato et al., 2008, Kim et al., 2006, Feairheller et al., 2014). Longer-term training programmes may be required to reduce C-IMT progression rate or, alternatively, patients at elevated CV risk may have greater propensity to exercise induced C-IMT regression.

CV risk factors including abnormal lipid profiles, physical inactivity, obesity and hypertension, are known to accelerate atherogenesis and increase C-IMT progression (Pursnani et al., 2014, Sato et al., 2008). The modification of these risk factors may be responsible for attenuating C- IMT progression. Tanaka et al. (2002) only recruited healthy individuals, whereas Kim et al. (2006) and Feairheller et al. (2014) included participants with multiple CV risk factors. In the latter two studies, exercise training resulted in concurrent reductions in C-IMT, triglycerides, BMI, fasting glucose and, increased VO_{2peak}. Exercise training interventions leading to CV risk factor reduction in those with elevated CV risk may be most likely to result in C-IMT regression. Shorter-term exercise training regimes in higher CVD risk patients such as those offered by many UK cardiac rehabilitation (CR) services may attenuate C-IMT progression.

Improving CV risk factors is a recognised benefit of CR (Taylor et al., 2004, Warburton et al., 2005, Carroll et al., 2011) and as such may deliver quantifiable changes in C-IMT. However, these studies reporting improved CV risk factor profiles in CR patients used greater exercise training doses than delivered in many UK CR programmes. Recent reports suggest that *some* UK CR programmes (previously referred to as phase III) may be sub-optimal in terms of improving CRF (Sandercock et al., 2013b, Sandercock et al., 2013a, Ingle and Carroll, 2013). The small cardiorespiratory fitness (CRF) improvement shown to result from UK CR programmes may indicate that CV risk factors and subsequently, C-IMT progression are also unaffected. This however remains speculative. There are currently no studies reporting the effects of a UK CR

exercise training regimes on changes in C-IMT. Whether or not the exercise dose prescribed to patients in UK CR programmes is sufficient to affect C-IMT progression/regression is unknown. Using the Panasonic CardioHealth Station [CHS] (Panasonic Biomedical Sales Europe BV, Leicestershire, UK), the following study was conducted to determine whether a 16 session (eight week), low to moderate intensity UK CR exercise training regime could attenuate C-IMT progression. A twelve month follow up visit was also conducted to determine longer-term C-IMT changes. Analysis was performed on data obtained from an ongoing study investigating the cardiovascular (CV) and respiratory adaptations in response to standard UK exercise based CR.

5.3   Methods

5.3.1   Ethical Approval

Ethical approval for the overarching study was obtained from the Humber Bridge NHS Research Ethics Committee - Yorkshire and the Humber on the 27th September 2013, (12/YH/0278). All aspects of this study conform to the declaration of Helsinki 1964 and its subsequent revisions. Patient recruitment commenced on March 12th 2014 and remains ongoing. For the purpose of this thesis, data was censored on 15th July 2015 to facilitate timely analysis.

5.3.2   Study Outline

The study was conducted in collaboration with Hull's CR service which follows the Department of Health (2010) 'best care pathway' for referral and delivery of CR. A description of the programme, study recruitment and group assignment process has been detailed in Chapter 3. In brief, patients expressing an interest in the study were provided with a patient information sheet which detailed the study protocol. Patient's opting to participate in exercise based CR were assigned to the training group (TG) and those freely choosing not to participate in structured exercise training were assigned to the control group (CG). Exercise training regimes

conformed to the recommendations of the Association of Chartered Physiotherapists in Cardiac Rehabilitation (ACPICR, 2015) and the British Association of Cardiac Prevention and Rehabilitation (BACPR, 2012b, BACR, 2006). All patients were permitted to participate in other recommended components of a comprehensive CR programme (BACPR, 2012b). Group randomisation was not performed as this was deemed unethical given the current evidence base in support of the benefits of exercise based CR.

Following group assignment patients were invited to the Academic Cardiology laboratory at Castle Hill Hospital on three occasions. For patients in the TG group, initial appointments (visit 1) were planned to coincide with the start date of their exercise class. Controls were invited to attend visit 1 at similar times following their cardiac event (approximately 28 days). Informed consent was taken by a medical doctor prior to any investigations being conducted. Following visit 1, all patients were instructed to follow the advice of their healthcare team including physical activity or exercise recommendations. Follow-up appointments (visit 2) for patients in the TG were arranged to coincide with the completion of the exercise training regime (approximately 8 to 12 weeks later). For controls, visit 2 was planned approximately 8 to 12 weeks following visit 1. A third visit (visit 3) was arranged for both groups 12 months after visit 1. Inclusion and exclusion criteria are detailed in Table 1. All patients were clinically stable at the time of recruitment.

Table 1 – Study inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Clinically stable patients	Clinically unstable patients
Recent MI, CABG, PCI, CHF or hospital admission for newly diagnosed exertional angina	Valvular heart disease
Aged 30 to 85 years	Patients with congenital heart conditions, significant co-morbidities including severe CHF, advanced cancer and conditions preventing the patient from providing informed consent
Willing to undetake all tests described in the PIS	Current drug abusers, excessive alcohol drinkers and patients currently serving a sentence with HM prison
Absence of contraindications to exercise	Patients unwilling or unable to participate in key aspects of the study
Contractually capable and mentally able to understand and follow the instructions of the health professional team	Ongoing clinical complications, open wounds or systemic infections
Able to provide signed informed consent	Women who are pregnant or breastfeeding

5.3.3 Exercise Training Group

Hull's CR exercise training regime has been comprehensively detailed in Chapter 3. Exercise was conducted twice per week for eight weeks (16 sessions) at an intensity of approximately 40-60% heart rate reserve (HRR). Patients perceived to be fitter were permitted to exercise up to an intensity of 70% HRR at the discretion of the CR physiotherapist. Karvonen and Vuorimaa (1988) method of estimating heart rate (HR) training zones was used for patients younger than 45 years and Tanaka et al. (2001) method was used for those older than 45 years. Borg's (1982) rating of perceived (RPE) exertion was also used to aid exercise prescription. Patients were advised to work towards an RPE of 11 to 14. The CR team also estimated functional capacity to aid exercise prescription. A submaximal cycle ergometry protocol with increments 30 or 25 W increments every two minutes was used. Exercise testing was terminated when patients achieved 70% of their HRR, a Borg score of 14 to 15 or, the development of angina symptoms. Data obtained from the exercise test included HR, RPE, O_2 saturation (SPO_2) where available and, metabolic

equivalents (MET's) estimated from the BACPR's reference tables (unpublished).

5.3.4 Anthropometric Measurements

Details of the methods used to determine height (cm), body mass (Kg), body mass index (BMI; Kg·m^{-2}), waist (cm) and hip (cm) measurements are provided in Chapter 3.

5.3.5 Duel X-Ray Absorptiometry Scan

Duel X-Ray Absorptiometry [DXA] (Lunar iDXA, GE Healthcare, Buckinghamshire, UK) was used to determine body composition. Daily calibration was performed using a control block of known composition. Patients were fully informed of the investigation risks including radiation exposure. Metallic objects such as wedding rings were removed. Patients were aligned within a rectangular positioning grid with their head positioned at the top of the scanning field. Left and right shoulders and, arms were placed symmetrically. Fingers were positioned away from the body where possible. Patients' torsos were positioned to allow the spine to follow the sagittal line of the body. Legs were aligned to the rest of the body. A Velcro belt was loosely placed around both legs at the anterior tibial crest to prevent movement during the scan. Patients were asked not to talk whilst being scanned to avoid movement artefact and increased measurement variability. Patient height and body mass were entered for automated calculation of radiation dose. Composition analysis was performed by integrated software. For the purpose of this chapter, total mass (Kg), total body fat (%) and android body fat (%) were used for analysis.

5.3.6 Assessment of Carotid Intima-Media Thickness

The Panasonic CHS is a commercially available automated ultrasound system for the measurement of C-IMT. The CHS has low measurement variability in healthy and, cardiac

populations when investigations are conducted by experienced and inexperienced operator's alike (Appendix 3, Nichols et al., 2014c, Vanoli et al., 2013b). The CHS is equipped with a broadband probe (5-13 MHz) with a centre frequency optimised for carotid imaging. When correctly positioned over the CCA, automated on-board software locates the vessel's far wall using a region of interest tool (ROI). The CHS automatically captures a sequence of images at end-diastole by monitoring vessel distension characteristics and 'freezes' when pre-defined C-IMT boundary quality criteria are met. Multiple measurements taken from a 1cm segment of the CCA located 1cm proximally from the carotid bifurcation were obtained. Mean and maximum (max) IMT were recorded to three decimal places (Figure 1). Image quality was inspected and trace lines modified where required. To enhance measurement reproducibility, the probe is equipped with an accelerometer and gyroscope that tracks the angle (˚) of insonation relative to ground. Each C-IMT measurement is recorded with the angle that the image was taken.

5.3.7   Insonation Protocol

For assessment of the right CCA, patients were required to lay supine on a firm horizontal bed with their head rotated to the left (45°) against a foam gauge (Figure 2). The anterior aspect of the right CCA was examined by placing the transducer in a transverse orientation across the proximal segment of the artery. The operator orientated themselves to their location by checking the position of local anatomy and then scanning distally until reaching the CCA bulb and bifurcation. Throughout this process, the examiner assessed the clarity of the intima-media boundary and adjusted the gain and focus accordingly. Once at the bifurcation, the operator repeated the process in a lateral aspect.
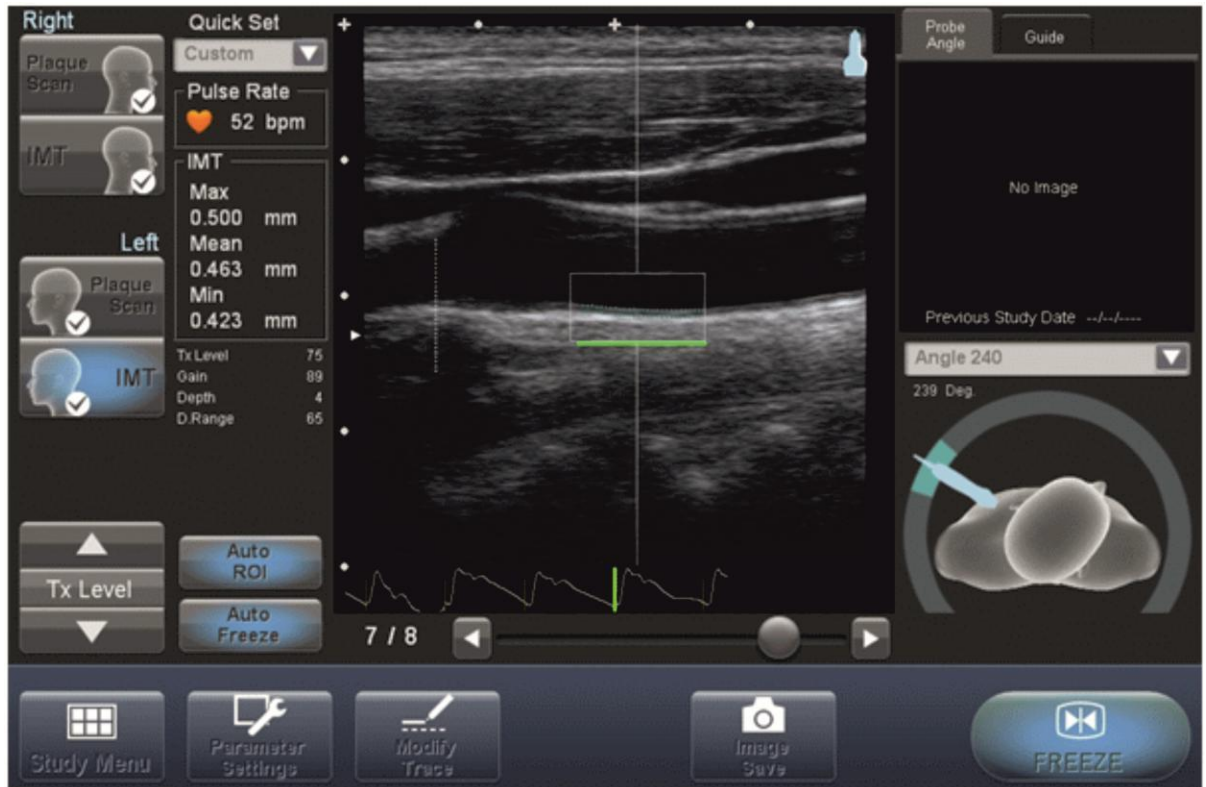
Figure 1 – Image of the left common carotid artery at a lateral aspect (239˚). Insonation angle is displayed and recorded by the CardioHealth Station (bottom right). The region of interest (ROI) is defined by the white rectangle (centre) and can be reliably positioned 1cm proximal from the bifurcation by placing the white vertical line (centre left) over the tip of the carotid flow divider. The mean and maximum carotid intima-media thickness measurements are calculated from the edge detection software (blue dotted lines) and values are displayed at the top left-hand side of the screen.

Figure 2 – Use of a standardised foam gauge angled to 45˚ to standardise head position during repeat carotid intima-media thickness scans.

When at the bulb of the CCA for the second time the operator rotated the transducer into the longitudinal plane to reveal the length of the artery (Figure 1). C-IMT was then measured at the right anterior (150°), lateral (120˚) and posterior (90˚) aspects. Once measurements for the right CCA were complete the process was repeated on the left CCA in the anterior (210°), lateral (230°) and posterior (270°) aspects.

5.3.8   Statistical Analysis

As discussed in Chapter 3, at the time of analysis the number of patients returning for visit 2 was substantially greater than those who had returned for visit 3. Initial analysis was therefore performed exclusively on data obtained between visit 1 and 2. Secondary analysis was then conducted on the smaller sub-sample size of patients returning for visit 3.

Statistical analysis was performed using SPSS version 22 (IBM, New York, USA) and Microsoft Excel 2007 (Microsoft, Redmond WA, USE). Patients were excluded from analysis if they failed to attend any follow up visit. Normal distribution was assessed using histograms and the Shapiro-Wilk test. The Shapiro-Wilk test is the preferred test for normality in instances where samples sizes are small (Ghasemi and Zahediasl, 2012). Continuous normally distributed variables are displayed as mean and standard deviation (± SD). Non-normally distributed data are displayed as median and range, and categorical data as percentages. With the exception of baseline characteristics and insonation angle which were analysed using parametric methods, statistical significance (α <0.05) was determined using non-parametric tests that included Friedman analysis of repeated measures, Wilcoxon signed rank tests and Mann-Whitney U. Wilcoxon signed rank tests were used for post-hoc analysis when Friedman analysis yielded a significant main effect. Effect sizes and the minimal clinically important difference used in Chapter 3 were not used as all C-IMT data was non-normally distributed. Due to the use of non-parametric tests no analysis of covariance was conducted. Spearman correlations (r) were used to determine the association between independent and dependent variables. An r value of

<0.25, 0.26 to 0.50, 0.51 to 0.75, and, >0.75 were considered weak, moderate, fair and strong relationships respectively (Berg and Latin, 2008). Coefficient of determination (r^2) was calculated as the square of r.

Analysis was conducted using the mean and max C-IMT measurements calculated by the CHS. Because distribution of atherosclerosis around the CCA is irregular (Tajik et al., 2012) it is important that C-IMT measurements are obtained at similar insonation angles on each testing cycle if a true treatment effect is to be identified. Agreement between insonation angles (˚) at visit 1 and visit 2 was conducted using Bland-Altman analysis (Bland and Altman, 1999). A Breusch-Pagen test was performed to check assumptions of homoscedasticity. Coefficient of variation (CoV%) was determined for insonation angles at visit 1 and 2 to assess within-group angle variability. CoV% was defined as within-group SD divided by group mean, multiplied by 100 (Atkinson and Nevill, 1998).

5.4 Results

5.4.1 Group Characteristics

Patient characteristics have been comprehensively reported in Chapter 3 of this thesis. 38 patients had attended visit 1 at the time of data analysis. 34 patients (85.3% male; age 62.1 ± 8.8 years; BMI 29.5 ± 4.5 Kg·m^{-2}) met the study inclusion criteria. *n*=4 patients were excluded due to failure to attend visit 2, of those *n*=2 failed to attend on medical grounds and *n*=2 were lost to follow (see Chapter 3). Patient baseline characteristics are shown in Table 2. There were no significant group differences for age (0.2 years; 95% CI -6.3 to 6.7 years; p=0.946), BMI, (0.2 Kg·m^{-2}; 95% CI -3.5 to 3.2 Kg·m^{-2}; p=0.946) or ejection fraction (1.3 %; 95% CI -4.3 to 7.0 %; p=0.632). Type 2 DM was more prevalent in the CG than the TG (13.6% vs. 58.3%) as was the number of patients still smoking (0.0% vs. 25.0%). Patient medications are listed in Table 3. There were no changes to patient medications between visit 1 and 2.

5.4.2 Exercise Training

A full description of the CR programme's exercise training characteristics has been reported in Chapter 3 and are summarised in Table 4. Median CV exercise duration increased from 11.5 minutes (range: 6.0 to 22.5 minutes) at visit 1 to 20.5 minutes (range 11.5 to 48 minutes; p<0.001) at visit 2. Borg scores increased from 11.5 (range 9.0 to 12.5) at visit 1 to 12.0 at visit 2 (range: 8.3 to 14.3; p=0.020). Most patients did not exceed an RPE of 13 during their CR programme (see Chapter 3; Figure 5). 'Median Peak HR' did not change significantly between session 1 (95 bpm; range: 72 to 114 bpm) and session 16 (98 bpm; range: 73 to 119 bpm; p=0.920). 'Median Peak HR 'was always within 40-60% HRR irrespective of whether HRR was estimated or determined from CPET data.

5.4.3 Baseline C-IMT Measurements

Baseline C-IMT measurements are shown in Table 5.There were no significant differences between mean C-IMT measurements in the right anterior aspect, lateral and posterior. Further, no significant group differences were detected for left mean C-IMT measurements in the anterior, lateral and posterior aspects. Max C-IMT measurements in the right anterior, lateral and posterior were not significantly different as were left anterior, lateral and posterior aspects.

5.4.4 Circumferential C-IMT Distribution

When C-IMT measurements (visit 1) for each angle of insonation were pooled according to CCA side (i.e. mean of anterior, lateral and posterior mean C-IMT measurements), there were no significant differences between right (median: 0.741 mm; range -0.500 to 1.360 mm) and left mean C-IMT measurements (median: 0.748 mm; range: 0.490 to 1.110 mm; p=0.388). There were no significant differences between right (median: 0.863 mm; range: 0.580 to 1.570 mm) and left mean-*max* C-IMT measurements (median: 0.857 mm; range 0.510 to 1.450 mm;

163

p=0.412).

Friedman analysis showed no significant differences between right posterior, lateral and anterior mean C-IMT measurements (Figure 3a; p=0.336). Likewise, no significant differences between left anterior, lateral and posterior mean C-IMT was found (Figure 3a; p=0.882). There were no significant differences between right anterior, lateral and posterior (Figure 3b; p=0.823) or, left anterior, lateral and posterior max C-IMT measurements (Figure 3b; p=0.900). There was no indication of irregular C-IMT distribution throughout the CCA.

5.4.5 Insonation Angle Variability

As previously reported using the CHS (Nichols et al., 2014c), insonation angle variability remained low (Table 6). Both right (visit 1: 100.9 ± 2.6˚; visit 2: 101.1 ± 2.7˚) and left posterior measurements (visit 1: 257.2 ± 3.9˚; visit 2: 257.8 ± 3.8˚) were taken more laterally than specified in the protocol. However CoV for both right (visit 1: 2.6%; visit 2: 2.6%) and left (visit 1: 1.5%; visit 2: 1.5%) posterior measurements remained low. Right lateral measurements demonstrated the greatest CoV% (visit 1: 4.6%; visit 2: 3.9%). Left lateral insonation angle significantly increased from visit 1 to 2 (mean bias: 3.97˚; p=0.003). The limits of agreement (LoA) for insonation angle were widest in the left anterior aspect (-15.2 to 15.0˚). All other mean bias and LoA data are reported in Table 5 and Figure 4.

Table 2 – Patient Baseline Characteristics (mean ± SD)

Variable	All	Treatment Group (n =22)	Control Group (n =12)
Participants (% male)	n =34 (85.3)	n =22 (81.8)	n =12 (91.7)
Age (years)	62.1 ± 8.8	62.1 ± 8.5	61.9 ± 9.6
BMI (Kg·m^{-2})	29.5 ± 4.5	29.4 ± 4.2	29.6 ± 5.1
W/H Ratio	0.95 ± 0.08	0.95 ± 0.09	0.97 ± 0.05
Resting SBP (mmHg)	129 ± 23	127 ± 20	134 ± 29
Resting DBP (mmHg)	81 ± 10	81 ± 12	60 ± 11
Resting HR (bpm)	58 ± 10	56 ± 6	54 ± 10
Resting EF (%)	55.1 ± 7.6	55.6 ± 6.4	54.3 ± 9.8
FEV_1/FVC Ratio	0.77 ± 0.8	0.78 ± 0.08	0.75 ± 0.06
STEMI + PPCI (%)	14.7 (n =5)	13.6 (n =3)	16.7 (n =2)
STEMI + Staged PCI	2.9 (n =1)	4.5 (n =1)	0.0 (n =0)
STEMI + POBA	2.9 (n =1)	4.5 (n =1)	0.0 (n =0)
NSTEMI + PCI	26.5 (n =9)	18.2 (n =4)	41.7 (n =5)
NSTEMI	5.9 (n =2)	9.1 (n =2)	0.0 (n =0)
Exertional Angina	8.8 (n =3)	9.1 (n =2)	8.3 (n =1)
PCI	32.4 (n =11)	36.4 (n =8)	25.0 (n =3)
CABG	5.9 (n =2)	4.5 (n =1)	8.3 (n =1)
Hypertension (%)	57.1 (n =16)	50.0 (n =11)	41.7 (n =5)
Hyperlipidaemia (%)	79.4 (n =27)	81.8 (n =18)	75.0 (n =9)
Previous MI (%)	23.5 (n =8)	18.1 (n =4)	33.3 (n =4)
Previous CABG (%)	5.9 (n =5.9)	4.5 (n =1)	8.3 (n =1)
Previous PCI (%)	14.7 (n =5)	9.1 (n =2)	25.0 (n =3)
Previous TIA (%)	5.9 (n =2)	4.5 (n =1)	8.3 (n =1)
Atrial Fibrillation (%)	5.9 (n =2)	4.5 (n =1)	8.3 (n =1)
Type 2 DM (%)	29.4 (n =10)	13.6 (n =3)	58.3 (n =7)
Asthma (%)	5.9 (n =2)	9.1 (n =2)	0.0 (n =0)
COPD (%)	5.9 (n =2)	4.5 (n =1)	8.3 (n =1)
Smoking Cessation (%)	5.9 (n =2)	4.5 (n =1)	8.3 (n =1)
Ex-Smoker (%)	52.9 (n= 18)	59.1 (n =13)	41.7 (n =5)
Smoker (%)	8.8 (n =3)	0.0 (n =0)	25.0 (n =3)
Cancer (%)	11.8 (n =4)	13.6 (n =3)	8.3 (n =1)

Kg·m^{-2}= Kilograms per Metre squared; W/H Ratio = Waist to Hip Ratio; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; mmHg = Millimetres of Mercury; HR = Heart Rate; bpm = Beats Per Minute; EF = Ejection Fraction; FEV_1 = Forced Expiratory Volume in One Second; FVC = Forced Vital Capacity; STEMI = ST Elevation Myocardial Infarction; PPCI = Primary Percutaneous Coronary Intervention; PCI = Percutaneous Coronary Intervention; POBA = Plain Old Balloon Angioplasty; NSTEMI = Non-ST Elevation Myocardial Infarction; CABG = Coronary Artery Bypass Graft; MI = Myocardial Infarction; TIA = Transient Ischaemic Attack; Type 2 DM; Type 2 Diabetes Mellitus; COPD = Chronic Obstructive Pulmonary Disease

Table 3 – Patient Medications

Medication	All (*n* =34)	Treatment Group (*n* =22)	Control Group (*n* =12)
Aspirin (%)	97.1 (*n* =33)	100.0 (*n* =22)	91.7 (*n* =11)
Clopidogrel (%)	26.5 (*n* =9)	36.4 (*n* =8)	8.3 (*n* =1)
Ticagrelor (%)	55.9 (*n* =19)	45.5 (*n* =10)	75.0 (*n* =9)
Beta-Blocker (%)	91.2 (*n* =31)	95.5 (*n* =21)	83.3 (*n* =10)
ACE-inhibitor (%)	52.9 (*n* =18)	50.0 (*n* =11)	58.3 (*n* =7)
AR Blocker (%)	11.8 (*n* =4)	13.6 (*n* =3)	8.3 (*n* =1)
Statin (%)	94.1 (*n* =32)	95.5 (*n* =21)	91.7 (*n* =11)
Fibrate (%)	2.9 (*n* =1)	0.0 (*n* =0)	8.3 (*n* =1)
Diuretic (%)	8.8 (*n* =8.8)	4.5 (*n* =1)	16.7 (*n* =2)
Nitrate (%)	23.5 (*n* =23.5)	22.7 (*n* =5)	25.0 (*n* =3)
GTN (%)	97.1 (*n* =33)	95.5 (*n* =21)	100.0 (*n* =12)

ACE = Angiotensin Converting Enzyme Inhibitor; AR = Angiotensin Receptor Blocker; GTN = Glyceryl Trinitrate

Table 4 – Summary of exercise training programme characteristics

Programme Characteristic	Value (Median: Range)
Structured Exercise Sessions Undertaken by TG	16 (6 to 16)
Additional Home Exercise Sessions Undertaken by TG	7.5 (0 to 84)
Home Exercise Sessions Undertaken by CG	21 (0 to 78)
CV Exercise Duration at First CR Session (minutes)	11.5 (6.0 to 22.5)†
CV Exercise Duration at Sixteenth CR Session (minutes)	20.5 (11.5 to 48.0)†
RPE at First Session	11.5 (9.0 to 12.5)*
RPE at Sixteenth Session	12 (8.3 to 14.3)*
Median Peak HR at First Session (bpm)	95 (72 to 114)‡
Median Peak HR at Sixteenth Session (bpm)	98 (73 to 119)‡

TG = Training Group; CG = Control Group; CV = Cardiovascular; CR = Cardiac Rehabilitation; RPE = Rating of Perceived Exertion; HR = Heart Rate; BPM = Beats Per Minute

† * ‡ = Significant Difference Between Paired Variables

Table 5 – Mean and maximum C-IMT measurements at visit 1 (mean (range))

Insonation Angle	Training Group Visit 1 Mean C-IMT (mm)	Control Group Visit 1 Mean C-IMT (mm)	Training Group Visit 1 Max C-IMT (mm)	Control Group Visit 1 Max C-IMT (mm)
Right Anterior	0.719 (Range: 0.511 to 1.160)	0.704 (Range: 0.531 to 1.130)	0.865 (0.550 to 1.780)	0.845 (0.610 to 1.200)
Right Lateral	0.737 (Range: 0.467 to 1.626)	0.674 (Range: 0.540 to 1.122)	0.850 (0.540 to 1.850)	0.800 (0.580 to 1.230)
Right Posterior	0.766 (Range: 0.497 to 1.322)	0.675 (Range: 0.501 to 1.209)	0.825 (0.580 to 1.540)	0.825 (0.539 to 1.280)
Left Anterior	0.812 (Range: 0.522 to 1.005)	0.745 (Range: 0.442 to 1.200)	0.930 (0.577 to 1.270)	0.910 (0.540 to 1.350)
Left Lateral	0.741 (Range: 0.451 to 1.139)	0.729 (Range: 0.522 to 1.221)	0.850 (0.540 to 1.390)	0.890 (0.610 to 1.310)
Left Posterior	0.759 (Range: 0.559 to 1.283)	0.739 (Range: 0.519 to 0.983)	0.825 (0.660 to 1.810)	0.870 (0.630 to 1.240)

C-IMT = Carotid Intima-Media Thickness; mm = millimetres

* = Significant Difference
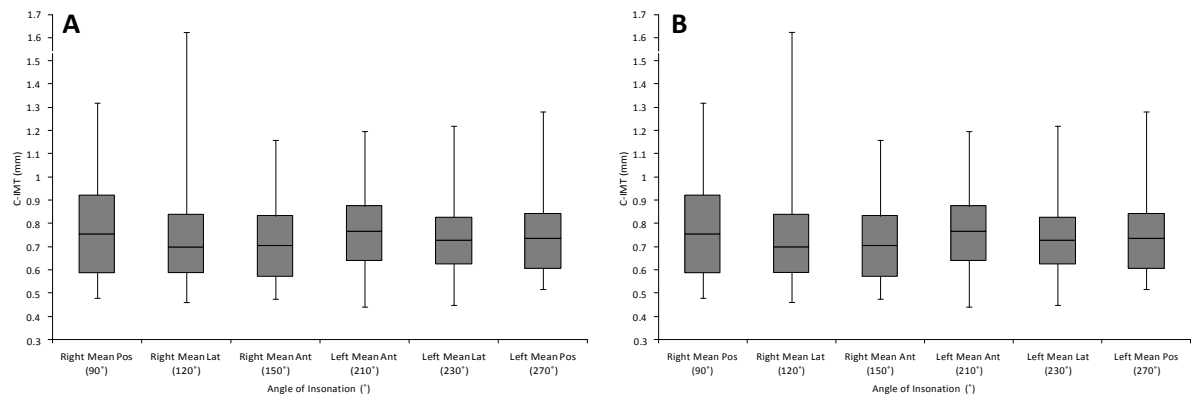
Figure 3 – Box-plot 'A' shows the median (IQR and range) of the mean C-IMT at the right posterior, lateral and anterior aspects and, left anterior, lateral and posterior aspects. Box-plot 'B' shows the median (IQR and range) of the maximum C-IMT at the right posterior, lateral and anterior aspects and, left anterior, lateral and posterior aspects.

C-IMT = Carotid Intima-Media Thickness; mm = Millimetres; Pos = Posterior; Lat = Lateral; Ant = Anterior; ˚ = Degrees; IQR = Interquartile Range

Table 6 –Insonation angle variability with respect to specified angle range in ultrasound protocol (mean ±SD)

	Right Anterior (140-160˚)		Right Lateral (110-130˚)		Right Posterior (80-100˚)		Left Anterior (200-220˚)		Left Lateral (220-240˚)		Left Posterior (260-280˚)	
	Visit 1	Visit 2	Visit 1	Visit 2	Visit 1	Visit 2	Visit 1	Visit 2	Visit 1	Visit 2	Visit 1	Visit 2
Mean Angle (˚)	141.4 ± 3.9	142.2 ± 3.1	121.1 ± 5.6	120.3 ± 4.8	100.9 ± 2.6	101.1 ± 2.7	215.1 ± 5.4	215 ± 4.7	233.3 ± 5.1	237.2 ± 5.6	257.2 ± 3.9	257.8 ± 3.8
CoV%	2.7	2.2	4.6	3.9	2.6	2.6	2.6	2.2	2.2	2.4	1.5	1.5
Mean Bias (˚)	0.76 (p=0.343)		-0.79 (p=0.481)		0.21 (p=0.716)		-0.12 (p=0.928)		3.97 (p=0.003)		0.5 (p=0.612)	
LoA (˚)	-10.5 to 10.0		-13.5 to 11.9		-6.3 to 6.8		-15.2 to 15.0		-11.8 to 17.8		-9.8 to 10.8	

˚ = Angle – degrees; CoV = Coefficient of Variation; LoA = Limits of Agreement
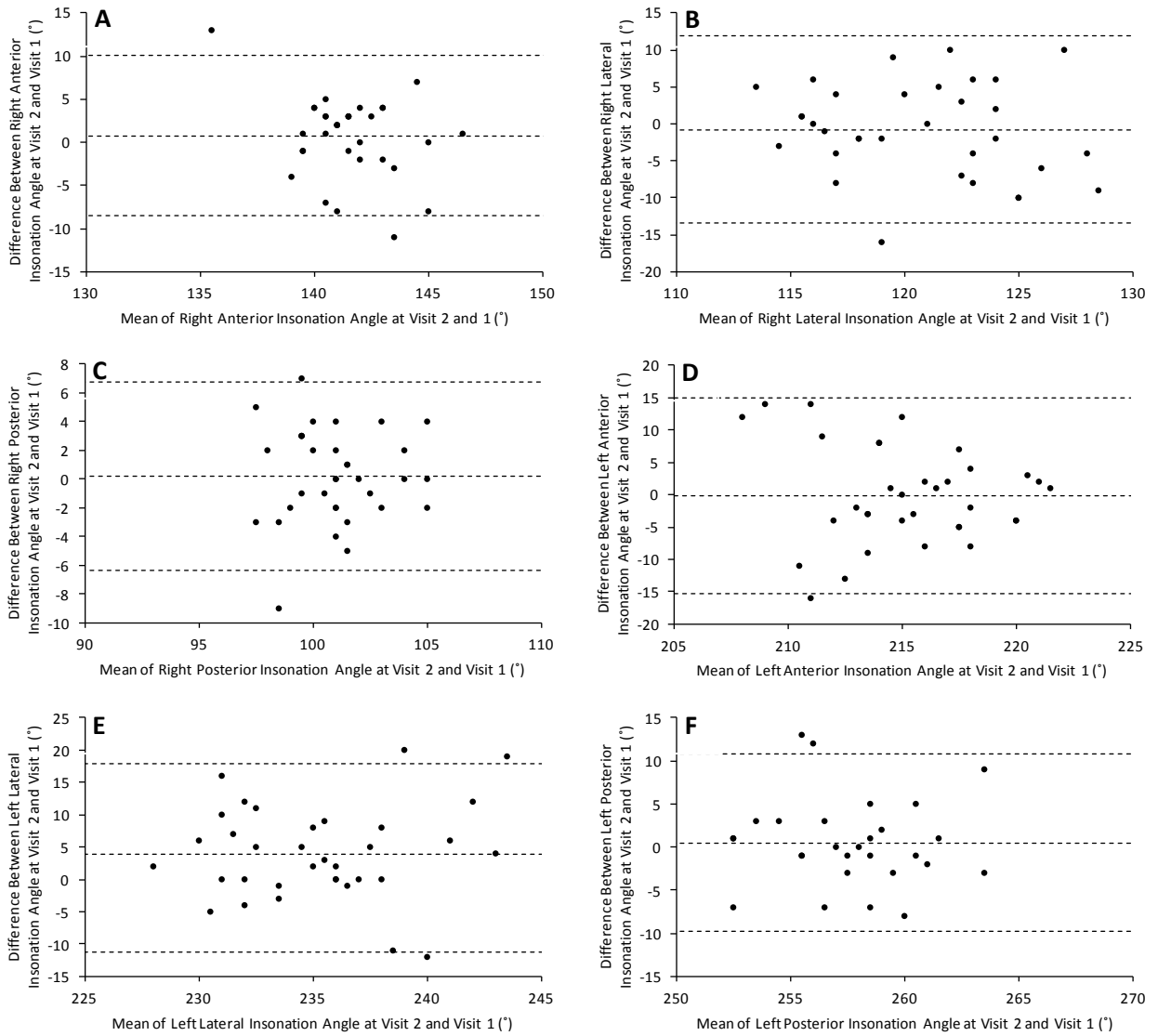
Figure 4 –Agreement between right anterior (A), right lateral (B), right posterior (C), left anterior (D), left lateral (E) and left posterior (F) insonation angles for visit 1 and 2. Panel E shows a significant mean bias of 4.0˚ (p=0.003).

5.4.6   C-IMT Changes Following Cardiac Rehabilitation

Table 7 shows the median change in mean C-IMT between visit 1 and 2. The CG experienced a significant mean C-IMT increase in the right lateral aspect (median change: 0.070 mm; range -0.060 to 0.200 mm; p=0.038). All other mean C-IMT measurements between visit 1 and 2 remained unchanged in both groups. There were no changes in max C-IMT at visit 2 in either group (Table 8). The TG significantly reduced mean C-IMT between visit 1 and 3 in the left lateral aspects (Table 8; p=0.032). Non-parametric post-hoc analysis (Wilcoxon signed ranks test) demonstrated that differences occurred between visit 2 and 3 (median change: -0.054 mm; range -0.160 to 0.020 mm; p=0.015). All other changes to mean and max C-IMT at 12 months were not significant (Table 9 and 10).

Table 7 – Median change in mean C-IMT between visit 1 and 2 (range)

Insonation Angle	Training Group			Control Group		
	Visit 1 C-IMT (mm)	Visit 2 C-IMT (mm)	Median Change	Visit 1 C-IMT (mm)	Visit 2 C-IMT (mm)	Mean Change
Right Anterior	0.719 (0.511 to 1.160)	0.755 (0.422 to 1.328)	-0.014 (-0.230 to 0.350; p=0.426)	0.704 (0.531 to 1.130)	0.718 (0.660 to 1.120)	0.027 (-0.400 to 0.310; p=0.583)
Right Lateral	0.737 (0.467 to 1.626)	0.759 (0.520 to 1.635)	-0.002 (-0.290 to 0.190; p=0.414)	0.674 (0.540 to 1.122)	0.698 (0.565 to 1.198)	0.070 (-0.060 to 0.200; p=0.038)*
Right Posterior	0.766 (0.497 to 1.322)	0.717 (0.495 to 1.501)	-0.004 (-0.460 to 0.180; p=0.506)	0.675 (0.501 to 1.209)	0.622 (0.523 to 1.217)	0.015 (-0.090 to 0.230; p=0.410)
Mean of Right CCA	-0.752 (0.500 to 1.360)	0.763 (0.480 to 1.490)	-0.004 (-0.320 to 0.160; p=0.709)	0.657 (0.540 to 1.150)	0.663 (0.590 to 1.100)	0.029 (-0.100 to 0.200; p=0.183)
Left Anterior	0.812 (0.522 to 1.005)	0.863 (0.515 to 1.404)	0.011 (-0.110 to 400; p=0.211)	0.745 (0.442 to 1.200)	0.703 (0.583 to 1.226)	-0.017 (-0.140 to 0.290; p=0.695)
Left Lateral	0.741 (0.451 to 1.139)	0.734 (0.498 to 1.365)	0.043 (-0.210 to 0.350; p=0.140)	0.729 (0.522 to 1.221)	0.755 (0.537 to 1.160)	-0.038 (-0.280 to 0.260; p=0.638)
Left Posterior	0.759 (0.559 to 1.283)	0.763 (0.514 to 1.172)	-0.019 (-0.330 to 0.300; p=0.795)	0.739 (0.519 to 0.983)	0.723 (0.516 to 1.278)	0.085 (-0.150 to 0.300; p=0.075)
Mean of Left CCA	0.761 (0.520 to 1.100)	0.769 (0.530 to 1.310)	0.016 (-0.100 to 0.210; p=0.158)	0.733 (0.490 to 1.110)	0.713 (0.610 to 1.170)	0.022 (-0.100 to 0.160; p=0.433)

C-IMT = Carotid Intima-Media Thickness; mm = millimetres; CCA = Common Carotid Artery

* = Significant Difference; † = Significant Difference between Paired Variables

Table 8 – Median change in maximum C-IMT between visit 1 and 2 (range)

Insonation Angle	Training Group Median-Max C-IMT (Range)			Control Group Median-Max C-IMT (Range)		
	Visit 1 C-IMT (mm)	Visit 2 C-IMT (mm)	Median Change	Visit 1 C-IMT (mm)	Visit 2 C-IMT (mm)	Median Change
Right Anterior	0.865 (0.550 to 1.780)	0.890 (0.500 to 1.424)	-0.025 (-0.780 to 0.190; p=0.296)	0.845 (0.610 to 1.200)	0.830 (0.660 to 1.120)	-0.045 (-0.190 to 0.160; p=0.609)
Right Lateral	0.850 (0.540 to 1.850)	0.860 (0.620 to 1.850)	0.039 (-0.380 to 0.360; p=0.513)	0.800 (0.580 to 1.230)	0.840 (0.654 to 1.460)	0.080 (-0.090 to 0.300; p=0.071)
Right Posterior	0.825 (0.580 to 1.540)	0.850 (0.610 to 1.925)	0.035 (-0.350 to 0.390; p=0.149)	0.825 (0.539 to 1.280)	0.795 (0.580 to 1.500)	0.035 (-0.110 to 0.380; p=0.272)
Mean of Right CCA	0.887 (0.580 to 1.570)	0.942 (0.580 to 1.730)	0.001 (-0.270 to 0.170; p=0.709)	0.785 (0.590 to 1.240)	0.802 (0.690 to 1.360)	0.032 (-0.060 to 0.200; p=0.071)
Left Anterior	0.930 (0.577 to 1.270)	1.000 (0.580 to 1.580)	0.040 (-0.230 to 0.430; p=0.053)	0.910 (0.540 to 1.350)	0.920 (0.710 to 1.770)	0.010 (-0.430 to 0.430; p=0.906)
Left Lateral	0.850 (0.540 to 1.390)	0.875 (0.620 to 1.580)	0.079 (-0.300 to 0.270; p=0.092)	0.890 (0.610 to 1.310)	0.905 (0.620 to 1.270)	-0.050 (-0.380 to 0.300; p=0.906)
Left Posterior	0.825 (0.660 to 1.810)	0.920 (0.580 to 1.310)	0.030 (-0.500 to 1.080; p=0.965)	0.870 (0.630 to 1.240)	0.840 (0.580 to 1.420)	0.080 (-0.240 to 0.310; p=0.213)
Mean of Left CCA	0.840 (0.510 to 1.450)	0.930 (0.640 to 1.490)	0.038 (-0.190 to 0.450; p=0.114)	0.900 (0.590 to 1.290)	0.836 (0.710 to 1.460)	-0.011 (-0.140 to 0.200; p=0.583)

C-IMT = Carotid Intima-Media Thickness; mm = millimetres; CCA = Common Carotid Artery

* = Significant Difference; † = Significant Difference between Paired Variables

Table 9 – Median change in mean C-IMT between visit 1 and 3 (range)

Insonation Angle	Training Group Mean C-IMT				Control Group Mean C-IMT (*n* =1)			
	Visit 1 C-IMT (mm)	Visit 2 C-IMT (mm)	Visit 3 C-IMT (mm)	Post Intevention Change	Visit 1 C-IMT (mm)	Visit 2 C-IMT (mm)	Visit 3 C-IMT (mm)	Post Intevention Change
Right Anterior	0.626 (0.512 to 0.859)	0.743 (0.537 to 0.979)	0.662 (0.500 to 1.072)	-0.012 (-0.130 to 0.350; p=0.895)	0.699	0.781	0.717	0.018
Right Lateral	0.777 (0.526 to 1.128)	0.850 (0.660 to 0.850)	0.741 (0.430 to 0.873)	-0.060 (-0.250 to 0.170; p=0.717)	0.706	0.810	0.797	0.091
Right Posterior	0.692 (0.497 to 1.000)	0.800 (0.548 to 0.855)	0.655 (0.500 to 0.910)	-0.021 (-0.330 to 0.060; p=0.641)	0.840	0.866	0.929	0.089
Mean of Right CCA	0.734 (0.520 to 0.980)	0.801 (0.550 to 0.890)	0.669 (0.480 to 0.840)	-0.027 (-0.140 to 0.120; p=0.641)	0.748	0.819	0.814	0.066
Left Anterior	0.827 (0.522 to 0.941)	0.871 (0.515 to 0.927)	0.692 (0.491 to 0.914)	-0.031 (-0.300 to 0.040; p=0.236)	0.855	0.845	0.875	0.020
Left Lateral	0.715 (0.479 to 0.834)	0.685 (0.516 to 0.909)†	0.633 (0.462 to 0.815)†	-0.017 (-0.160 to 0.020; p=0.032)*	0.723	0.984	0.875	0.152
Left Posterior	0.756 (0.559 to 0.961)	0.642 (0.514 to 0.917)	0.682 (0.506 to 0.807)	-0.053 (-0.170 to 0.070; p=0.687)	0.853	0.701	0.958	0.105
Mean of Left CCA	0.777 (0.520 to 0.890)	0.792 (0.530 to 0.880)	0.687 (0.490 to 0.790)	-0.034 (-0.200 to 0.020; p=0.607)	0.810	0.843	0.903	0.093

C-IMT = Carotid Intima-Media Thickness; mm = millimetres; CCA = Common Carotid Artery

* = Significant Difference

Table 10 – Median change in maximum C-IMT between visit 1 and 3 (range)

Insonation Angle	Training Group Max C-IMT				Control Group Max C-IMT (*n* =1)			
	Visit 1 C-IMT (mm)	Visit 2 C-IMT (mm)	Visit 3 C-IMT (mm)	Post Intevention Change	Visit 1 C-IMT (mm)	Visit 2 C-IMT (mm)	Visit 3 C-IMT (mm)	Post Intevention Change
Right Anterior	0.851 (0.580 to 1.080)	0.930 (0.580 to 1.080)	0.770 (0.580 to 1.280)	-0.080 (-0.270 to 0.430; p=0.639)	0.880	0.960	0.770	-0.110
Right Lateral	0.880 (0.620 to 1.230)	0.850 (0.660 to 1.200)	0.970 (0.580 to 1.040)	-0.040 (-0.260 to 0.380; p=1.00)	0.960	1.000	1.000	0.040
Right Posterior	0.780 (0.580 to 1.130)	0.850 (0.650 to 1.190)	0.770 (0.540 to 1.040)	-0.050 (-0.170 to 0.230; p=0.175)	0.970	0.920	1.040	0.070
Mean of Right CCA	0.890 (0.610 to 1.120)	0.993 (0.660 to 1.060)	0.812 (0.567 to 1.070)	-0.037 (-0.060 to 0.160; p=0.417)	0.937	0.960	0.937	0.000
Left Anterior	1.00 (0.577 to 1.120)	1.040 (0.580 to 1.070)	0.810 (0.540 to 1.120)	-0.001 (-0.390 to 0.110 ; p=0.341)	1.040	0.962	0.930	-0.110
Left Lateral	0.810 (0.0.540 to 1.040)	0.810 (0.620 to 1.030)	0.700 (0.540 to 0.950)	-0.030 (-0.350 to 0.070; p=0.121)	0.810	1.110	0.906	0.096
Left Posterior	0.847 (0.660 to 1.190)	0.730 (0.580 to 1.040)	0.850 (0.540 to 1.000)	-0.040 (-0.340 to 0.150; p=0.772)	1.120	0.880	1.150	0.030
Mean of Left CCA	0.899 (0.590 to 1.080)	0.920 (0.640 to 0.980)	0.808 (0.540 to 0.950)	-0.033 (-0.140 to 0.080; p=0.223)	0.990	0.984	0.995	0.005

Max = Maximum; C-IMT = Carotid Intima-Media Thickness; mm = millimetres; CCA = Common Carotid Artery

5.4.7 Changes in C-IMT progression Rate

The progression rate of right (TG median change: -0.004mm [-0.01%]; range -0.320 to 0.160mm; CG median change: 0.029mm [0.04%]; range -0.100 to 0.200mm; p=0.182) and left (Figure 5A; TG median change: 0.016mm [0.02%]; range -0.100 to 0.210mm; CG median change: 0.022mm [0.03%]; range -0.100 to 0.160mm; p=0.885) pooled-mean C-IMT (anterior, lateral and posterior) did not differ by group between visit 1 and 2. No mean C-IMT progression rate differences were detected for individual angles of insonation either (Figure 5A). P-values are shown in Appendix 4, Table 1. The pooled-max C-IMT progression rate in right (TG median change: 0.001mm [<0.01%]; range 0.270 to 0.170mm; CG median change: 0.032mm [0.04%]; range 0.060 to 0.200mm; p=0.367) and left CCA (Figure 5B; TG median change: 0.038mm [0.04%]; range 0.190 to 0.450mm; CG median change: -0.011mm [-0.01%); range 0.140 to 0.200mm; p=0.719) did not differ. No significant between group max C-IMT progression rate differences were detected for individual angles of insonation (Appendix 4, Table 2).

5.4.8 Association of C-IMT with Cardiovascular Risk Factors

Correlation strengths for mean and max C-IMT are reported in Table 11 and 12 respectively. A full list of correlation p-values are reported in Appendix 5, Tables 1 and 2. Only figures for mean C-IMT are displayed. The pooled-mean C-IMT for the right CCA was positively associated with age (Figure 6A; r^2=22.4; r=0.473; p=0.005). Individually, mean C-IMT was associated with age in the right anterior (r^2=26.8; r=0.518; p=0.002), lateral (r^2=23.9; r=0.489; p=0.004) and posterior aspects (r^2=12.7; r=0.356; p=0.039). In the left CCA, age was only correlated with mean anterior C-IMT (Figure 7; r^2=11.6; r=0.340; p=0.009). Pooled-max right C-IMT was associated with age (r^2=22.5; r=0.474; p=0.005) as was max C-IMT in the right anterior (r^2= 31.9; r=0.565; p=0.001) and lateral aspects (r^2=31.9; r=0.565; p=0.002).
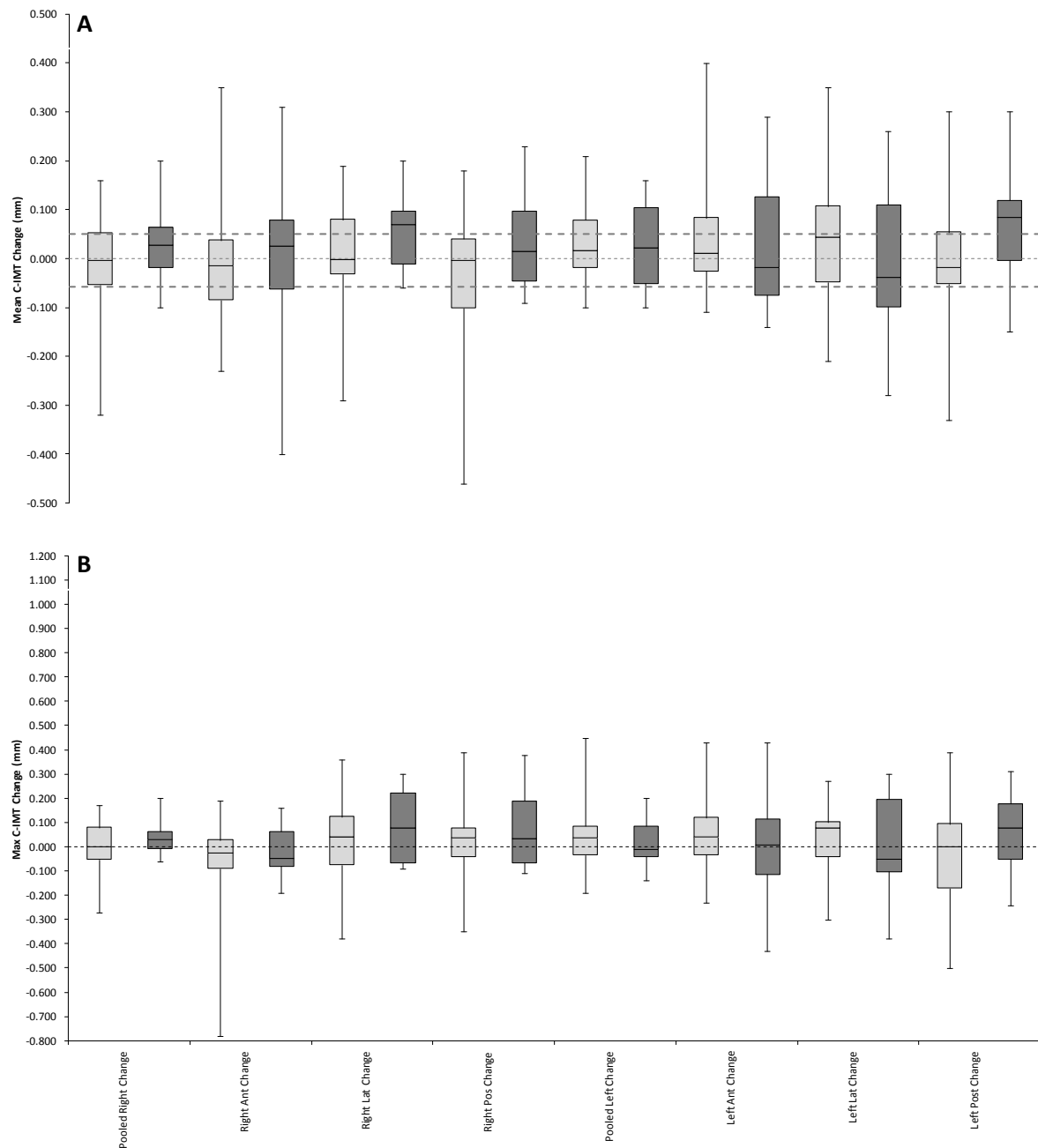
Figure 5 – Box-plot 'A' shows median (IQR and range) mean C-IMT progression rate differences between the TG (light grey) and CG (dark grey) between visits 1 and 2. 'Pooled' change is the mean of C-IMT measurements taken from either the right of left CCA. Grey dashed line (middle line) indicates measurement variability (LoA) defined by Nichols et al. (2014c). Box-plot 'B' shows median (IQR and range) differences in maximum C-IMT progression rates. LoA for maximum C-IMT change have not been published.

C-IMT = Carotid Intima-Media Thickness; mm = Millimetres; Pos = Posterior; Lat = Lateral; Ant = Anterior; IQR = Interquartile Range; TG = Training Group; CCA = Common Carotid Artery; LoA = Limits of Agreement

Table 11 – Association (r) between cardiovascular risk factors and mean C-IMT at different insonation angles

Cardiovascular Risk Factor	Angle of Insonation							
	Right Anterior	Right Lateral	Right Posterior	Pooled Right Side C-IMT	Left Anterior	Left Lateral	Left Posterior	Pooled Left Side C-IMT
Age (Years)	0.518*	0.489*	0.356*	0.473*	0.340*	0.144	0.152	0.266
BMI (Kg·m^{-2})	-0.306	-0.142	-0.108	0.266	-0.073	-0.138	0.016	-0.119
Waist Circumference (cm)	-0.195	-0.003	-0.019	-0.075	0.023	0.059	0.104	0.017
W/H Ratio	-0.044	0.076	0.163	0.070	0.137	0.018	0.077	0.046
Total Body Fat (%)	-0.165	-0.018	-0.141	-0.126	0.083	0.104	0.242	0.098
Android Body Fat (%)	-0.306	-0.177	-0.228	-0.257	-0.045	0.023	0.141	-0.008
VO$_{2peak}$ (ml·kg^{-1}·min^{-1})	-0.188	-0.193	0.009	-0.132	-0.313	-0.429*	-0.405*	-0.393*
Peak METs	-0.137	-0.156	-0.108	-0.074	-0.253	-0.277	-0.357*	-0.308
SBP (mmHg)	0.150	0.287	0.177	0.226	0.072	-0.038	-0.007	0.045
DBP (mmHg)	0.099	0.130	0.138	0.122	0.115	-0.075	-0.110	-0.010

BMI = Body Mass Index; C-IMT= Carotid Intima-Media thickness; Kg·m^{-2}= Kilograms per Metre squared; cm = centimetres; W/H Ratio = Waist to Hip Ratio; VO$_{2peak}$ = Peak O$_2$ uptake; METs = Metabolic Equivalents;

SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; mmHg = Millimetres of Mercury

* = Significant Correlation

Table 12 – Association (r) between cardiovascular risk factors and maximum C-IMT at different insonation angles

Cardiovascular Risk Factor	Angle of Insonation							
	Right Anterior	Right Lateral	Right Posterior	Pooled Right Side C-IMT	Left Anterior	Left Lateral	Left Posterior	Pooled Left Side C-IMT
Age (Years)	0.565*	0.565*	0.303	0.474*	0.306	0.055	0.072	0.097
BMI (Kg·m^{-2})	-0.240	-0.133	-0.114	-0.193	-0.015	-0.082	0.009	-0.025
Waist Circumference (cm)	-0.165	-0.043	-0.017	-0.093	0.138	0.100	0.141	0.177
W/H Ratio	-0.003	0.011	0.148	0.060	0.171	0.017	0.106	0.157
Total Body Fat (%)	-0.168	-0.033	-0.154	-0.140	0.098	0.116	0.177	0.133
Android Body Fat (%)	-0.310	-0.182	-0.212	0.254	-0.006	-0.058	-0.091	0.052
VO$_{2peak}$ (ml·kg^{-1}·min^{-1})	-0.191	-0.166	-0.034	-0.135	-0.290	-0.383*	-0.311	-0.327
Peak METs	-0.153	-0.170	0.068	-0.071	-0.179	-0.292	-0.283	-0.272
SBP (mmHg)	0.177	0.327	0.208	0.227	0.111	0.031	-0.031	0.013
DBP (mmHg)	0.072	0.134	0.111	0.099	0.095	-0.137	-0.164	-0.092

BMI = Body Mass Index; C-IMT= Carotid Intima-Media thickness; Kg·m^{-2}= Kilograms per Metre squared; cm = centimetres; W/H Ratio = Waist to Hip Ratio; VO$_{2peak}$ = Peak O$_2$ uptake; METs = Metabolic Equivalents;

SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; mmHg = Millimetres of Mercury
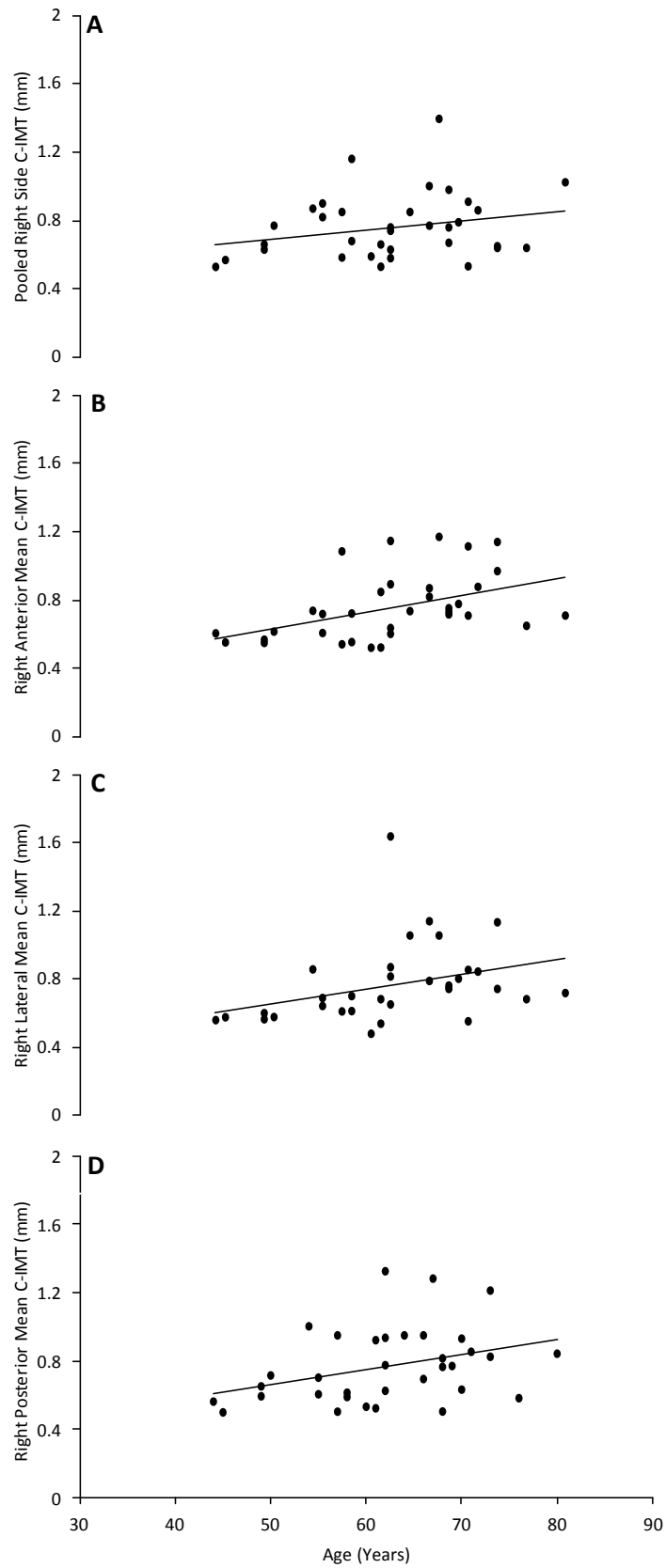
* = Significant Correlation

Figure 6 – Significant positive correlations between age and C-IMT for pooled right sided C-IMT measurements (A) as well as in the right anterior (B), lateral (C) and posterior (D) aspects.

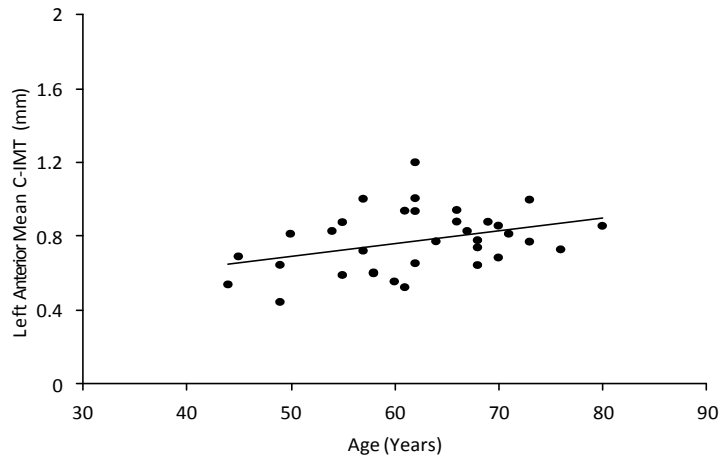C-IMT = Carotid Intima-Media Thickness; mm = Millimetres

Figure 7 – Significant positive correlations between age and C-IMT in the left anterior aspect.

C-IMT = Carotid Intima-Media Thickness; mm = Millimetres

VO_{2peak} was negatively correlated with pooled-left sided mean C-IMT measurements (Figure 8A; r^2=15.4; r=-0.393; p=0.021) as well as mean left lateral (Figure 8B; r^2=18.4; r=-0.429; p=0.011) and posterior C-IMT (Figure 8C; r^2=16.4; r=-0.405; p=0.021). VO_{2peak} was correlated with max C-IMT in the left lateral aspect only (r^2=14.7; r=-0.383; p=0.025). Peaks MET's were negatively correlated with mean C-IMT in the left posterior aspect (Figure 9; r^2=12.74; r=-0.357; p=0.045). When partial correlations were conducted to control for the effect of age on the apparent association between VO_{2peak} and C-IMT, correlations only remained significant for mean C-IMT in left lateral aspect (r^2=16.0; r=-0.400; p=0.028) and max C-IMT in the right lateral aspect only (r^2=17.5; r=-0.418; p=0.021). No significant correlations were noted between mean or max C-IMT and other standard CV risk factors including BMI, waist circumference, waist to hip ratio, total body fat percentage, android body fat percentage or resting BP.

5.5 Discussion

Our data shows that short-term low to moderate intensity UK CR exercise training does not reduce/improve C-IMT or attenuate its progression (visit 1 to 2). However, in controls, mean C-IMT significantly increased in the right lateral aspects during the intervention period. Mean C-

IMT showed some evidence of regression between visits 2 and 3 (8 to 52 weeks) in the left lateral aspect for patients in the training intervention. Failure to participate in the exercise component of CR may lead to faster C-IMT progression in the short-term.
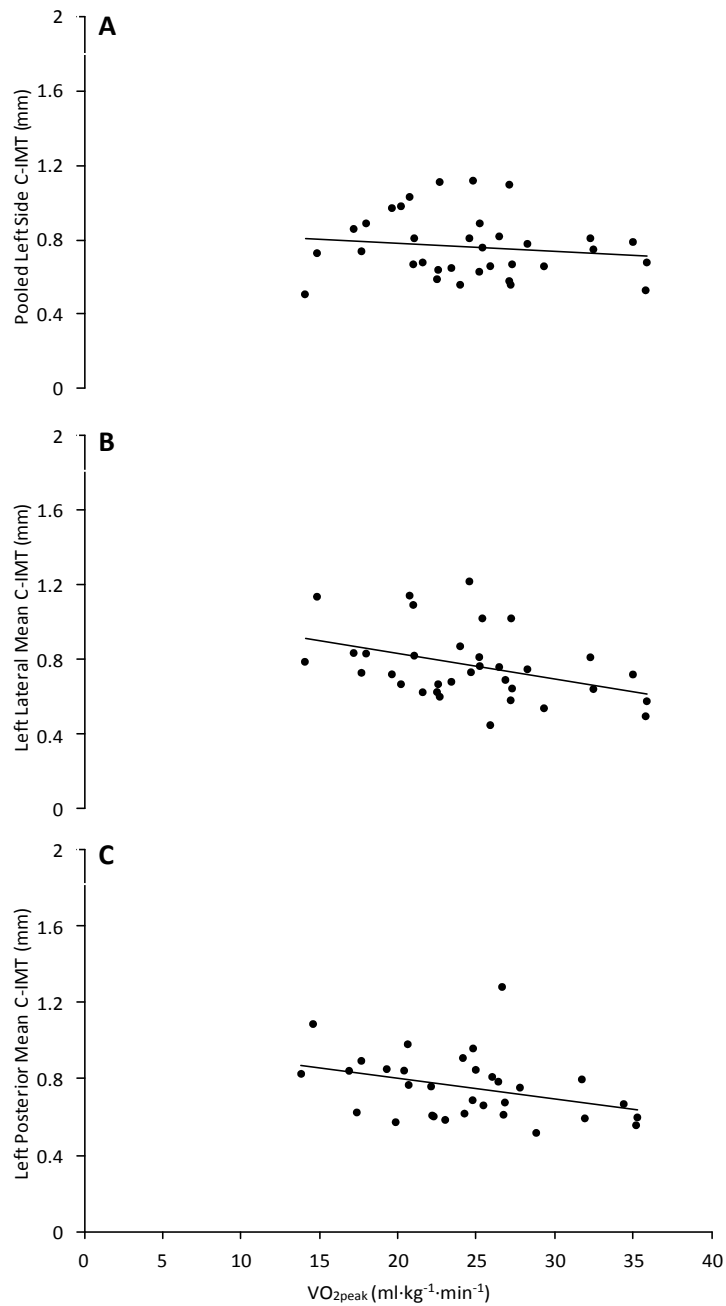

Figure 8 – Significant correlations between VO_{2peak} and pooled mean C-IMT (A) as well as left lateral (B) and posterior (C) C-IMT measurements

C-IMT = Carotid Intima-Media Thickness; mm = Millimetres; VO_{2peak} = Peak O_2 Uptake
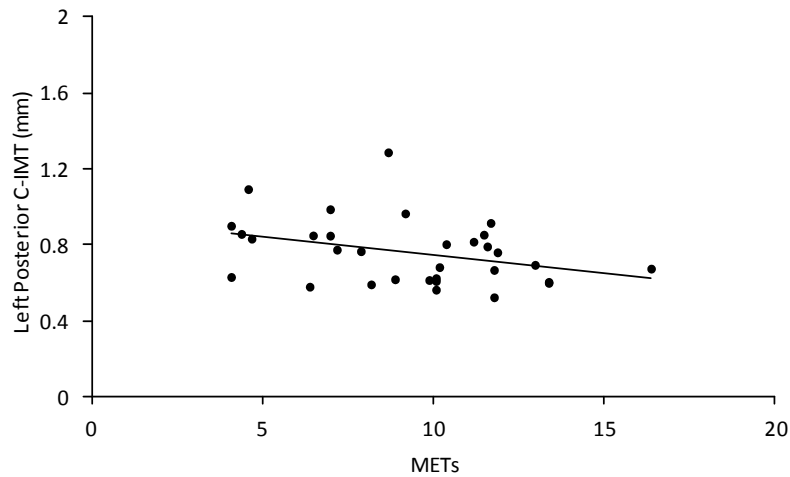
Figure 9 – Significant correlations between Peak METs and mean C-IMT in the left posterior aspect.

Conversely, patients participating in exercise based CR may experience C-IMT reduction in the longer-term. The increase in C-IMT observed in the CG between visit 1 and 2 may have resulted from poor adherence to secondary prevention advice. Whilst the dose of exercise prescribed in a routine CR exercise class appears inadequate to reduce C-IMT, reinforcement of secondary prevention advice during exercise classes may reduce the risk of atherosclerotic progression. The C-IMT reduction in the TG at visit 3 may also have resulted from positive behaviour changes in patients involved in exercise training, however, this could not be compared with usual care. Comprehensive lifestyle interventions and CV risk factor reduction *have* been shown to attenuate C-IMT and CHD progression (Kim et al., 2006, Okada et al., 2004, Hambrecht et al., 2004). Whilst it initially seems illogical that exercise training might only affect C-IMT progression at specific angles of insonation as seen in our study, the observation that C-IMT appears to progress at different rates in different arterial segments irrespective of whether measurements are derived from autopsy (Solberg and Eggen, 1971) or B-mode ultrasounds (Tajik et al., 2012) makes it reasonable to infer that C-IMT might also regress in such a manner. Alternatively, the cumulative effect of UK CR may simply be insufficient to meaningfully affect C-IMT.

Adequate exercise dose is needed for coronary atherosclerosis regression, as determined by angiography (Hambrecht et al., 2004, Niebauer et al., 1997), and the same may be true for C-

IMT. Studies demonstrating change in coronary or carotid plaque dimensions (Hambrecht et al., 2004, Feairheller et al., 2014, Sato et al., 2008, Niebauer et al., 1997) typically used longer or more intense exercise regimes than used in the present study and, by most UK CR programmes (ACPICR, 2015). The finding that C-IMT was not reduced followed exercise training suggests that the exercise dose was insufficient to affect atherosclerotic phenotype. Feairheller et al. (2014) showed that six months of exercise training was needed to significantly reduce the mean of six bilateral C-IMT measurements (6.4%) in African American men (*n*=5) and women (*n*=21) with CV risk factors including hypertension, hyperlipidemia and obesity. Conversely Tanaka et al. (2002) found that a shorter three month exercise training programme did not reduce C-IMT in apparently healthy men. Our findings support the work of Tanaka et al. (2002) as far as exercise training regimes of short duration do not appear to reduce C-IMT. However, Tanaka et al. (2002) did not investigate mean C-IMT progression rate differences between exercisers and non-exercises. Our finding that controls experienced a significant increase in right lateral C-IMT between visits 1 and 2, when patients in the TG did not supports the hypothesis that shorter-term regimes may attenuate C-IMT progression. However, as with C-IMT regression, studies of longer duration have reported more compelling effects. (Kim et al., 2006, Okada et al., 2004). This may be because C-IMT regression requires substantive improvements to CV risk factor status.

C-IMT progression, as with any other atherosclerotic phenotype is associated with prolonged exposure to CV risk factors (Libby and Theroux, 2005). A higher proportion of CG patients were active smokers (CG: 25.0%; TG 0.0%) and, diagnosed with T2DM (CG: 58.3%; 13.6%) which may account for the apparent faster C-IMT progression between visit 1 and 2, when compared to the TG. It seems likely that C-IMT reduction may therefore be predicated on CV risk factor improvement. A 12 month course of Simvastatin has been shown to reduce plaque plus media thickness (6.3%) with concurrent reductions in total cholesterol (30.0%) and LDL cholesterol [42.6%] (Jensen et al., 2004). Haskell et al. (1994) investigated the effects of intensive CV risk factor modification (four year follow-up) in a sample of *n*=300 men (86%) and women with

angiographically defined CHD. Reductions in LDL cholesterol, triglycerides, body weight and, improvements in HDL cholesterol and exercise capacity (METs) were associated with a slower rate of coronary atherosclerosis progression (47%) compared to usual-care. Similar findings were demonstrated by Niebauer et al. (1997) over a six year follow-up period. The limited number of studies demonstrating the beneficial effect of exercise training on C-IMT progression also shows concurrent improvement in CV risk factors. Feairheller et al. (2014) showed that C-IMT improved simultaneously with VO_{2peak}, triglycerides, BMI and plasma glucose, whilst Okada et al. (2004) demonstrated significant reductions in total cholesterol, low-density lipoproteins and, a significant increase in high-density lipoproteins. To the author's knowledge, no study has conducted analysis on the relative contributions of CV risk factor reduction on C-IMT progression rate following exercise training. However, it is reasonable to suggest CV risk factor reduction plays a pivotal role in C-IMT regulation.

Long-term changes to CV risk factor profiles (West et al., 2012) and short-term improvements in CRF following UK CR have been shown to be inadequate (Sandercock et al., 2013b). Variability in UK CR provision (Brodie et al., 2006) however *does* make it possible that the CR programme in this study provided more effective exercise training and/or secondary prevention initiatives than reported by West et al. (2012) and Sandercock et al. (2013b). Indeed, Chapter 3 demonstrated that following CR, MET change amongst training group patients was twice that recently documented by Sandercock et al. (2013b). If patients adhere to such a training programme, substantial CV risk factor modification is possible (Carroll et al., 2011). Our finding that mean C-IMT was significantly reduced in the left lateral aspect in the TG at visit 3 (median reduction -0.054mm), but not visit 2, suggests that patients in the TG may have adhered to their secondary prevention advice. Over longer time periods, C-IMT progression may have reduced or even reversed. However whilst it is conceivable that our CR programme had a lasting positive impact on CV risk health in the longer-term, it should be considered that this finding may have been incidental.

The mean C-IMT reduction in the TG between visits 2 and 3 (-0.054mm) did not exceed the

lower test-retest LoA (-0.057 mm) reported by Nichols et al. (2014c) in a healthy cohort of 18-40 year olds. In addition C-IMT change was restricted to a single insonation angle. Consequently, the detected 'significant' change may have been a 'false positive'. Because C- IMT did not exceed measurement error, it is not possible to confidently state that TG C-IMT was reduced. Conversely however, mean C-IMT increase in the lateral aspect of the right CCA in the controls between visits 1 and 2 exceeded the upper test-retest LoA (0.050 mm), as did left posterior mean C-IMT increase (Table 7). Although this latter measurement fell short of statistical significance (p=0.075) it does indicate a tendency for CG mean C-IMT to advance at a faster rate than in the TG. The failure of C-IMT change in the left posterior aspect to reach statistical significance may be due to study under powering. C-IMT measurement variability may necessitate greater participant numbers to detect statistically significant changes. The majority of studies discussed in this report recruited more than 40 participants. Taylor et al. (2005) reported that 100-200 participants may be required to show C-IMT progression rate differences. Evidence that the present study was underpowered can also be found by virtue of statistical tests failing to find significant differences between left and right C-IMT and, C-IMT at different insonation angles. Despite the findings of Chaubey et al. (2010) who reported that hypertension may reduce the differences between left and right C-IMT, inhomogeneous C-IMT distribution and left versus right sided C-IMT differences are established physiological phenomena (Tajik et al., 2012, Touboul et al., 2012).

5.5.1 C-IMT and Cardiovascular Risk Factors

The present study demonstrates that mean C-IMT was associated with age, VO_{2peak} and to a lesser extent, METs. Age was associated with mean C-IMT in all right CCA angles and, with the left CCA at the anterior aspect. Advancing age conferred greater mean C-IMT values. The weaker association of age with left C-IMT may be due to the preferential and cumulative effects that multiple modifiable CV risk factors appear to have on specific carotid segments,

(Taylor et al., 2005, Chaubey et al., 2010). Both left and right CCA's are subjected to regions of oscillatory and, low endothelial shear stress which accelerate endothelial damage and atherogenesis (Chatzizis et al., 2007). However, the left CCA appears uniquely susceptible to the effects of poor CV risk factor profiles (Kollias et al., 2010). This may in part be attributable to anatomical differences between the two arteries. The left CCA originates at the aortic arch whereas the right originates at the subclavian artery. Higher haemodynamic pressures from the aortic arch could lead to greater exposure to the effects of hypertension. Because hypertension initiates endothelial damage (Perticone et al., 2001) the left CCA may have greater susceptibility to the other CV risk factors such as dyslipidaemia which lead to atherogenesis. Our finding that mean C-IMT is inversely related to VO_{2peak} (and METs) in the left CCA may reflect the cardioprotective effect of a higher VO_{2peak} (Kodama et al., 2009). Conversely, the lack of association between VO_{2peak} in the right CCA and, the stronger association with age may reflect the right's lower exposure to CV risk factors. VO_{2peak} may influence C-IMT progression in the left CCA more than the right. Interestingly however, the present study failed to document a significant association between a number of CV risk factors and C-IMT. Of particular note is the lack of association between BP and C-IMT.

The lack of association between BP and C-IMT may be because a number of CV risk factors are thought to have a diminished relevance to CHD with advancing age. Abbott and colleagues (2002) reported a dissociation between hypertension and C-IMT. Although contested, (Pursnani et al., 2014), hypertension (and other CV risk factors) has been shown to have greater relevance to CHD incidence in younger individuals aged 45 to 54 (Abbott et al., 2002). The mean age of participants in our study was 62.1 ± 8.8 years. Alternatively, anti-hypertensive medication initiated following CHD diagnosis may have diminished the relationship between BP and C-IMT. BP at the time of recruitment is unlikely to be indicative of lifetime exposure to high BP. BP prior to recruitment is likely to have been somewhat higher than that documented at the time of recruitment.

5.6 Conclusions

A 'standard' eight week (16 sessions) low to moderate intensity, UK CR exercise training programme does not reduce C-IMT in the short term. There is limited data to suggest that C-IMT progression may advance at a faster rate when patients do not fully participate in a CR programme and its multivariate approach to CV risk factor modification. In the longer-term (visit 3), patients in the TG appear to experience a reduction in C-IMT. However, this is currently based on relatively weak evidence limited to one insonation angle. Moreover C-IMT change did not appear to exceed reported measurement variability. Further testing is needed before firm conclusions regarding the longer-term effects of UK CR exercise training on C-IMT can be drawn. Finally, VO_{2peak} was associated with left mean C-IMT but not right. Prior physical activity levels (as a determinant of current aerobic fitness) may be an important contributor in attenuating mean C-IMT progression by virtue of improved CV risk factors. VO_{2peak} appears to have a stronger relationship to left sided C-IMT it may be most relevant in assessing the effects of therapeutic strategies on C-IMT.

5.7 Limitations

The primary limitation of this study was the small sample size. C-IMT measurement variability may necessitate larger study numbers to generate a significant training response. Studies showing significant changes to C-IMT have typically used larger sample sizes (Sato et al., 2008, Kim et al., 2006, Okada et al., 2004). It is likely that findings such as the absence of a significant difference between right and left sided C-IMT and, the absence of a non-uniform C-IMT distribution reflects study under powering. Such physiological observations area now accepted 'norms' (Tajik et al., 2012, Touboul et al., 2012). If the present study is under powered to detect established C-IMT patterns our ability to detect a C-IMT exercise training response is likely to be limited too.

Finally, whilst the reporting of measurement variability is advocated (Bland and Altman, 1999) the application of LoA to determine whether a treatment response exceeds measurement variability is not frequently reported. We have applied LoA to attempt to distinguish a 'true' training response. It is important to note that these LoA were derived from a study reporting on healthy individuals, not patients with CHD (Nichols et al., 2014c). However, the Nichols et al. (2014c) investigation is the only study to publish LoA for intra-operator variability using the CHS. Although Vanoli et al. (2013b) have reported LoA for novice operators in CHD populations, LoA data was limited to inter-operator agreement. A further limitation of applying the LoA reported by Nichols et al. (2014c) is their variability data are for 7-day follow-up only. This may not reflect measurement variability over our 8 to 10 week and, 12 month follow up period.

5.8   References

Abbott, R. D., Curb, J. D., Rodriguez, B. L., Masaki, K. H., Yano, K., Schatz, I. J., . . . Petrovitch, H. (2002). Age-related changes in risk factor effects on the incidence of coronary heart disease. *Annals of epidemiology, 12*(3), 173-181.

ACPICR. (2015). Standards for physical activity and exercise in the cardiovascular population. In P. Heather, B. Helen, B. Samantha, B. John, Laura Burgess, G. Keri, G. Fiona, Tim Grove, Sally Turner & W. Catrin (Eds.), (3rd ed.): Association of Chartered Physiotherapists in Cardiac Rehabilitation (ACPICR).

Amato, M., Montorsi, P., Ravani, A., Oldani, E., Galli, S., Ravagnani, P. M., . . . Baldassarre, D. (2007). Carotid intima-media thickness by B-mode ultrasound as surrogate of coronary atherosclerosis: correlation with quantitative coronary angiography and coronary intravascular ultrasound findings. *European Heart Journal, 28*(17), 2094-2101. doi: 10.1093/eurheartj/ehm244

Atkinson, G., & Nevill, A. (1998). Statistical Methods For Assessing Measurement Error (Reliability) in Variables Relevant to Sports Medicine. *Sports Medicine, 26*(4), 217-238. doi: 10.2165/00007256-199826040-00002

BACPR. (2012). Standards and Core Components for Cardiovascular Disease Prevention and Rehabilitation. http://www.bacpr.com/resources/

BACR. (2006). *British Association For Cardiac Rehabilitation: Exercise instructor training module* (4th ed.). Leeds: Human Kinetics.

Baldassarre, D., Veglia, F., Hamsten, A., Humphries, S. E., Rauramaa, R., de Faire, U., . . . Mannarino, E. (2013). Progression of carotid intima-media thickness as predictor of vascular events results from the IMPROVE study. *Arteriosclerosis, Thrombosis, and Vascular Biology, 33*(9), 2273-2279. doi: 10.1161/ATVBAHA.113.301844

Berg, K. E., & Latin, R. W. (2008). *Essentials of research methods in health, physical education, exercise science, and recreation*: Lippincott Williams & Wilkins.

Bland, J. M., & Altman, D. G. (1999). Measuring agreement in method comparison studies. *Statistical Methods in Medical Research, 8*(2), 135-160. doi: 10.1177/096228029900800204

Borg, G. A. (1982). Psychophysical bases of perceived exertion. *Medicine and Science in Sports and Exercise, 14*(5), 377-381.

Brodie, D., Bethell, H., & Breen, S. (2006). Cardiac rehabilitation in England: a detailed national survey. *European Journal of Cardiovascular Prevention & Rehabilitation, 13*(1), 122- 128. doi: 10.1097/01.hjr.0000192741.04103.d3

Carroll, S., Tsakirides, C., Hobkirk, J., Moxon, J. W. A., Moxon, J. W. D., Dudfield, M., & Ingle, L. (2011). Differential Improvements in Lipid Profiles and Framingham Recurrent Risk Score in Patients With and Without Diabetes Mellitus Undergoing Long-Term Cardiac Rehabilitation. *Archives of Physical Medicine and Rehabilitation, 92*(9), 1382-1387. doi: 10.1016/j.apmr.2011.04.013

Chatzizisis, Y. S., Coskun, A. U., Jonas, M., Edelman, E. R., Feldman, C. L., & Stone, P. H. (2007). Role of Endothelial Shear Stress in the Natural History of Coronary Atherosclerosis and Vascular RemodelingMolecular, Cellular, and Vascular Behavior. *Journal of the American College of Cardiology, 49*(25), 2379-2393. doi: 10.1016/j.jacc.2007.02.059

Chaubey, S., Nitsch, D., Altmann, D., & Ebrahim, S. (2010). Differing effect of modifiable cardiovascular risk factors on intima-media thickening and plaque formation at different sites of the arterial vasculature. *Heart, 96*(19), 1579-1585. doi: 10.1136/hrt.2009.188219

Department of Health. (2010). *Department of Health's commissioning pack on cardiac rehabilitation*

Feairheller, D. L., Diaz, K. M., Kashem, M. A., Thakkar, S. R., Veerabhadrappa, P., Sturgeon, K. M., . . . Lee, H. (2014). Effects of moderate aerobic exercise training on vascular health and blood pressure in african americans. *The Journal of Clinical Hypertension, 16*(7), 504-510.

Ghasemi, A., & Zahediasl, S. (2012). Normality tests for statistical analysis: a guide for non-statisticians. *International Journal of Endocrinology and Metabolism, 10*(2), 486.

Grundy, S. M., Pasternak, R., Greenland, P., Smith, S., & Fuster, V. (1999). Assessment of Cardiovascular Risk by Use of Multiple-Risk-Factor Assessment Equations: A Statement for Healthcare Professionals From the American Heart Association and the American College of Cardiology. *Circulation, 100*(13), 1481-1492. doi: 10.1161/01.cir.100.13.1481

Hambrecht, R., Walther, C., Möbius-Winkler, S., Gielen, S., Linke, A., Conradi, K., . . . Schuler, G. (2004). Percutaneous Coronary Angioplasty Compared With Exercise Training in Patients With Stable Coronary Artery Disease: A Randomized Trial. *Circulation, 109*(11), 1371-1378. doi:10.1161/01.cir.0000121360.31954.1f

Ingle, L., & Carroll, S. (2013). Cardiac rehabilitation and exercise training. *Heart*. doi: 10.1136/heartjnl-2013-304015

Karvonen, J., & Vuorimaa, T. (1988). Heart rate and exercise intensity during sports activities. *Sports Medicine, 5*(5), 303-311.

Kim, S. H., Lee, S. J., Kang, E. S., Kang, S., Hur, K. Y., Lee, H. J., . . . Lee, H. C. (2006). Effects of lifestyle modification on metabolic parameters and carotid intima-media thickness in patients with type 2 diabetes mellitus. *Metabolism, 55*(8), 1053-1059. doi: http://dx.doi.org/10.1016/j.metabol.2006.03.017

Kodama, S., Saito, K., Tanaka, S., & et al. (2009). Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: A meta-analysis. *Journal of the American Medical Association, 301*(19), 2024-2035. doi: 10.1001/jama.2009.681

Kollias, A., Psilopatis, I., Karagiaouri, E., Glaraki, M., Grammatikos, E., Destounis, A., . . . Stergiou, G. (2010). ADIPOSITY, BLOOD PRESSURE AND CAROTID INTIMA-MEDIA THICKNESS IN GREEK CHILDREN AND ADOLESCENTS: 9B. 03. *Journal of hypertension, 28*, e433-e434.

Libby, P., & Theroux, P. (2005). Pathophysiology of Coronary Artery Disease. *Circulation, 111*(25), 3481-3488. doi: 10.1161/CIRCULATIONAHA.105.537878

Lorenz, M. W., Polak, J. F., Kavousi, M., Mathiesen, E. B., Völzke, H., Tuomainen, T.-P., . . . Thompson, S. G. (2012). Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. *The Lancet, 379*(9831), 2053-2062. doi: http://dx.doi.org/10.1016/S0140-6736(12)60441-3

Nichols, S., Milner, M., Meijer, R., Carroll, S., & Ingle, L. (2014). Variability of automated carotid intima-media thickness measurements by novice operators. *Clinical Physiology and Functional Imaging*.

Niebauer, J., Hambrecht, R., Velich, T., Hauer, K., Marburger, C., Kälberer, B., . . . Kübler, W. (1997). Attenuated Progression of Coronary Artery Disease After 6 Years of Multifactorial Risk Intervention: Role of Physical Exercise. *Circulation, 96*(8), 2534- 2541. doi: 10.1161/01.cir.96.8.2534

O'Leary, D. H., & Bots, M. L. (2010). Imaging of atherosclerosis: carotid intima–media thickness. *European Heart Journal, 31*(14), 1682-1689. doi: 10.1093/eurheartj/ehq185

Okada, K., Maeda, N., Tatsukawa, M., Shimizu, C., Sawayama, Y., & Hayashi, J. (2004). The influence of lifestyle modification on carotid artery intima-media thickness in a suburban Japanese population. *Atherosclerosis, 173*(2), 327-335.

Perticone, F., Ceravolo, R., Pujia, A., Ventura, G., Iacopino, S., Scozzafava, A., . . . Verdecchia, P. (2001). Prognostic significance of endothelial dysfunction in hypertensive patients. *Circulation, 104*(2), 191-196.

Pignoli, P., Tremoli, E., Poli, A., Oreste, P., & Paoletti, R. (1986). Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. *Circulation, 74*(6), 1399-1406. doi: 10.1161/01.cir.74.6.1399

Polak, J. F., Pencina, M. J., Pencina, K. M., O'Donnell, C. J., Wolf, P. A., & D'Agostino, R. B. (2011). Carotid-Wall Intima–Media Thickness and Cardiovascular Events. *New England Journal of Medicine, 365*(3), 213-221. doi: doi:10.1056/NEJMoa1012592

Pursnani, S., Diener-West, M., & Sharrett, A. R. (2014). The effect of aging on the association between coronary heart disease risk factors and carotid intima media thickness: an analysis of the Atherosclerosis Risk in Communities (ARIC) cohort. *Atherosclerosis*.

Sandercock, G., Cardoso, F., & Almodhy, M. (2013). Cardiorespiratory fitness changes in patients receiving comprehensive outpatient cardiac rehabilitation in the UK: a multicentre study. *Heart, 99*(17), 1298-1299. doi: 10.1136/heartjnl-2013-304085

Sandercock, G., Cardoso, F., Almodhy, M., & Pepera, G. (2013). Cardiorespiratory fitness changes in patients receiving comprehensive outpatient cardiac rehabilitation in the UK: a multicentre study. *Heart, 99*(11), 785-790. doi: 10.1136/heartjnl-2012-303055

Sato, S., Makita, S., Uchida, R., Ishihara, S., & Majima, M. (2008). Physical activity and progression of carotid intima-media thickness in patients with coronary heart disease. *Journal of Cardiology, 51*(3), 157-162. doi: http://dx.doi.org/10.1016/j.jjcc.2008.02.005

Scholl, J., Bots, M. L., & Peters, S. A. E. (2015). Contribution of cardiorespiratory fitness, relative to traditional cardiovascular disease risk factors, to common carotid intima–media thickness. *Journal of Internal Medicine, 277*(4), 439-446. doi: 10.1111/joim.12271

Tajik, P., Meijer, R., Duivenvoorden, R., Peters, S. A., Kastelein, J. J., Visseren, F. J., . . . Grobbee, D. E. (2012). Asymmetrical distribution of atherosclerosis in the carotid artery: identical patterns across age, race, and gender. *European Journal of Preventive Cardiology, 19*(4), 687-697.

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

Tanaka, H., Seals, D. R., Monahan, K. D., Clevenger, C. M., DeSouza, C. A., & Dinenno, F. A. (2002). Regular aerobic exercise and the age-related increase in carotid artery intima-media thickness in healthy men. *Journal of Applied Physiology, 92*(4), 1458-1464.

Taylor, A., Shaw, L. J., Fayad, Z., O'Leary, D., Brown, B. G., Nissen, S., . . . Raggi, P. (2005). Tracking atherosclerosis regression: a clinical tool in preventive cardiology. *Atherosclerosis, 180*(1), 1-10. doi: http://dx.doi.org/10.1016/j.atherosclerosis.2004.12.024

Taylor, R. S., Brown, A., Ebrahim, S., Jolliffe, J., Noorani, H., Rees, K., . . . Oldridge, N. (2004). Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *The American Journal of Medicine, 116*(10), 682-692. doi: http://dx.doi.org/10.1016/j.amjmed.2004.01.009

Touboul, P. J., Hennerici, M. G., Meairs, S., Adams, H., Amarenco, P., Bornstein, N., . . . Woo, K. S. (2012). Mannheim Carotid Intima-Media Thickness and Plaque Consensus (2004–2006–2011). *Cerebrovascular Diseases, 34*(4), 290-296.

Vanoli, D., Wiklund, U., Lindqvist, P., Henein, M., & Näslund, U. (2013). Successful novice's training in obtaining accurate assessment of carotid IMT using an automated ultrasound system. *European Heart Journal – Cardiovascular Imaging, 15*(6), 637-642. doi: 10.1093/ehjci/jet254

Warburton, D. E., McKenzie, D. C., Haykowsky, M. J., Taylor, A., Shoemaker, P., Ignaszewski, A. P., & Chan, S. Y. (2005). Effectiveness of high-intensity interval training for the rehabilitation of patients with coronary artery disease. *The American Journal of Cardiology, 95*(9), 1080-1084.

West, R. R., Jones, D. A., & Henderson, A. H. (2012). Rehabilitation after myocardial infarction trial (RAMIT): multi-centre randomised controlled trial of comprehensive cardiac rehabilitation in patients following acute myocardial infarction. *Heart, 98*(8), 637-644. doi: 10.1136/heartjnl-2011-300302

CHAPTER 5 – Effect of exercise dose manipulation on VO_{2peak} assessed using 'gold standard' methods in patients with coronary heart disease

6.1 Abstract

Objective: Recent data suggests that UK cardiac rehabilitation (CR) programmes only provide modest cardiorespiratory fitness (CRF) improvements. Insufficient exercise training dose has been suggested as possible cause. However, there are insufficient UK studies using 'gold standard' methods to report VO_{2peak} change following routine CR. Moreover, there are no studies that have reported manipulations within a routine UK CR programme –incorporating additional exercise sessions to evaluate the effect of higher exercise training doses on VO_{2peak} improvements. The aim of this study was to determine VO_{2peak} changes following routine CR compared to higher-dose exercise based on maximal cardiopulmonary exercise test (CPET) data. Pilot data was obtained from a multicentre clinical trial (UK site) designed to determine patient adherence to a personalised CR exercise sessions delivered via a novel tele-monitoring (TM) system.

Methods: Patients with a recent diagnosis of coronary heart disease (CHD) were recruited and randomised to either a routine CR group (4 to 24 exercise sessions; 8-12 weeks; 40-60% heart rate reserve) or, routine CR plus a personalised guided exercise (GEx) plan via a TM device. Patients performed a maximal symptom limited CPET prior to (visit 1), and following completion of a CR regime (visit 2). Repeated measures ANOVA, minimally clinically important differences and partial eta squared effect sizes were used to identify changes in VO_{2peak} and supplementary CPET variables.

Results: *n*=27 patients met the analysis inclusion criteria (88.9% male; age 59.5 ± 10.0 years; body mass index [BMI] 29.6 ± 3.8 kg·m^{-2}). For $VO_{2peak,}$ there was no significant main (p=0.058) or group effect (p=0.674). There was a significant interaction effect for VO_{2peak} changes (routine CR -0.29 ml·kg^{-1}·min^{-1}; 95% CI -1.75 to 1.16 ml·kg^{-1}·min^{-1}; p=0.841; GEx treatment 2.08 ml·kg^{-1}·min^{-1}; 95% CI 1.88 to 3.97 ml·kg^{-1}·min^{-1}; p=0.014). There was also a significant main effect for the ventilatory anaerobic threshold [VAT] (1.85 ml·kg^{-1}·min^{-1}; 95% CI 1.08 to 2.62 ml·kg^{-1}·min^{-1}; p=<0.001) but no group effect (p=0.240). There was a significant interaction effect for VAT (routine CR 0.35 ml·kg^{-1}·min^{-1}; 95% CI -0.56 to 1.25 ml·kg^{-1}·min^{-1}; p=0.391; GEx treatment 3.35 ml·kg^{-1}·min^{-1}; 95% CI 2.11 to 4.59 ml·kg^{-1}·min$^{-1;}$ p=<0.001). There was also a significant main effect for VE/VCO$_2$ slope (-3.23; 95% CI -5.21 to -1.26; p=0.002) but no group (p=0.119) or interaction effect p=0.034). Receiver operating characteristics (ROC) curve analysis showed that increasing the number of exercise session increased the likelihood of VO_{2peak} improvements (0.789; 95% CI 0.627 to 0.952; p=0.012). Thirteen exercise sessions delineated the point above which, patients could expect an improvement in VO_{2peak} (sensitivity 0.900; specificity 0.632).

Conclusion: Only the GEx treatment group experienced an improvement in VO_{2peak} and VAT. Sub-group analysis showed that VO_{2peak} and VAT changes in routine CR patients were comparable to those not undertaking structured exercise. A positive associated between the numbers of exercise sessions completed at the likelihood of experiencing a VO_{2peak} improvement was identified. Increasing the total exercise dose may be a feasible way of improving VO_{2peak} within the short period of time that patients are enrolled to CR programmes.

6.2 Introduction

Following The World Health Organisation (1993) publication on 'rehabilitation after cardiovascular disease', cardiac rehabilitation (CR) has increasingly become standard therapy for patients suffering a cardiac event. CR has been shown to substantially reduce patient mortality (Heran et al., 2011, Beauchamp et al., 2013, Witt et al., 2004) in studies lasting longer than 12 months (RR 0.74; 95% CI 0.63 to 0.87). Taylor et al. (2006) suggest that approximately half of the 28% mortality reduction observed in their study was attributable to the exercise component of CR alone. The mechanisms behind this mortality benefit remain to be determined. However, there is an abundance of evidence linking increased peak oxygen uptake (VO_{2peak}) with reduced morbidity and mortality (Dorn et al., 1999, Vanhees et al., 1995, Dugmore et al., 1999, Kodama et al., 2009, Myers et al., 2002, Belardinelli et al., 2001).

A 1% VO_{2peak} increase (Vanhees et al., 1995) or 1 metabolic equivalent (MET) improvement (Myers et al., 2002) in CHD patients may confer a 2% to 12% mortality reduction, respectively. Consequently, increasing VO_{2peak} via structured exercise training has become one of the primary therapeutic targets of CR (ACPICR, 2015). However, whilst VO_{2peak} change remains the most widely employed method of assessing the effect of exercise training on peak aerobic capacity, other markers of CRF obtained from a cardiopulmonary exercise test (CPET) such as the ventilatory anaerobic threshold (VAT) and the VE/VCO_2 slope may also respond positively to exercise training (Guazzi et al., 2004, Warburton et al., 2005).

Although the VAT and VE/VCO_2 slope are likely to carry *some* prognostic value in patients with coronary heart disease [CHD] (Van de Veire et al., 2006, Tsurugaya et al., 2006), their independent prognostic power is yet to be substantiated. Contemporary research has focused on peri-operative risk assessment (Wilson et al., 2010, West et al., 2011) and prognosis of patients with chronic heart failure [CHF] (Agostoni et al., 2013, Gitt et al., 2002, Ingle et al., 2007a). Despite this, the presence of an abnormally low VAT may affect a patient's ability to conduct daily activities without experiencing fatigue. Moreover, because the VAT is known to

improve following exercise training (Sullivan et al., 1989b, Wisløff et al., 2007, Fukuda et al., 2013), it should be considered a valuable outcome measure for studies investigating the therapeutic effects of exercise training in CHD populations.

Similar to the VAT, the prognostic value of poor ventilatory efficiency (characterised by VE/VCO$_2$ slope elevation) in CHD population is undetermined. However, irrespective of patient group, elevation of the VE/VCO$_2$ slope likely indicates abnormal cardiopulmonary and cardiovascular perfusion, diffusion, and/or mal-adaptation of the periphery (Poole et al., 2012, Clark et al., 1996). A reduction in VE/VCO$_2$ slope gradient may signal a more tightly regulated cardiovascular, ventilatory and metabolic response to exercise and may also be a valuable outcome measure for CHD populations. Although a number of studies have reported that exercise training improves ventilatory efficiency (Arena et al., 2008, Guazzi et al., 2004), it is yet to be determined if UK CR programmes are effective in achieving this. Furthermore, there is currently no contemporary published data obtained from 'gold standard' CPET to demonstrate that VO$_{2peak}$, VAT improve following completion of routine CR in the UK. Recent reports on mortality outcomes and change in surrogate measures of CRF have suggested that UK CR may be ineffectual. The efficacy of UK CR programmes was brought in to question after data emerged showing that mortality rates were not improved at two years (RR 0.98; 95% CI 0.74 to 1.30), nor seven to nine years [RR 0.99; 95% CI 0.85 to 1.15] (West et al., 2012).

Furthermore, evidence has emerged that improvements in cardiorespiratory fitness (CRF) following routine UK CR programmes may not be in-line with published literature from clinical trials (Sandercock et al., 2013b). Sandercock and colleagues (2013) reported a 0.52 MET CRF improvement in their multicentre study, whilst Houchen-Wolloff et al. (2014) reported that only 48.6% of patients achieved the minimal clinically important improvement in their study. Indeed, Chapter 3 of this thesis indicates that a routine low to moderate intensity CR programme does improve VO$_{2peak}$ or other indices of CRF. These findings suggest that UK CR exercise training may not be sufficient to increase CRF and decrease mortality rates.

Despite some variation in exercise frequency and duration (Doherty and Lewin, 2012), there is a relatively consistent approach to CR exercise delivery across the UK. CR programmes vary from one to three sessions per week. The median number of exercise sessions reported nationally is 11.6 sessions (Brodie et al., 2006). Exercise circuit training incorporating alternating cardiovascular (CV) and active recovery exercise stations are routinely prescribed at intensities between 40-60% of a patients' heart rate reserve [HRR], with some lower risk individuals permitted to progress to 70%. (BACR, 2006, ACPICR, 2015). However, exercise training doses used in clinical trials are often higher than those seen in most UK CR programmes.

Clinical trials cited in a recent meta-analysis (Heran et al., 2011) typically involved a greater number of weekly exercise sessions delivered over a longer time period (Belardinelli et al., 2001, Hugh and Mullee, 1990, Bäck et al., 2008, Haskell et al., 1994, Miller et al., 1984). Exercise intensities also tended to be higher and prescribed with greater accuracy using maximal exercise testing protocols (Bäck et al., 2008, Haskell et al., 1994, Miller et al., 1984, Ingle and Carroll, 2013) as opposed to submaximal exercise testing protocols that are widely employed by many UK CR programmes.

Whilst UK CR appears to lack the training stimulus required to elicit substantial training responses, evidence supporting this is weak in comparison to that demonstrating its efficacy. The few studies to openly challenge the benefits of CR can be contested for reporting on an outdated model of CR (West et al., 2012), not having a control group, being of retrospective design and reporting MET's rather than 'gold standard' exercise test parameters (Sandercock et al., 2013b). However, despite the limitations of METs and sub-maximal exercise testing protocols, Sandercock et al. (2013b) and Houchen-Wolloff et al. (2014) are some of the only studies to date presenting critical data of UK CR programmes. Furthermore METs are widely used in UK CR centres and in the context of published literature reporting substantial CRF improvements (Balady et al., 1996, Gee et al., 2014, Sandercock et al., 2011), the finding that

UK CR improves CRF by 0.5 METs (Sandercock et al., 2013b) should be viewed with some concern.

Although Sandercock and colleagues (2013) were limited by the constraints of current UK practice, reporting CRF change in METs makes it difficult to accurately quantify the effects of exercise training. Peak MET estimation has multiple limitations (Byrne et al., 2005, Wasserman et al., 2011) and VO_{2peak} obtained through CPET is the only reliable way of determining peak aerobic capacity.

International studies have also presented findings based on CPET data and found that low doses of moderate continuous exercise [VO_{2peak} visit 1 = 13.8 ± 3.6 ml·kg^{-1}·min^{-1}; visit 2 = 13.4 ± 2.7 ml·kg^{-1}·min^{-1}; (post-hoc p-value not reported)], (Cardozo et al., 2015) and low training volumes do not improve VO_{2peak} (Madssen et al., 2014). On the contrary, the delivery of additional exercise sessions via a tele-monitoring (TM) system as adjunctive therapy to routine CR has been shown to significantly increase VO_{2peak} [VO_{2peak} visit 1 = 2110 ± 607ml, VO_{2peak} visit 2 = 2360 ± 475ml; p=0.001] (Frederix et al., 2015). Increased training dose appears to play a role in maximising VO_{2peak} improvements for patients undertaking CR (Uddin et al., 2015).

Although not yet widely utilised, delivering exercise training via a TM system is a feasible way to deliver CR (Maddison et al., 2014, Frederix et al., 2015, Dalleck et al., 2011) and may afford a practical opportunity to increase the training dose for patients undertaking routine CR in the UK. Pilot data was obtained from a multicentre clinical trial designed to determine patient adherence to CR delivered via a novel TM system. One hospital from the UK, Spain and Germany took part in this investigation (Castle Hill Hospital [UK], Hospital Clínico Universitario San Carols de Madrid [Spain] and Department of Cardiology, Pulmonary and Angiology RWTH Aachen University [Germany]). We aimed to determine whether routine CR (4 to 24 exercise sessions; 8-12 weeks; 40-60% HRR) improved VO_{2peak} and, whether routine CR in conjunction with a personalised exercise regime (20 week progressive training plan) based on a maximal CPET and delivered by a TM system achieved superior VO_{2peak} improvements. Changes to the VAT and VE/VCO$_2$ slope were also included as secondary outcome measures.

6.3 Methods

6.3.1   Ethical approval

The guided exercise (GEx) study was a phase 1 multicentre clinical trial (pilot study) designed to determine patient adherence to exercise training via a TM system. Ethical approval was granted from the Yorkshire and the Humber – Sheffield National Research Ethics Committee (12/YH/0072), and The University of Hull, Sport, Health and Exercise Science research ethics committee (Appendix 6). Patients were recruited to the study between January and March 2012.

6.3.2   Study Outline

Patients were enrolled a minimum of 28 days post cardiac event. Study inclusion and exclusion criteria are shown in Table 1. Following telephone screening by a specialist medical registrar, patients from Hull, East Riding of Yorkshire (ERY), Scarborough and Grimsby CR services were invited to attend the Academic Cardiology research laboratory at Castle Hill Hospital (visit 1). Consent (Appendix 7) was taken by a registered healthcare professional prior to study participation. All patients were clinically stable at the time of consent. A follow up visit was arranged at approximately three (visit 2) and six months after participants' initial visit. Due to a high patient attrition rate, only data for visit 1 and 2 were included for analysis (12 weeks of exercise training).

All participants agreed to participate in routine CR as delivered by their local NHS trust. Patients were sequentially randomised to receive routine CR only (routine CR group), or routine CR plus exercise delivered through the GEx TM system. Patients in the GEx treatment group were instructed to exercise according to a personalised exercise protocol.

Table 1 – GEx study patient inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Recent MI, elective PCI or patients with CHD	Severe congestive heart failure – NYHA class IV
EF > 30%	EF < 30%
Patients willing to exercise	Inability to exercise
Eligibility for a standard CR programme	Recent cardiac surgery < 4 weeks
Computer literate	Inability to use a computer
Adults able to provide informed consent	Participants committed to an institution or penitentiary by judicial or official order
Signed informed consent	Employees of the investigator
	ICD/CRT device or pacemaker
	Open thorax wound
	Women who are pregnant or breast feeding

MI = Myocardial Infarction; PCI = Percutaneous Coronary Intervention; CHD = Coronary Heart Disease; NYHA = New York Heart Association; EF = Ejection Fraction; ICD = Implantable Cardioverter Defibrillator; CRT = Cardiac Resynchronisation Therapy

6.3.3 Routine Cardiac Rehabilitation

CR provision remains inequitable across the UK (Doherty and Lewin, 2012, Brodie et al., 2006). This was reflected by the varied characteristics of CR programmes in the Yorkshire and Humber region. Hull and Grimsby's CR programmes both consisted of 16 exercise sessions delivered over 8 weeks. Scarborough's CR programme varied between 4 and 14 sessions 'depending on the needs of the patient', whilst the ERY CR programme consisted of 24 sessions conducted over 12 weeks. Patients referred to CR in the ERY had limited access to healthcare professional lead programmes (previously known as phase III). Patients were often referred directly to exercise instructor lead programmes (previously known as phase IV). Despite this, there was consistency in prescription of exercise intensity and training modality. Interval circuit training with alternating CV and active recovery exercises were adopted by all CR teams. At the time of recruitment, exercise was prescribed at 40-60% of patient's estimated heart rate reserve [HRR] (BACR, 2006, ACPICR, 2015) using the formula:

$$HRR = 220\text{-age (years)} - RHR - 30 \text{ (if } \beta B) \text{ Training}$$

$$zone = (40 \text{ to } 60\% \text{ HRR}) + RHR$$

Where 220 is a theoretical maximal heart rate (HR), - 30 is an adjustment for the attenuating effect of a beta-blockade (βB) on HR (where appropriate) and RHR is the patients resting HR. All CR teams aimed for patients to achieve 20-30 minutes of CV exercise per session before their final visit.

6.3.4   Guided Exercise Equipment

The GEx TM equipment is a closed loop disease management system providing remote exercise prescription for CR patients. The system provided continuous patient feedback relating to exercise performance and health status to the healthcare co-ordinator. The system allows the healthcare team to remotely modify exercise prescriptions and provide patient support.

A vest-top capable of monitoring ECG and respiratory rate was provided to GEx treatment patients to allow continuous monitoring during exercise. Patient-system interface was via a personal digital assistant [PDA] (HTC QTEK S200 Taoyuan City, Taiwan) with a wireless connection to a bespoke 'patient station', similar to a tablet computer. ECG data and respiratory rate were transmitted from vest to PDA and then to the patient station. The combination of these devices allowed real-time exercise tuition from the patient station to ensure patient safety and exercise adherence. Upon completion of exercise training, data was transmitted from the patient station to the healthcare professional via a secure internet website. No equipment references are available for these products because they are currently experimental. The products met safety and quality standards outlined in IEC 62304 "Medical Device Software, Software Lifecycle Processes" legislation. An automated blood pressure cuff (AND UA-767PBT, Oxon, United Kingdom) was provided for measurements of brachial blood pressure prior to exercise.

When a patient completed an exercise session, the healthcare professional received their exercise training data via the secure website. ECG rhythm strips and vital signs including

respiratory rate could be reviewed. CV endurance and musculoskeletal conditioning exercises were then modified (where needed) in response to patients' training data. Exercise training intensities were based on a CPET conducted at visit 1.

Table 2– Test termination criteria

Indications for exercise termination Chest pain
suggestive of ischaemia
Ischemic ECG changes Complex
ectopy
Second or third degree heart block
Fall in systolic pressure 20 mm Hg from the highest value during the test Hypertension (250mmHg systolic; 120mmHg diastolic)
Severe desaturation: SpO_2 less than 80% when accompanied by symptoms and signs of severe hypoxemia
Sudden pallor
Loss of coordination
Mental confusion
Dizziness or faintness
Signs of respiratory failure

ECG = Electrocardiogram; mmHg = Millimetres of Mercury; SpO_2 = Peripheral Oxygen Saturation

6.3.5 Cardiopulmonary Exercise Testing

At both visits, patients undertook a symptom-limited maximal CPET following a 25 W, two minute stage, incremental cycle ergometer protocol (GE Healthcare e-Bike, Chalfont St Giles, United Kingdom). Patients started pedalling at 25 W without a prior unloaded cycling phase. Exercise was terminated if patients experienced chest pain or achieved any of the test termination criteria (Table 2) outline by the American Thoracic Society (2003). Patients were deemed to have achieved peak CPET criteria when two or more of the criteria listed in Table 3 were observed.

An ECG (Mason-Likar configuration) was monitored continuously throughout CPET via a GE Case System (GE Healthcare, Chalfont St Giles, United Kingdom). Blood lactate ([La⁻]b) concentration was analysed via finger capillary samples (Lactate Plus, Cranlea Human Performance Ltd, Birmingham, United Kingdom) taken at the end of each two minute stage. Blood pressure (BP) was monitored every two minutes using an automated ECG-gated BP monitor (Tango, SunTech

Medical, Eynsham, United Kingdom). Peak HR and BP were both defined as the highest recorded reading during the CPET.

Breath-by-breath metabolic gas measurements were collected and analysed using an Innocor metabolic cart (Innovision, Glamsbjerg, Denmark). Data were exported as breath-by-breath values and averaged over 15 seconds using Microsoft Excel (Microsoft, Redmond WA, USE). VO_{2peak} and peak respiratory exchange ratio (RER) were both averaged over the final 30 seconds of the CPET. Patients were asked to rate their perception of exercise intensity at the end of every two minute stage during and at peak exercise using the 6-20 Borg score (Borg, 1982). Instructions for the use of the Borg score were given prior to CPET using a standardised list of terms. Phrases such as 'increased breathing', 'sweaty', 'laboured breathing', 'burning muscles' and 'complete exhaustion' were used to help patients understand how to rate and perceive exercise intensity.

Calibration was conducted in a temperature controlled room (21°C) prior to each exercise test. An integrated system registering ambient O_2 concentration was used for one point calibration. The detected O_2 concentration was defined as 20.93% by the metabolic cart. Flow metre calibration was performed using a three litre syringe. Five x 2 flow simulations were performed at arbitrarily assigned low (x2), medium (x2) and high (x1) flow rates to simulate a range of ventilatory rates. Acceptable volume offset values were defined as 0.8 to 1.2. Flow-gas delay calibration was performed by breathing into the Innocor's mouth piece and taking 10 to 12 sharp in-breaths, each followed by a slow expiration.

Table 3 – Peak Exercise Test Criteria

A plateau in VO_2 (or failure to increase by >150 ml·min^{-1}) with an increased workload
Failure to achieve 90% of age predicted HR maximum
A Peak RER $\geq$ 1.10
An RPE > 17 on the 6-20 Borg scale

VO_2 = Oxygen Uptake; HR = Heart Rate; RER = Respiratory Exchange Ratio; RPE = Rating of Perceived Exertion

6.3.6 GEx Exercise Prescription

Patients randomised to the GEx treatment group were asked to complete a three component training intervention comprising warm-up, conditioning phase and a cool down. The warm-up consisted of a five minute walk or cycle followed by five minutes of static stretching. The warm up was designed to elicit a progressive transition from baseline HR (HR_{base}: defined as the mean 15 second HR taken one minute prior to exercise training), to the target HR (defined as 80% of the lower training zone (HR_{low}) for the conditioning component:

$$\Delta_{warm-up} = (0.8 \times HR_{low} - HR_{base}) \times 0.2$$

During the conditioning phase, patients were instructed to keep their HR within their prescribed training zone. Exercise training zones were prescribed based on HR at $[La^-]b$ concentrations of 1 to 1.5 mmol in weeks 0-3 (initial phase) and 1.8 to 2.3 mmol from improvement phase *a* through to the maintenance phase (Figure 1).

The cool down component consisted of a five minute low intensity activity such as walking. Target cool down HR was calculated using the formula:

$$HR_{Cool-down} = HR_{Train} - 50\% \times (HR_{train} - HR_{base})$$

Where HR_{Train} is the mean HR achieved during the final minute of the conditioning phase and HR_{base} is the baseline HR observed prior to starting exercise. Following completion of the cool down, a further five minutes of static stretching was conducted.

Continuous HR and respiratory rate monitoring allowed real-time patient tuition during the exercise programme. Where required, patients were instructed by the GEx system to decrease or increase their exercise intensity to maintain an appropriate exercise HR.

To accommodate inexperienced exercisers or patients with severe cardiorespiratory deconditioning, exercise prescriptions increased in frequency, intensity and duration over the course of the first nine weeks (Figure 1). Exercise training started as a cardiovascular endurance

(CV) programme only (initial phase) and progressed to CV exercise plus resistance training at improvement phase *a*. Improvement phase *b* and *c* required increased exercise duration and frequency. The maintenance phase required a further increase in frequency. Resistance training was conducted using rubber resistance bands. Patients were offered a range of bands with varied resistances and were asked to select one that would allow completion of a 15 repetition set of exercises. Types of resistance training varied depending on patient ability and co-morbidities of the patient. Typical exercises included shoulder shrugs, front raises, hip flexion and hip extension. At the time of visit 2, patients had completed all improvement phases and three weeks of the maintenance phase.

6.3.7   Statistical Analysis

Statistical analysis was performed using SPSS version 22 (IBM, New York, USA). Patients were excluded from analysis if they failed to attend visit 2 or did not complete a valid CPET at either visit. Continuous normally distributed variables are displayed as mean with 95% confidence intervals (95% CI) or Standard deviation (SD) where specified. Non-normally distributed data are displayed as median with range, and categorical data are reported as percentages. Normal distribution was assessed using histograms and the Shapiro-Wilk test. The Shapiro-Wilk test is the preferred test for normality in instances where samples sizes are <50 (Ghasemi and Zahediasl, 2012).

Phase	Length	Type/Frequency	Duration	Intensity (Borg)
Initial	3 Weeks	Endurance x 2/w	3 x 10-30 min	11
Improvement - *a*	2 Weeks	Endurance x 2/w Resistance x 2/w	3 x 10-30 min	12-13
Improvement - *b*	2 Weeks	Endurance x 2/w Resistance x 2/w	3 x 15-45 min	12-13
Improvement - *c*	2 Weeks	Endurance x 3/w Resistance x 3/w	3 x 15-45 min	12-13
Maintenance phase	12 Weeks +	Endurance x 3/w - Daily Resistance x 3/w	3 x 20-60 min	12-13

Figure 1 – GEx training intensification strategy. Grey boxes denote the parameter for exercise intensification during each phase.

/w = Per Week; min = Minute

Statistically significant differences ($\alpha < 0.05$) were calculated using repeated measures and one-way analysis of variance (ANOVA) with Bonferroni correction. Where appropriate, analysis of covariance (ANCOVA) and treatment interactions (time x group) were analysed. Where the assumption of normal distribution was not met, Log_{10} and square root transformation were performed to facilitate parametric analysis. Where data transformation was successful, arithmetic means were reported for meaningful interpretation. Where parametric assumptions were not met, non-parametric analysis was performed using a Wilcoxon test. Pearson (or Spearman for non-parametric data) correlations were conducted to determine the association between independent and dependent variables. An r value of <0.25, 0.26 to 0.50, 0.51 to 0.75, and, >0.75 were considered weak, moderate, fair and strong relationships respectively (Berg and Latin, 2008). Correlations were deemed to be significant if the associated p-value was <0.05. Despite recommendation to the contrary, pilot studies often place emphasis on significance testing, however, such studies may not be sufficiently powered to achieve a 5% significance threshold (Thabane et al., 2010, Lancaster et al., 2004). Pilot studies reporting only p-values should be interpreted with caution (Lee et al., 2014) and it is good practice to consider

other measures of treatment efficacy. Furthermore statistical significance does not always confer clinical benefits. In this study, treatment effect was considered using traditional hypothesis testing in conjunction with the minimal clinically important difference (MCID). The definition of the MCID was originally suggested by Jaeschke (1989) as:

"the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management"

There is no 'gold standard' method for determining the MCID, however, for the purpose of this study it was calculated as:

$$MCID = Pooled\ SD \times 0.2$$

Where pooled SD is the pooled standard deviation of a population's baseline score for a specified outcome variable and 0.2 is the fraction of that which any score change must exceed to be deemed clinically meaningful (Page, 2014, Lemieux et al., 2007).

$$Pooled\ SD = \sqrt{\frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2}}$$

Where n is group 1 or 2 and S_2^2 is the squared SD for that group. In the absence of wide 95% CI that substantially cross 0, changes exceeding the MCID in either a positive or negative direction were classed as clinically meaningful. Because the MCID is open to interpretation, partial eta^2 (η_p^2) effect sizes were also calculated with 0.01, 0.06 and 0.14 representing small, medium and large effect sizes respectively (Richardson, 2011).

Receiver operating characteristics (ROC) were used to identify any dose response for VO_{2peak} in relation to increasing the number of exercise sessions completed. Participants were binned into

two groups based on whether they had achieved the MCID for VO_{2peak} (state variable). The number of exercise sessions conducted was used as the test variable. Secondary analysis was then conducted using any improvement in VO_{2peak} as the state variable. The area under the curve (AUC) and the test variable with the highest sensitivity and specificity were calculated.

At visit two, it became apparent that a small number of patients had not complied with their randomised treatment. *Some* patients originally assigned to routine CR reported not attending their exercise classes and *some* members of the GEx treatment group chose not to use the equipment. This presented an opportunity to introduce a control group and compare the effect of no structured exercise, routine CR, and routine CR plus the GEx system. Analysis was conducted by re-grouping patients based on their actual care plan. These new groups were control, routine CR, and GEx treatment. The control group included patients who had declined structured CR, routine CR included patients that had only taken part in CR as offered by a local healthcare authority and the GEx treatment group consisted of those who had utilised GEx TM equipment.

6.4   Results

6.4.1   Group Characteristics

n=44 patients were recruited to the GEx study. A total of *n*=17 patients were excluded, *n*=14 of which were from the GEx treatment group. In the GEx treatment group, *n*=12 discontinued the study due to equipment failure, one left the study due to health deterioration and one was lost to follow-up. Three patients assigned to routine CR were also lost to follow-up. Baseline characteristics for all remaining patients are shown in Table 4. A total of *n*=27 participants (88.9% male; age 59.5 ± 10.0 years; body mass index [BMI] 29.6 ± 3.8 $kg \cdot m^{-2}$) were included for analysis. There were no significant differences between groups for age (4.5 years; 95% CI -3.9 to 12.4 years; p=0.294) or BMI (0.3 $kg \cdot m^{-2}$; 95% CI -2.9 to 3.5 $kg \cdot m^{-2}$; p=0.841) at baseline. The primary reason for referral to CR was MI (59.3%) followed by elective PCI (37.0%). 44.4% of participants

had also sustained a previous MI. Secondary prevention medications are listed in Table 5.

Table 3

Variable	All	Routine CR	Gex Treatment
Participants (%)	100 (*n* =27)	63 (*n* =17)	37 (*n* =10)
Gender (% male)	88.9 (*n* =24)	94.1 (*n* =16)	80.0 (*n* =8)
Age (years)	59.5 ± 10.0	61.1 ± 8.4	56.8 ± 12.2
BMI (kg·m^2)	29.6 ± 3.8	29.7 ± 3.4	29.4 ± 4.6
MI (%)	59.3 (*n* =16)	58.8 (*n* =10)	60.0 (*n* =6)
Elective PCI (%)	37.0 (*n* =10)	35.3 (*n*= 6)	40.0 (*n* =4)
CABG (%)	3.7 (*n* =1)	5.9 (*n* =1)	0.0 (*n* =0)
Type 2DM (%)	18.5 (*n*= 5)	17.6 (*n*= 3)	20 (*n*= 2)
PMH of MI (%)	44.4 (*n* =12)	41.2 (*n* =7)	50 (*n* =5)
Previous CABG (%)	11.1 (*n* =3)	17.6 (*n*= 3)	0.0 (*n* =0)
Asthma (%)	3.7 (*n* =1)	5.9 (*n* =1)	0.0 (*n* =0)
COPD (%)	7.4 (*n* =2)	5.9 (*n* =1)	10 (*n* =1)
Atrial Fibrillation (%)	11.1 (*n* =3)	11.8 (*n* =2)	10 (*n* =1)
Smoking (%)	14.8 (*n* =4)	11.8 (*n* =2)	20 (*n* =2)

SD = Standard Deviation; BMI = Body Mass Index; MI = Myocardial Infarction; PCI = Percutaneous Coronary Intervention; CABG = Coronary Artery Bypass Graft; Type 2 Dm; Type 2 Diabetes Mellitus; PMH = Past Medical History; COPD = Chronic Obstructive Pulmonary Disease

Table 5 –Patient medications at visit 1

Medication	All (*n* =27)	Routine CR (*n* =17)	GEx Treatment (*n* =10)
Aspirin (%)	96.3 (*n*= 26)	94.1 (*n* =16)	100.0 (*n* =10)
Clopidogrel (%)	55.6 (*n* =15)	52.9 (*n* =9)	60.0 (*n* =6)
Ticagrelor (%)	37.0 (*n* =10)	35.3 (*n* =6)	40.0 (*n* =4)
Anti-coagulant (%)	3.7 (*n* =1)	5.9 (*n* =1)	0.0 (*n* =0)
Beta-Blocker (%)	81.5 (*n* =22)	94.1 (*n* =16)	60.0 (*n* =6)
ACE-inhibitor (%)	59.3 (*n* =16)	52.9 (*n* =9)	70.0 (*n* =7)
Statin (%)	96.3 (*n*= 26)	100.0 (*n* =17)	90.0 (*n* =9)
Diuretic (%)	18.5 (*n* =5)	11.8 (*n*= 2)	30.0 (*n* =3)
Nitrate (%)	70.4 (*n* =19)	64.7 (*n* =11)	80.0 (*n* =8)

ACE = Angiotensin Converting Enzyme

There was substantial variability in the number of exercise sessions attended (Table 6) by patients assigned to routine CR. Patients completed a median of 10 (range: 0 to 16) exercise sessions. Patients from Hull attended the most sessions (16; range 0 to 16) followed by patients from the ERY (11; range: 1 to 16) and Grimsby (10; range: 4 to 16). Patients in the GEx treatment group completed significantly more exercise sessions (median 46; range: 0 to 62; p=0.009) exercise sessions. Most patients in the GEx treatment group did not attend a structured exercise class provided by their local NHS provider (60%) whereas only 29% of the routine CR group did

not. Patients in the GEx treatment group conducted significantly more exercise sessions than patients undertaking routine CR (p=0.009) No adverse events were recorded during the course of any CR programme.

Table 5 –Number of exercise sessions attended by locality (Range)

Locality	All	Routine CR	GEx Treatment
All localities	15 (62; n =27)	10 (16; n = 17)	46 (62; n = 10)
Hull	16 (62; n = 6)	16 (16; n = 5)	62 (0; n =1)
ERY	12 (45; n =9)	11 (15; n =8)	46 (0; n =1)
Grimsby	12 (16; n =3)	10 (12; n =2)	16 (0; n =1)
Scarborough	54 (0; n =1)	0 (0; n =0)	54 (0; n =1)
No Venue	23 (46; n =8)	0 (0; n =2)	46 (46; n =6)

ERY = East Riding of Yorkshire

6.4.2 Changes in Cardiorespiratory Fitness and Ventilatory Efficiency

Data for VO_{2peak} and VAT were not normally distributed however Log_{10} transformation successfully normalised data distribution. Covariates considered for VO_{2peak} change were baseline VO_{2peak}, change in peak HR as well as peak RER between visit 1 and 2. Covariates considered for VE/VCO_2 slope were baseline VE/VCO_2 slope, change in peak RER as well a change in peak HR between visit 1 and 2. Baseline VAT was the only covariate considered for VAT change.

There was a significant moderate correlation between baseline VO_{2peak} and VO_{2peak} change (r=-0.398; p=0.040) as well as VO_{2peak} change and RER change (r=0.419; p=0.033). No significant correlation was found between VO_{2peak} change and peak HR change (r=0.210; p=0.304). VE/VCO_2 slope change was moderately correlated with baseline VE/VCO_2 slope (r=-0.485; p=0.010). There was no significant correlation between VE/VCO_2 slope change and peak RER change (r=0.361; p=0.070) or VE/VCO_2 slope change and peak HR change (r=-0.179; p=0.372). No significant correlation was found between VAT change and baseline VAT (r=0.169; p=0.409). Covariates included in CRF analysis were baseline VO_{2peak} and RER change for change in VO_{2peak} and baseline VE/VCO_2 slope for VE/VCO_2 slope change.

6.4.3 Change in VO_{2peak}

n=13 patients achieved peak CPET criteria at visit 1 and, visit 2. There was no significant main effect (0.89 ml·kg^{-1}·min^{-1}; 95% CI -0.30 to 2.09 ml·kg^{-1}·min^{-1}; p=0.058; η_p^2 = 0.136) or group effect (control 21.48 ml·kg^{-1}·min^{-1}; 17.82 to 25.14 ml·kg^{-1}·min^{-1}; GEx treatment 23.50 ml·kg^{-1}·min^{-1}; 95% CI 18.73 to 28.27 ml·kg^{-1}·min^{-1}; p=0.674; η_p^2 = 0.007) for VO_{2peak}. There was however a significant interaction effect [Figure 2a, Table 7] (p=0.035). VO_{2peak} significantly increased in the GEx treatment group (2.08 ml·kg^{-1}·min^{-1}; 95% CI 1.88 to 3.97 ml·kg^{-1}·min^{-1}; p=0.014) whilst VO_{2peak} amongst routine CR patients (-0.29 ml·kg^{-1}·min^{-1}; -1.75 to 1.16 ml·kg^{-1}·min^{-1}; p=0.841). The effect size for the interaction was large (η_p^2=0.166), with a VO_{2peak} change in the GEx treatment group exceeding the MCID (1.56 ml·kg^{-1}·min^{-1}). The inclusion of baseline VO_{2peak} did not significantly alter the interaction (routine CR adjusted mean; -0.34 ml·kg^{-1}·min^{-1}; 95% -1.71 to 1.04 ml·kg^{-1}·min^{-1}; GEx treatment adjusted mean: 2.16 ml·kg^{-1}·min^{-1}; 95% CI 0.364 to 3.95 ml·kg^{-1}·min^{-1} p=0.032; η_p^2 = 0.178). The inclusion or peak RER change reduced the significance of the interaction (routine CR adjusted mean; -0.16 ml·kg^{-1}·min^{-1}; 95% -1.61 to 1.29 ml·kg^{-1}·min^{-1}; GEx treatment adjusted mean: 1.72 ml·kg^{-1}·min^{-1}; 95% CI -0.121 to 3.57 ml·kg^{-1}·min^{-1}, p=0.115; η_p^2 = 0.104) however the mean change in the GEx treatment group was still larger than the MCID.

6.4.4 Change in VAT

The main effect for VAT was significant (1.85 ml·kg^{-1}·min^{-1}; 95% CI 1.08 to 2.62 ml·kg^{-1}·min^{-1}; p<0.001) with a corresponding large effect size (η_p^2=0.508) and a mean change that exceeded the MCID (0. 92 ml·kg^{-1}·min^{-1}). There was no significant group effect (control 13.87 ml·kg^{-1}·min^{-1}; 95% CI 11.54 to 16.20 ml·kg^{-1}·min^{-1}; GEx treatment 16.54 ml·kg^{-1}·min^{-1}; 95% CI 13.33 to 19.74 ml·kg^{-1}·min^{-1}; p=0.240; η_p^2 = 0.057), however there was a significant interaction effect [Figure 2b, Table 7] (p<0.001; η_p^2= 0.405). The GEx treatment group significantly increased their VAT (3.35

ml·kg^{-1}·min^{-1}; 95% CI 2.11 to 4.59 ml·kg^{-1}·min^{-1}; p<0.001) compared to changes in routine CR (0.35 ml·kg^{-1}·min^{-1}; 95% CI -0.56 to 1.25 ml·kg^{-1}·min^{-1}; p=0.391). Only the GEx treatment achieved the MCID for VAT.

6.4.5   Change in VE/VCO$_2$ Slope

The main effect for VE/VCO$_2$ was significant [Figure 2c, Table 6] (-3.23; 95% CI -5.21 to -1.26; p=0.002) with large corresponding effect size (η_p^2=0.312) and a mean change greater than the MCID (-0.89). There were no significant group (-4.13; -8.77 to 0.50; p = 0.078; η_p^2 = 0.119) or interaction effects (-3.06; 95% CI -5.46 to -0.65; p = 0.858; η_p^2 = 0.001). Both groups (routine CR: -3.06; 95% CI -5.46 to -0.65; GEx treatment: -3.40; 95% CI -6.54 to -0.27) exceeded the MCID for VE/VCO$_2$ slope reduction. Inclusion of baseline VE/VCO$_2$ failed to significantly alter the interaction effect (routine CR adjusted mean; -3.73 ml·kg^{-1}·min^{-1}; 95% -5.76 to -1.68 ml·kg^{-1}·min^{-1}; GEx treatment adjusted mean: -2.27 ml·kg^{-1}·min^{-1}; 95% CI -4.96 to 0.42 ml·kg^{-1}·min^{-1}, p=0.392; η_p^2=0.031).

6.4.6   Other Clinical and Exercise Test Variables

BMI and resting haemodynamic variables are presented in Table 7 with key peak CPET variables. Peak Borg score remained non-normally distributed despite attempting data transformation. On non-parametric analysis. There was a significant main effect for BMI (p=0.029; η_p^2=0.176), but no significant group (p=0.798; η_p^2=0.003) or interaction effect (p=0.637; η_p^2=0.009). Despite a significant main effect and large effect size, the MCID (0.54 kg·m^{-2}) was not achieved by either group. Main effect (p=0.171; η_p^2=0.171) and group effect (p=0.340; η_p^2=0.037) for resting systolic BP were not significant however there was a significant interaction effect (p=0.002; η_p^2=0.317). Routine CR saw a significant reduction in systolic BP (-

12 mmHg; 95% CI -18 to -6 mmHg; p=0.001) whereas GEx treatment did not (5 mmHg; 95% CI -3 to 13 mmHg; p=0.220). There was a significant main effect for diastolic BP (-4 mmHg; 95% CI -9 to 0 mmHg; p=0.040; (η_p^2=0.159), but no group (p=0.162; η_p^2=0.077) or interaction effect (p=0.059; η_p^2=0.059). No main (p=0.052; η_p^2=0.143), group (p=0.395; η_p^2=0.029) or interaction effect was observed for resting HR (p=0.951; η_p^2<0.001).

There was a main effect for RER (p=0.001; η_p^2=0.367), but no group (p=0.798; η_p^2=0.003) or interaction effect (p=0.233; η_p^2=0.059). Nor were there any significant differences in peak Borg scores between visits for GEx treatment (0; range 5) or routine CR (1; range 12). No main (p=0.672; η_p^2=0.007), group (p=0.146; η_p^2=0.083) or interaction effects (p=0.767; η_p^2=0.004) for peak HR was found. The main effect for HRR was also non-significant (p=0.328) as was the group (p=0.224; η_p^2=0.224) and interaction effect (p=0.820; η_p^2=0.002). Likewise, the main effect for systolic BP was non-significant (p=0.594; η_p^2=0.012), as was group (p=0.522; η_p^2=0.017) and interaction effect (p=0.609; η_p^2=0.011). There was no significant main (p=0.056; η_p^2=0.138), group (p=0.699; η_p^2=0.006) or interaction effect (p=0.744; η_p^2=0.004) for diastolic BP nor was there a main (p=0.683; η_p^2=0.007) group (p=0.238; η_p^2=0.026) or interaction effect (p=0.424; η_p^2=0.026) for rate pressure product. There was a significant main effect for Peak Watts (p=0.016; η_p^2=0.212) but no group (p=0.830; η_p^2=0.002) or interaction effect (p=0.508; η_p^2=0.018). Total exercise duration demonstrated a significant main effect (p=0.003; η_p^2=0.307), but no group effect (p=0.798; η_p^2=0.003). The interaction effect of exercise duration was significant (p=0.034; η_p^2=0.168).

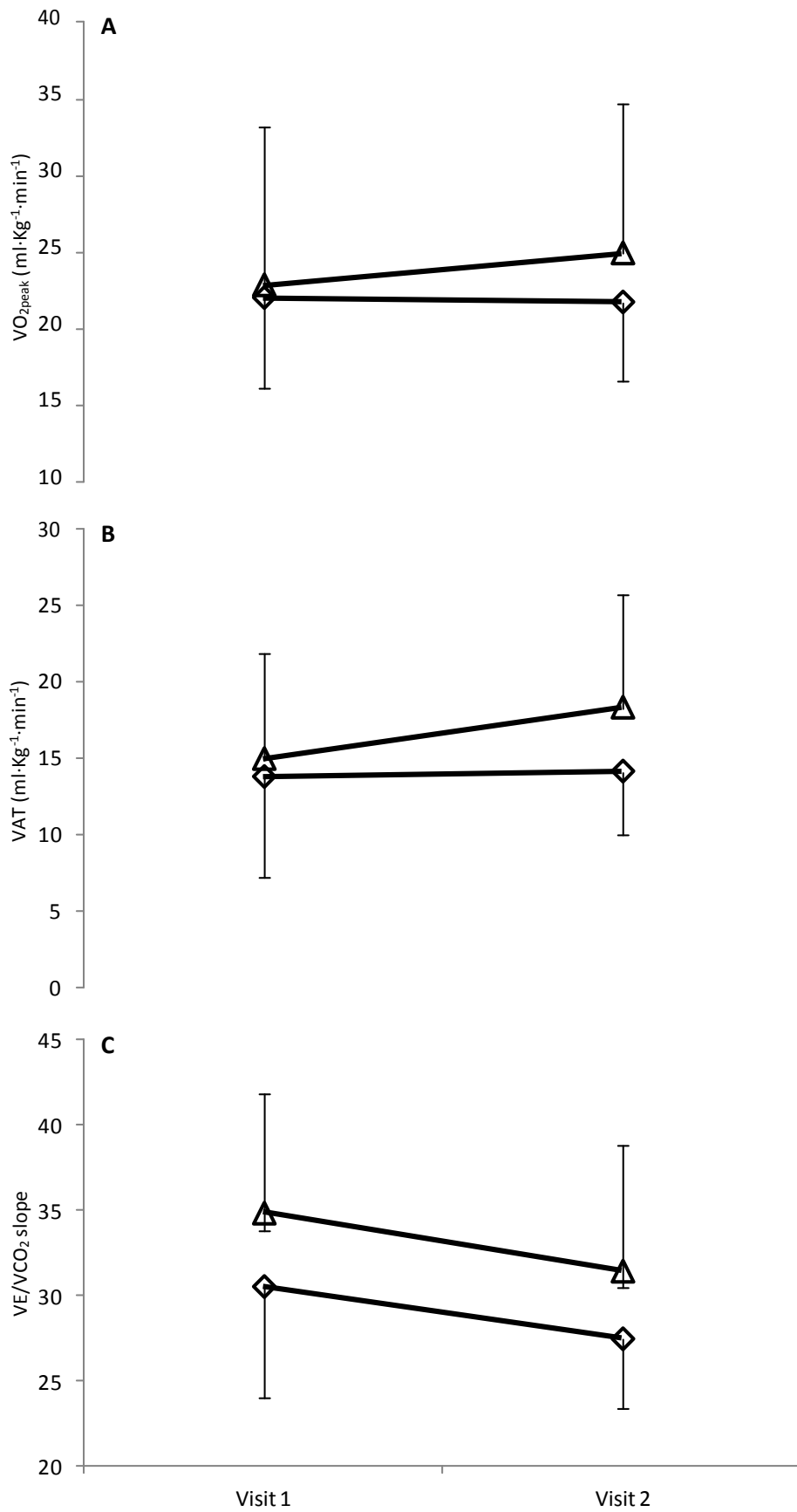**Figure 2** – Figure shows significant interaction effect for VO_{2peak} (panel A) and VAT (panel B) as well as main effect for VE/VCO_2 slope (panel C).

* = Significant Interaction; Δ = GEx Treatment Group; ◊ = Routine CR;

Table 7 – Change in key cardiopulmonary exercise test variables (mean ± SD; mean change with 95% CI)

	Routine CR (±SD)		Mean Change (95% CI)	GEx Treatment (±SD)		Mean Change (95% CI)	*P*-Value		
	Visit 1	Visit 2		Visit 1	Visit 2		Time	Group	Time x Group
VO_{2peak} $(ml·kg^{-1}·min^{-1})$	21.63 ± 5.87	21.34 ± 5.12	-0.29 (-1.75 to 1.16)	22.46 ± 10.29	24.54 ± 9.81	2.08 (1.88 to 3.97)	0.058	0.674	0.035*
VO_2 at VAT $(ml·kg^{-1}·min^{-1})$	13.69 ± 3.56	14.04 ± 3.63	0.35 (-0.56 to 1.25)	14.86 ± 5.97	18.21 ± 6.90	3.35 (2.11 to 4.59)	<0.001*	0.240	<0.001*
VE/VCO_2 Slope	30.54 ± 6.54	27.48 ± 4.14	-3.06 (-5.46 to -0.65)	34.84 ± 6.97	31.44 ± 7.36	-3.40 (-6.54 to -0.27)	0.002*	0.119	0.858

SD = Standard Deviation; 95% CI = 95% Confidence Interval; VO_{2peak} = Peak Oxygen Uptake; VO_2 at VAT = Oxygen Uptake at Ventilatory Anaerobic Threshold; VE = Minute Ventilation; VCO_2 = Carbon Dioxide Elimination
*Significant P-Value

6.4.7 Exercise Dose Response

Spearman correlation showed a moderate positive association between the number of exercise sessions conducted and the change in VO_{2peak} (r=0.434, p=0.024). Non-parametric ROC curve analysis (Figure 3) also showed that increasing the number of exercise sessions increased the likelihood of an improvement in VO_{2peak} at least as large as the MCID (AUC 0.789: 95% CI 0.627 to 0.952; p=0.012). Thirteen exercise sessions was shown to delineate the number of training sessions above which, VO_{2peak} improvements beyond the MCID were likely (sensitivity: 0.900; specificity 0.632).

When ROC curve analysis was repeated with 'any improvement in VO_{2peak}' listed as the state variable, increasing the number of exercise sessions no longer predicted improvements in VO_{2peak} and the AUC marginally fell short of statistical significance (AUC 0.716; 95% CI 0.528 to 0.903; p=0.051). Although not significant, 13 exercise sessions was again found to have the highest sensitivity and specificity (sensitivity: 0.706; specificity: 0.667).
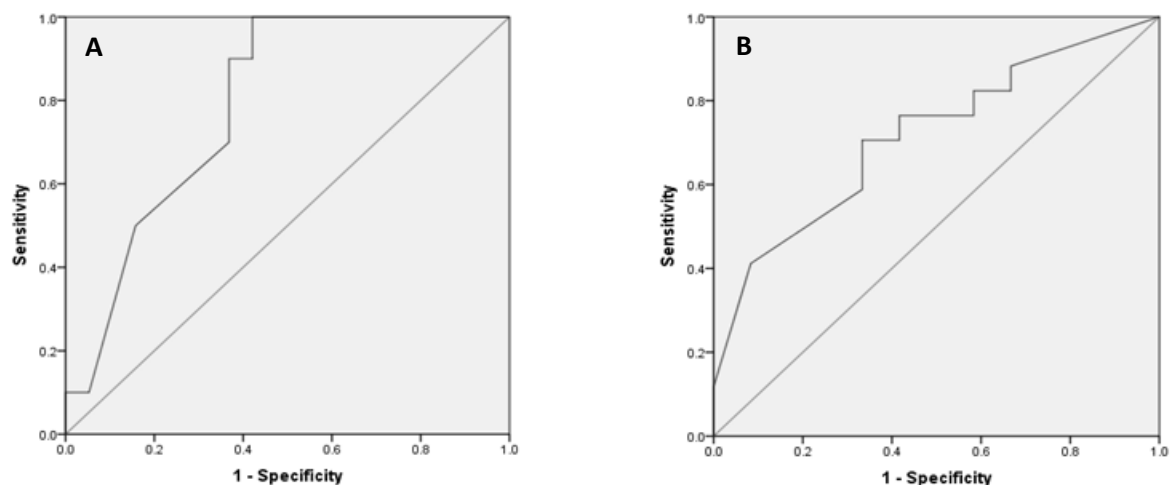

Figure 3 –ROC curves showing dose response relationship to increased number of exercise sessions. Completion of more exercise sessions increased the likelihood of patients achieving the MCID (A), but not *any* improvement in VO_{2peak} (B). Thirteen exercise sessions was shown to delineate the number of sessions above which, improvements in VO_{2peak} were expected.

Table 8 – Change in resting measurements and secondary exercise outcomes (mean ± SD; mean change with 95% CI)

Variable	Routine CR (±SD)		Mean Change (95% CI)	GEx Treatment (±SD)		Mean Change (95% CI)	P- Value		
	Visit 1	Visit 2		Visit 1	Visit 2		Time	Group	Time x Group
BMI (Kg·m^{-2})[b]	29.7 ± 3.4	29.3 ± 3.3	-0.4 (-0.9 to 0.1)	29.4 ± 4.6	28.8 ± 5.4	-0.6 (-1.3 to 0.1)	0.029*	0.798	0.637
Resting SBP (mmHg)[b]	141 ± 19	129 ± 17	-12 (-18 to -5)	139 ± 20	144 ± 21	5 (-3 to 13)	0.171	0.340	0.002*
Resting DBP	83 ± 11	74 ± 9	-8 (-14 to -3)	84 ± 7	83 ± 9	0 (-7 to 6)	0.040*	0.162	0.059
Resting HR (bpm)[b]	63 ± 16	59 ± 8	-4 (-8 to 1)	66 ± 6	63 ± 6	-4 (-10 to 2)	0.052	0.396	0.951
Peak RER[b]	1.03 ± 0.05	1.06 ± 0.05	0.03 (0.00 to 0.06)	1.01 ± 0.12	1.07 ± 0.12	0.06 (0.02 to 0.10)	0.001*	0.781	0.233
Peak Borg Score[a]	19 (Range: 13 to 20)	16 (Range: 9 to 20)	1 (Range: -8 to 4; p=0.054)	18 (Range 13 to 20)	17 (Range 15 to 20)	0 (Range: -3 to 2; p=0.785)	-	-	-
HR Max (bpm)[b]	125 ± 24	125 ± 23	0 (-7 to 7)	140 ± 25	138 ± 24	-2 (-11 to 7)	0.672	0.145	0.767
HRR (bpm)[b]	63 ± 15	66 ± 19	3 (-3 to 9)	73 ± 24	75 ± 25	2 (-6 to 9)	0.328	0.224	0.820
Peak SBP (mmHg)[b]	179 ± 22	184 ± 22	5 (-7 to 17)	187 ± 32	187 ± 25	0 (-15 to 16)	0.594	0.522	0.609
Peak DBP (mmHg)[b]	90 ± 14	97 ± 16	7 (-1 to 15)	93 ± 15	98 ± 12	5 (-5 to 15)	0.056	0.699	0.744
RPP[b]	226.21 ± 65.28	236.00 ± 61.95	9.79 (-10.23 to 29.80)	262.46 ± 68.03	259.26 ± 66.14	-3.20 (-29.30 to 22.89)	0.683	0.238	0.424
Peak Watts[b]	110.29 ± 41.5	116.18 ± 43.24	5.88 (-1.80 to 13.56)	112.50 ± 62.64	122.50 ± 59.45	10.00 (-0.02 to 20.02)	0.016*	0.830	0.508
Total Exercise Duration (Secs)[b]	586.29 ± 195.12	620.65 ± 244.15	34.35 (-35.04 to 103.75)	583.80 ± 287.52	704.70 ± 263.83	120.90 (30.42 to 211.38)	0.003*	0.798	0.034*

SD = Standard Deviation; CI = Confidence Intervals; kg·m^{-2} = Kilograms per Metre Squared; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; mmHg = Millimetres of Mercury; HR = Heart Rate; bpm = Beats per Minute; RER = Respiratory Exchange Ratio; = RPP = Rate Pressure Product; Secs = Seconds;

[b] = Parametric Test; [a] = Non-Parametric Test; * = Significant Difference

6.5 Post Hoc Analysis - Chosen Care Plan

When attending their second visit, some patients reported not attending routine CR or not using their GEx TM equipment. Based on self-reported information, patients were regrouped according to their actual treatment. The aim of doing so was to determine any differences in CRF improvements for patients not undertaking structured exercise, conducting routine CR or supplementing routine CR with the GEx TM system. Two patients randomised to the GEx treatment group had received faulty equipment and were reassigned to a no-exercise control group having not undertaken any structured exercise. Three patients who were originally randomised to routine CR reported not undertaking any structured exercise and were also re- assigned to the no-exercise control group. One further patient who was originally randomised to the GEx treatment group received faulty equipment but did participate in routine CR. They were therefore reassigned to the routine CR group. Figure 4 summarises the process used to reassign patients to new groups.

6.5.1 Change in VO_{2peak}

After regrouping patients, the main effect for VO_{2peak} was not significant (0.71 ml·kg^{-1}·min^{-1}; 95% CI -0.58 to 2.00 ml·kg^{-1}·min^{-1}; p=0.134; η_p^2 = 0.091), nor was the group (Control 20.54 ml·kg^{-1}·min^{-1}; 95% CI 13.64 to 27.44 ml·kg^{-1}·min^{-1}; Routine CR 22.21 ml·kg^{-1}·min^{-1}; 95% CI 18.22 to 26.19 ml·kg^{-1}·min^{-1}; GEx Treatment 23.49 ml·kg^{-1}·min^{-1}; 95% CI 17.65 to 29.32 ml·kg^{-1}·min^{-1}; p=0.860 η_p^2 = 0.012) or interaction effect (Control -0.48 ml·kg^{-1}·min^{-1}; 95% CI -3.19 to 2.23 ml·kg^{-1}·min^{-1}; Routine CR -0.01 ml·kg^{-1}·min^{-1}; 95% CI -1.55 to 1.58 ml·kg^{-1}·min^{-1}; GEx treatment 2.63 ml·kg^{-1}·min^{-1}; 95% CI 0.34 to 4.92 ml·kg^{-1}·min^{-1}; p=0.099). The effect size for the interaction effect however was large η_p^2 = 0.175) and the GEx treatment group was the only group to experience a VO_{2peak} increase MCID (1.55 ml·kg^{-1}·min^{-1}). Furthermore the 95% CI did not cross 0 (Table 8, Figure 4a). The failure for these CI to reach statistical significance could be attributed to analysis of log transformed data and representation of arithmetic means.

6.5.2 Change in VAT

There was a significant main effect for VAT (1.69 ml·kg^{-1}·min^{-1}; 95% CI 0.77 to 2.60 ml·kg^{-1}·min^{-1} p=0.002; η_p^2 = 0.355). No significant group effect (Control 13.71 ml·kg^{-1}·min^{-1}; 95% CI 9.33 to 18.09 ml·kg^{-1}·min^{-1}; Routine CR 14.19 ml·kg^{-1}·min^{-1}; 95% CI 11.66 to 16.72 ml·kg^{-1}·min^{-1}; GEx treatment 17.20 ml·kg^{-1}·min^{-1}; 95% CI 13.20 to 21.20 ml·kg^{-1}·min^{-1}; p=0.548; η_p^2 = 0.051) was found. There was however a significant interaction (p=0.044). The GEx treatment group significantly increased their VAT (3.56 ml·kg^{-1}·min^{-1}; 95% CI 1.85 to 5.27 ml·kg^{-1}·min^{-1}; p=0.001) whilst the control group (0.92 ml·kg^{-1}·min^{-1}; 95% CI -1.10 to 2.65 ml·kg^{-1}·min^{-1}; p=0.475) and routine CR group did not (0.72 ml·kg^{-1}·min^{-1}; 95% CI -0.36 to 1.80 ml·kg^{-1}·min^{-1}; p=0.139) Table 8, Figure 4b). A large effect size for the interaction effect was also shown η_p^2 = 0.237). The GEx treatment group was the only group to experience a VAT increase greater than the MCID (0.92 ml·kg^{-1}·min^{-1}).

6.5.3 VE/VCO$_2$ Slope

The main effect for VE/VCO$_2$ slope was significant (p=0.008; η_p^2 = 0.261). The mean slope decrease (-3.04; 95%CI -5.20 to - 0.88) exceeded the MCID (-1.34). Although there was no significant group effect (p = 0.214) there was a large effect size for group effect (η_p^2 = 0.214) [Table 9, Figure 4c]. Group differences exceeding the MCID were between the GEx treatment and routine CR groups (4.62; 95 CI -2.21 to 11.39) as well as the GEx treatment and control groups (4.49; 95% CI -4.18 to 13.16). No clinically important difference between routine CR and the control group was found (-0.12; 95% CI -7.77 to 7.52).
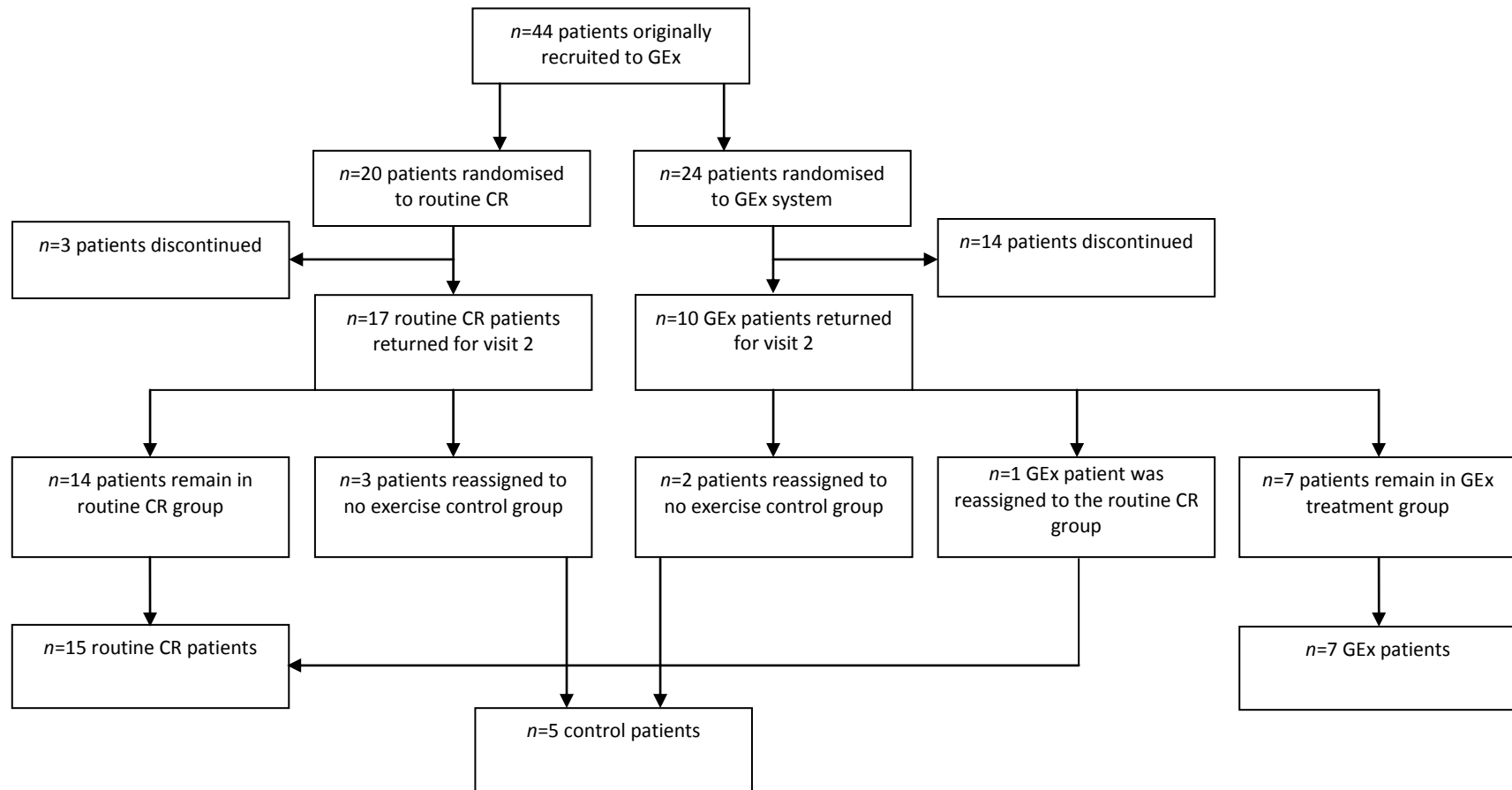
Figure 4 – Flow diagram showing the process of reassigning patients to new groups when deviation from initial randomisation was reported.
GEx = Graded Exercise; CR = Cardiac Rehabilitation;

There were no significant interactions (Control -2.80; 95% CI -7.33 to 1.73; Routine CR -3.46; 95% CI -6.08 to -0.85; GEx treatment -2.86; 95% CI -6.69 to 0.96; p=0.947; $\eta_p^2 = 0.005$).

6.6 Discussion

Patients in the GEx treatment group experienced a significant improvement in VO_{2peak} and VAT compared to the routine CR group. Patients utilising the GEx system undertook a greater number of exercise training sessions (routine CR 10; range 0 to 16; GEx treatment 46; range 0 to 62; p=0.009) to achieve those improvements. Increasing the number of exercise sessions appeared to increase the likelihood of achieving a clinically meaningful improvement in VO_{2peak} (r=0.434; p=0.024; AUC 0.789: 95% CI 0.627 to 0.952; p=0.012). Patients conducting 13 or more training sessions were more likely to achieve VO_{2peak} improvements than those who conducted less. The feedback provided by the GEx system may also have played a role in improving CRF by increasing exercise adherence and optimising patient time in training zone. When measured using 'gold standard' methods, the exercise dose prescribed in routine CR programmes appears insufficient to increase VO_{2peak} or VAT. Despite this, both groups experienced an improvement in ventilatory efficiency, demonstrated by a significant reduction in the VE/VCO_2 slope.

Discrepancy between peak CRF improvement in the present study and those of other studies may be due to the different methods used to quantify CRF. Whilst VO_{2peak} is considered the 'gold-standard' measurement of peak aerobic fitness, most CR programmes and many studies in the UK do not conduct CPET. Instead, sub-maximal exercise testing and estimation of METs through predictive VO_2 equations are used. The inaccuracies of doing so can lead to erroneous measurements of CRF.

Table 6 – Change in key cardiopulmonary exercise test variables (mean ± SD; mean change with 95% CI)

	Routine CR (±SD)		Mean Change (95% CI)	GEx Treatment (±SD)		Mean Change (95% CI)	*P*-Value		
	Visit 1	Visit 2		Visit 1	Visit 2		Time	Group	Time x Group
VO_{2peak} (ml·kg·min^{-1})	21.63 ± 5.87	21.34 ± 5.12	-0.29 (-1.75 to 1.16)	22.46 ± 10.29	24.54 ± 9.81	2.08 (1.88 to 3.97)	0.058	0.674	0.035*
VO_2 at VAT (ml·kg·min^{-1})	13.69 ± 3.56	14.04 ± 3.63	0.35 (-0.56 to 1.25)	14.86 ± 5.97	18.21 ± 6.90	3.35 (2.11 to 4.59)	<0.001*	0.240	<0.001*
VE/VCO_2 Slope	30.54 ± 6.54	27.48 ± 4.14	-3.06 (-5.46 to -0.65)	34.84 ± 6.97	31.44 ± 7.36	-3.4 (-6.54 to -0.27)	0.002*	0.119	0.858

SD = Standard Deviation; 95% CI = 95% Confidence Interval; VO_{2peak} = Peak Oxygen Uptake; VO_2 at VAT = Oxygen Uptake at Ventilatory Anaerobic Threshold; VE = Minute Ventilation; VCO_2 = Carbon Dioxide Elimination
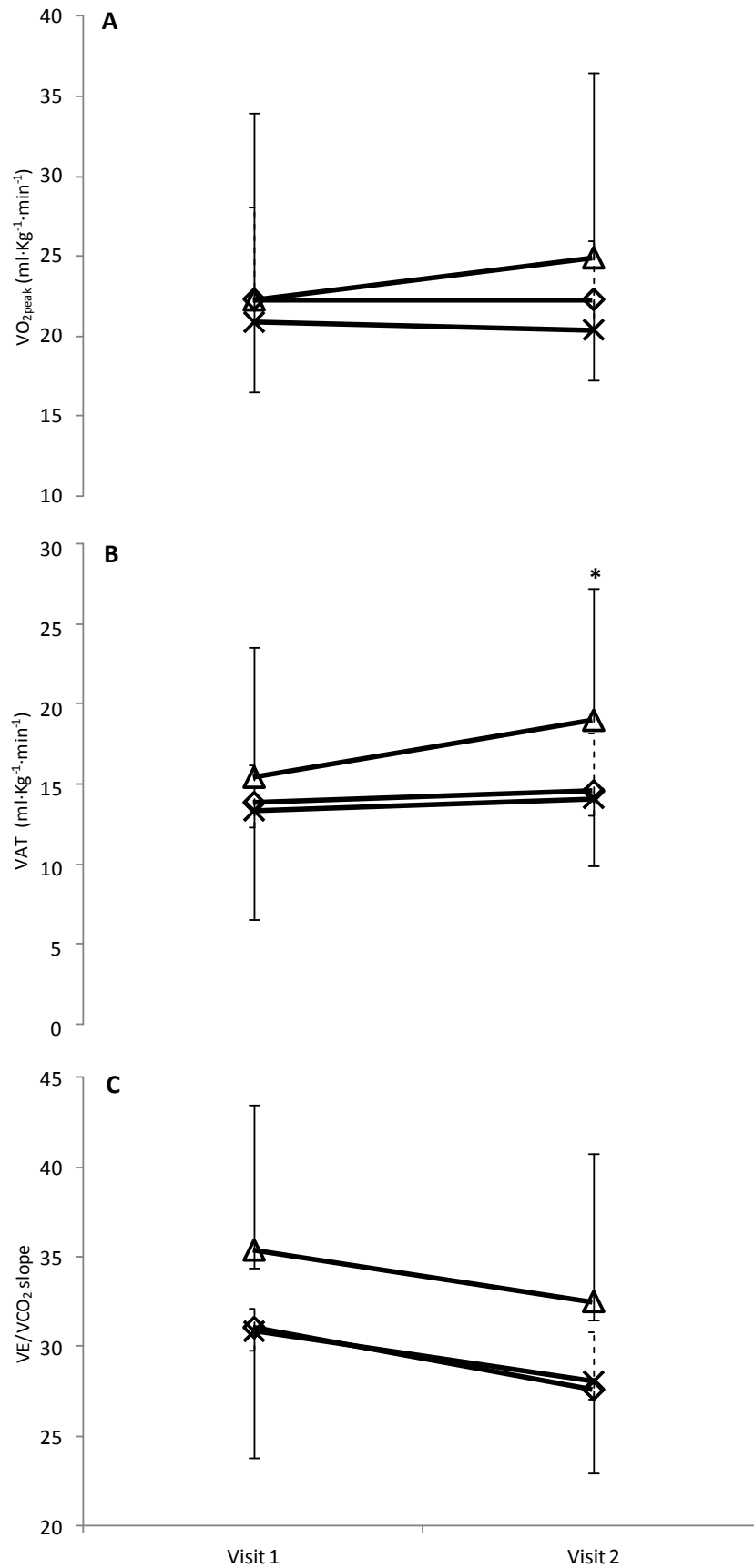*Significant P-Value

Figure 5 – Figure shows large effect size for VO_{2peak} interaction (panel A), significant interaction effect for VAT (panel B) and significant main effect for VE/VCO_2 slope (panel C).

* = Significant Interaction; Δ = GEx Treatment Group; ◊ = Routine CR; X = Control Group

METs are based on VO_2 equations predicated on an assumption that VO_2 increases linearly with work rate. This relationship is in fact weaker in patients with cardiovascular disease and such equations may overestimate VO_2 (Wasserman et al., 2011). Where studies report MET change, readers must assume that a MET increase confers an increase in VO_{2peak}. However all that the reader can be certain of is that there was an increase in work rate. Studies reporting meaningful improvements in METs may not have found meaningful improvements in $VO_{2peak,}$. Change in METs and VO_{2peak} are not synonymous, a factor that should be given consideration when evaluating the efficacy of UK based CR programmes (Ingle and Carroll, 2013).

Although these are plausible explanations as to why the results of the present study differ to that of published research, these findings may also indicate ineffective exercise training. There are currently limited data to affirm or refute the efficacy of CR exercise practices in the UK (Sandercock et al., 2013b, West et al., 2012) and controversially, there is substantial disparity between CR in UK clinical practice and international studies.

Despite current ACPICR (2015) guidance, there is only limited data reporting CRF benefits of exercise training lasting for approximately 30 minutes per session, twice per week for approximately 8 weeks at 40-60% of estimated HRR (Hugh and Mullee, 1990, Kovoor et al., 2006, Yu et al., 2003) and an absence of contemporary data detailing VO_{2peak} change. Conversely, a substantial body of evidence has reported CRF and VO_{2peak} improvements when exercise prescriptions are based on maximal exercise tests and/or training is delivered 3 or more times per week for 12 weeks or more (Ades et al., 2009a, Carroll et al., 2011, Dendale et al., 2005, Dugmore et al., 1999, Lavie and Milani, 1996, Wisløff et al., 2007). On this basis, CR services may not be implementing evidence based practice and it is therefore unsurprising that outcomes appear sub-optimal.

6.6.1 VO$_{2peak}$ Change Following GEx TM Treatment

In contrast to routine CR (-1%), the GEx treatment cohort experienced an 8% increase in VO$_{2peak}$. When re-grouped the GEx treatment group was still the only group to experience an increase in VO$_{2peak}$ exceeding than the MCID (11%). These findings are comparable to studies of similar duration, frequency and modality (Nieuwland et al., 2000, Warburton et al., 2005) and if sustained, may confer a reduction in preventable morbidity and mortality (Keteyian et al., 2008).

To achieve this, patients undertaking GEx treatment had to participate in more exercise sessions than those undertaking routine CR (routine CR 10; range 16; GEx Treatment 46; range 62). ROC curve analysis showed that clinically meaningful improvements in VO$_{2peak}$ were associated with the number of exercise sessions attended. Cumulative exercise dose appeared to have an important role in improving VO$_{2peak}$ when prescribing moderate intensity exercise to patients with CHD.

The VO$_{2peak}$ improvement amongst GEx treatment patients is unlikely to have occurred secondary to reduced body mass as no group experienced a clinically meaningful reduction in BMI. However, increased patient effort cannot be excluded as a possible cause because peak RER was higher at visit 2. The inclusion of peak RER in covariate analysis resulted in VO$_{2peak}$ change becoming non-significant (routine CR adjusted mean; -0.16 ml$\cdot$kg$^{-1}\cdot$min^{-1}; 95% -1.61 to 1.29 ml$\cdot$kg$^{-1}\cdot$min^{-1}; GEx treatment adjusted mean: 1.72 ml$\cdot$kg$^{-1}\cdot$min^{-1}; 95% CI -0.121 to 3.57 ml$\cdot$kg$^{-1}\cdot$min^{-1}p=0.115; η_p^2 = 0.104). Despite this, comparable peak Borg scores at visit 1 and 2 suggest similar efforts, and, the increase in peak RER was observed in both routine CR and GEx treatment groups. If the VO$_{2peak}$ improvement had resulted from greater patient effort then this might have been expected in both groups. Moreover the mean change in the GEx treatment group was still larger than the MCID. Therefore, VO$_{2peak}$ increase in the GEx treatment group is likely indicative of physiological adaptation.

Any physiological increase in VO$_{2peak}$ is predicated on an improvement in Q and/or a-vO$_2$.

Because approximately 85% of VO_{2peak} is underpinned by Q augmentation, in healthy individuals, central CV determinants are also thought to underpin VO_{2peak} improvement (Bassett and Howley, 2000). In cardiac populations however, the governing factors for VO_{2peak} increases are far less clear (Poole et al., 2012, Clark et al., 1996, Downing and Balady, 2011). In CHD, diastolic dysfunction (present in many CHD patients) has been strongly linked to decline in VO_{2peak} (Dekleva et al., 2014, Skaluba and Litwin, 2004). In addition, ischaemic myocardial dyskinesis may mean that SV fails to increase sufficiently leading to reduced VO_2 kinetics (Belardinelli et al., 2003, Chaudhry et al., 2009) and insufficient O_2 to meet the demands of the exercising muscle. Because of this, the principle limiting factor for peak exercise in CHD and CHF may still be centrally determined references (Critoph et al., 2014). However, reduced Q, delayed O_2 kinetics, and systemic vasoconstriction (references) may also drive peripheral changes that cause exercise intolerance at submaximal workloads (Shelton et al., 2010). Indeed, patients with CHD often suffer from endothelial dysfunction and vasoconstriction (Seals et al., 2008) which can ultimately lead to peripheral mal-adaption and exercise intolerance. Hence in CHD, both central and peripheral factors may determine improvements in VO_{2peak}

Previous studies have shown that exercise training improves diastolic/cardiac function in CHD and CHF populations (Sandri et al., 2012, Edelmann et al., 2011, Myers et al., 1999). It is therefore reasonable to consider that improved peak Q may have led to the VO_{2peak} increase in the GEx treatment group. Amongst the GEx treatment group, there was no increase in peak HR from visit 1 to visit 2 suggesting that if peak Q was the cause of the VO_{2peak} increase, it was secondary to improved peak SV, possibly due to improved diastolic function (Cardozo et al., 2015, Edelmann et al., 2011, Sandri et al., 2012, Dekleva et al., 2014). However, Murias and colleagues (2010a) demonstrated that in healthy older women, the relative contributions of different physiological adaptations contributing to increased VO_{2peak} vary across the time course of exercise training. In their study, improvements in Q were documented in the early phases of exercise training and improvements in a-vO2 diff in the later phases. Because of this, improved endothelial mediated vasodilatation mitochondrial density, and change in muscle

fibre type (type IIb to type IIa/type I) may also be responsible for the VO_{2peak} improvement (Hambrecht et al., 1997, Hambrecht et al., 1995, Wisløff et al., 2007, Hambrecht et al., 1998, Segal, 2005). Irrespective of cause, the increased exercise dose provided by the GEx TM equipment appears sufficient and therapeutically effective where increasing VO_{2peak} is the main objective.

6.6.2 Changes in VAT

As with VO_{2peak}, VAT only improved in the GEx treatment group. The mean increase was comparable to that of previous studies (Sullivan et al., 1989b, Giannuzzi et al., 2003). The superior VAT outcome may be due to the individualised training prescriptions obtained using $[La^-]b$ analysis. Exercise intensities of 1.8 to 2.3 mmol $[La^-]b$ are likely to lie at the point where an individual reaches their VAT (Binder et al., 2008). Furthermore, the GEx group were provided with continuous feedback by the TM system. Not only were patients motivated to exercise at the recommended frequency, but exercise intensity was monitored so that patients adhered to their optimised training strategy (1.8 to 2.3 mmol $[La^-]b$).

The observation that exercise training may induce CRF improvements when prescribed at the VAT has been demonstrated in healthy individuals (Keith et al., 1992, Hoffman, 1999, Londeree, 1997, Faude et al., 2009) and CHF/CHD populations (Holloszy and Coyle, 1984, Wisløff et al., 2007, Belardinelli et al., 1995). Adaptations including, change in muscle fibre type, increased mitochondrial and capillary density and, improved central perfusion may reduce haemodynamic disturbance and dependence on anaerobic metabolism. These adaptations *are* however, predicated on an appropriately prescribed and monitored dose of exercise. The imprecision of estimated HRR training zones, low intensity and short duration of non-steady state bouts of exercise (less than one minute in some instances) plus the low volume of exercise sessions may be insufficient to incur a VAT increase and may explain why VAT changes in routine CR were equivocal to the control group. Increasing a patients' VAT may

have important implications for longevity. The VAT has been shown to have significant prognostic power (Gitt et al., 2002, Wilson et al., 2010, Agostoni et al., 2013). Although in the present study VAT was determined in the majority of cases (Agostoni et al., 2013), and was generally $>11 \cdot ml \cdot kg^{-1} \cdot min^{-1}$ (Wilson et al., 2010, Gitt et al., 2002), the VAT declines with age and physical inactivity. Exercise programmes that preserve or improve the VAT therefore have good clinical rationale and may have a positive effect on morbidity and mortality rates. The improvement in VAT within the GEx treatment group can be considered an indication in treatment efficacy. On the contrary, the finding that routine CR did not improve VAT suggests inadequate exercise dose.

6.6.3   Changes in VE/VCO$_2$ Slope

The VE/VCO$_2$ slope is known for its prognostic value amongst patients with CHF (Arena et al., 2004, Robbins et al., 1999, Wilson et al., 2010, Ingle et al., 2007a, Arena et al., 2003). However, it has also been shown to have prognostic value in a heterogeneous group of cardiac patients including those with CHD (Tsurugaya et al., 2006). Moreover, elevations in the VE/VCO$_2$ slope are able to discriminate patients with CHD who have cardiac remodelling and heightened neurohormonal activation (Van de Veire et al., 2006).

A complex myriad of physiological mechanisms underpin VE/VCO$_2$ slope abnormality including ventilatory perfusion mismatch and chemoreceptor hypersensitivity (Tomita et al., 2003, Ciarka et al., 2006). Passino and colleagues (2006) found NT-proBNP to be *the* only independent predictor of VE/VCO$_2$ slope. Increased myocardial wall stress imposed by cardiac remodelling likely increases neurohormonal activation (indicating haemodynamic failure). In turn, adrenergic drive may be enhanced whilst exercise tolerance and ventilatory efficiency are depressed (Van de Veire et al., 2006). A reduction in myocardial wall stress may therefore result in improved ventilatory efficiency and reduced VE/VCO$_2$ slope gradient. Alternatively, peripheral changes to chemoreceptor sensitivity through exposure to exercise training may

induced a more appropriate ventilatory response to exercise (Arena et al., 2008). However because any improvement in central function is likely to cause a deferred improvement in peripheral function, it is only possible to speculate the driving factors behind any improvement in ventilatory efficiency.

In the present study, all three groups (including the control group) experienced an attenuation of the VE/VCO_2 slope. Because the control group also experienced a decline in the VE/VCO_2 slope, it is unlikely that exercise training was the primary causal mechanism. Exercise beyond the respiratory compensation point (RCP) results in a non-linear ventilatory increase causing the VE/VCO_2 slope gradient to increase. Failure to sustain exercise beyond the RCP for an equal duration at visit 1 and 2 may therefore have caused a reduction in the VE/VCO_2 slope gradient. However, there was no decline in exercise duration RER across all groups making it unlikely that the slope reduction was a result of failure to sustain RCP for a comparable duration.

Alternatively, as part of standard secondary prevention, it is common for patients to commence Angiotensin converting enzyme (ACE) inhibitor therapy. ACE inhibitors have been shown to reduce VE/VCO_2 slope (Guazzi et al., 1999, McConnell et al., 1998, Arena et al., 2008) by a factor of approximately 2. The recent addition of ACE inhibitors may have contributed to the attenuation of the VE/VCO_2 slope in our study. ACE inhibitors improve left ventricular filling pressures thereby reducing myocardial stress (Bay et al., 2003) and improving ventilatory efficiency. If so, improvements in NT-proBNP may also be expected (Passino et al., 2006). NT-proBNP (Appendix 8) analysed in our study (not reported due to multiple assay failures) showed a downward trend for the main effect (-38.88 ng/L; 95% CI -87.14 to 9.39 ng/L; p=0.097; η_p^2=0.162) with no interaction (p=0.193; η_p^2=0.103) or group effect (p=0.391; η_p^2=0.046). This might indicate that improvements to cardiac function, contributed to the reduction in VE/VCO_2 slope observed in all three groups. However, because ACE inhibitors act as a potent vasodilator, the effects of this medication on blood supply to the peripheral musculature are also possible. Because the date that patients initiated ACE-inhibitor therapy was not reported, it is not possible to confidently state that this group of medications were responsible for the

improvement in ventilatory efficiency. Irrespective of cause, no additional benefits were accrued with respect to VE/VCO$_2$ slope in patients undertaking exercise training.

6.7 Conclusion

This study indicates that routine CR programmes in the Hull and East Riding of Yorkshire area do not improve VO$_{2peak}$ or VAT. VO$_{2peak}$ and VAT only improved in response to the increased training dose of the GEx treatment group. Thirteen exercise sessions appeared to be the minimum number of exercise sessions require to elicit improvements in VO$_{2peak}$. Personalised exercise prescription may also have contributed to the improvement in peak and submaximal CRF outcomes. Whilst increasing VO$_{2peak}$ is a widely advocated objective of CR programmes, increasing patients' VAT may also be a valid and realistic therapeutic target for CR interventions. However, more CHD specific research is needed to quantify its impact on patient quality of life and prognosis. Although change in VE/VCO$_2$ slope was not exclusive to exercise training, other therapeutic factors may influence its attenuation. In the months following a cardiac event, natural recovery of myocardial performance, addition of beta- blockade or newly initiated ACE inhibitors may play a role in improving ventilatory efficiency.

Whilst the GEx TM system delivered superior CRF improvements, study attrition was high and largely due to equipment failure. The GEx TM system does not yet appear to be a realistic way to deliver CR. Equipment development is needed before serious consideration to its implementation is given. The findings of this study support the findings of Sandercock and colleagues (2013b). CR in the UK does not appear to deliver the CRF gains expected of evidence based service.

6.8 Limitations

The major limitation to this study is that it was originally designed to determine adherence to the GEx system, not improvements in VO_{2peak}. Although the study is a-priori, using the data for an alternative purpose may increase the chances of type 1 error. Bonferroni correction was used to correct for this, however the study is further compounded by the high attrition rate this reducing its statistical power. Furthermore, because of the high attrition rate we only analysed data from visit 1 and 2.

A further limitation is the choice of metabolic cart which has been reported to have large measurement variability. Although Sheth et al (2013) suggest that the Innocor is reliable, they do so based on mean measurement bias. The mean bias quantifies tendencies for one measurement to consistently report higher or lower values with respect to an initial measurement. It does not describe equipment variability (Bland and Altman, 1999). The upper range of measurement error for the Innocor was 19.1%. Given that expected VO_{2peak} improvements may be less than this, measurement variability may have masked some of the CRF changes.

6.9 References

Ades, P. A., Savage, P. D., Toth, M. J., Harvey-Berino, J., Schneider, D. J., Bunn, J. Y., . . . Ludlow, M. (2009). High-Calorie-Expenditure Exercise: A New Approach to Cardiac Rehabilitation for Overweight Coronary Patients. *Circulation, 119*(20), 2671-2678. doi: 10.1161/circulationaha.108.834184

Agostoni, P., Corra, U., Cattadori, G., Veglia, F., Battaia, E., La Gioia, R., . . . Piepoli, M. F. (2013). Prognostic value of indeterminable anaerobic threshold in heart failure. *Circ Heart Fail, 6*(5), 977-987. doi: 10.1161/circheartfailure.113.000471

American Thoracic Society. (2003). ATS/ACCP Statement on cardiopulmonary exercise testing. *American Journal of Respiratory and Critical Care Medicine, 167*(2), 211.

Arena, R., Humphrey, R., & Peberdy, M. A. (2003). Prognostic ability of VE/VCO2 slope calculations using different exercise test time intervals in subjects with heart failure. *European Journal of Cardiovascular Prevention & Rehabilitation, 10*(6), 463-468. doi: 10.1097/01.hjr.0000102817.74402.5b

Arena, R., Myers, J., Aslam, S. S., Varughese, E. B., & Peberdy, M. A. (2004). Peak VO2 and VE/VCO2 slope in patients with heart failure: a prognostic comparison. *American Heart Journal, 147*(2), 354-360. doi: 10.1016/j.ahj.2003.07.014

Association of Chartered Physiotherpists in Cardiac Rehabilitation [ACPICR]. (2015). Standards for physical activity and exercise in the cardiovascular population. In P. Heather, B. Helen, B. Samantha, B. John, Laura Burgess, G. Keri, G. Fiona, Tim Grove, Sally Turner & W. Catrin (Eds.), (3rd ed.): Association of Chartered Physiotherapists in Cardiac Rehabilitation (ACPICR).

Bäck, M., Wennerblom, B., Wittboldt, S., & Cider, Å. (2008). Effects of high frequency exercise in patients before and after elective percutaneous coronary intervention. *European Journal of Cardiovascular Nursing, 7*(4), 307-313.

Balady, G. J., Jette, D., Scheer, J., Downing, J., The Massachusetts Association of Cardiovascular, & Pulmonary Rehabilitation Database Co-investigators. (1996). Changes in Exercise Capacity Following Cardiac Rehabilitation in Patients Stratified According to Age and Gender: Results of the Massachusetts Association of Cardiovascular and Pulmonary Rehabilitation Multicenter Database. *Journal of Cardiopulmonary Rehabilitation and Prevention, 16*(1), 38-46.

Bassett, D., & Howley, E. T. (2000). Limiting factors for maximum oxygen uptake and determinants of endurance performance. *Medicine and Science in Sports and Exercise, 32*(1), 70-84.

Beauchamp, A., Worcester, M., Ng, A., Murphy, B., Tatoulis, J., Grigg, L., . . . Goble, A. (2013). Attendance at cardiac rehabilitation is associated with lower all-cause mortality after 14 years of follow-up. *Heart, 99*(9), 620-625. doi: 10.1136/heartjnl-2012-303022

Belardinelli, R., Paolini, I., Cianci, G., Piva, R., Georgiou, D., & Purcaro, A. (2001). Exercise training intervention after coronary angioplasty: the ETICA trial. *Journal of the American College of Cardiology, 37*(7), 1891-1900. doi: 10.1016/s0735-1097(01)01236-0

Bethell, H. J., & Mullee, M. A. (1990). A controlled trial of community based coronary rehabilitation. *British Heart Journal, 64*(6), 370-375. doi:10.1136/hrt.64.6.370

Bland, J. M., & Altman, D. G. (1999). Measuring agreement in method comparison studies. *Statistical Methods in Medical Research, 8*(2), 135-160. doi: 10.1177/096228029900800204

Borg, G. A. (1982). Psychophysical bases of perceived exertion. *Medicine and Science in Sports and Exercise, 14*(5), 377-381.

British Association for Cardiac Rehabilitation. (2006). *British Association For Cardiac Rehabilitation: Exercise instructor training module* (4th ed.). Leeds: Human Kinetics.

Brodie, D., Bethell, H., & Breen, S. (2006). Cardiac rehabilitation in England: a detailed national survey. *European Journal of Cardiovascular Prevention & Rehabilitation, 13*(1), 122- 128. doi:10.1097/01.hjr.0000192741.04103.d3

Carroll, S., Tsakirides, C., Hobkirk, J., Moxon, J. W. A., Moxon, J. W. D., Dudfield, M., & Ingle, L. (2011). Differential Improvements in Lipid Profiles and Framingham Recurrent Risk Score in Patients With and Without Diabetes Mellitus Undergoing Long-Term Cardiac Rehabilitation. *Archives of Physical Medicine and Rehabilitation, 92*(9), 1382-1387. doi: 10.1016/j.apmr.2011.04.013

Ciarka, A., Cuylits, N., Vachiery, J.-L., Lamotte, M., Degaute, J.-P., Naeije, R., & van de Borne, P. (2006). Increased Peripheral Chemoreceptors Sensitivity and Exercise Ventilation in Heart Transplant Recipients. *Circulation, 113*(2), 252-257. doi: 10.1161/circulationaha.105.560649

Dendale, P., Berger, J., Hansen, D., Vaes, J., Benit, E., & Weymans, M. (2005). Cardiac Rehabilitation Reduces the Rate of Major Adverse Cardiac Events after Percutaneous Coronary Intervention. *European Journal of Cardiovascular Nursing, 4*(2), 113-116. doi: 10.1016/j.ejcnurse.2004.11.003

Doherty, P., & Lewin, R. (2012). The RAMIT trial, a pragmatic RCT of cardiac rehabilitation versus usual care: what does it tell us? *Heart, 98*(8), 605-606. doi: 10.1136/heartjnl- 2012-301728

Dorn, J., Naughton, J., Imamura, D., Trevisan, M., & Staff, f. t. N. P. (1999). Results of a Multicenter Randomized Clinical Trial of Exercise and Long-Term Survival in Myocardial Infarction Patients: The National Exercise and Heart Disease Project (NEHDP). *Circulation, 100*(17), 1764-1769. doi:10.1161/01.cir.100.17.1764

Dugmore, L., Tipson, R., Phillips, M., Flint, E., Stentiford, N., Bone, M., & Littler, W. (1999). Changes in cardiorespiratory fitness, psychological wellbeing, quality of life, and vocational status following a 12 month cardiac exercise rehabilitation programme. *Heart, 81*(4), 359-366.

Faude, O., Kindermann, W., & Meyer, T. (2009). Lactate Threshold Concepts. *Sports Medicine, 39*(6), 469-490. doi:10.2165/00007256-200939060-00003

Frederix, I., Driessche, N. V., Hansen, D., Berger, J., Bonne, K., Alders, T., & Dendale, P. (2015). Increasing the medium-term clinical benefits of hospital-based cardiac rehabilitation

by physical activity telemonitoring in coronary artery disease patients. *European Journal of Preventive Cardiology, 22*(2), 150-158. doi: 10.1177/2047487313514018

Gee, M. A., Viera, A. J., Miller, P. F., & Tolleson-Rinehart, S. (2014). Functional Capacity in Men and Women Following Cardiac Rehabilitation. *Journal of Cardiopulmonary Rehabilitation and Prevention, 34*(4), 255-262. doi: 10.1097/hcr.0000000000000066

Ghasemi, A., & Zahediasl, S. (2012). Normality tests for statistical analysis: a guide for non-statisticians. *International Journal of Endocrinology and Metabolism, 10*(2), 486.

Giannuzzi, P., Temporelli, P. L., Corrà, U., Tavazzi, L., & Group, f. t. E.-C. S. (2003). Antiremodeling Effect of Long-Term Exercise Training in Patients With Stable Chronic Heart Failure: Results of the Exercise in Left Ventricular Dysfunction and Chronic Heart Failure (ELVD-CHF) Trial. *Circulation, 108*(5), 554-559. doi: 10.1161/01.cir.0000081780.38477.fa

Gitt, A. K., Wasserman, K., Kilkowski, C., Kleemann, T., Kilkowski, A., Bangert, M., . . . Senges, J. (2002). Exercise Anaerobic Threshold and Ventilatory Efficiency Identify Heart Failure Patients for High Risk of Early Death. *Circulation, 106*(24), 3079-3084. doi: 10.1161/01.cir.0000041428.99427.06

Guazzi, M., Palermo, P., Pontone, G., Susini, F., & Agostoni, P. (1999). Synergistic efficacy of enalapril and losartan on exercise performance and oxygen consumption at peak exercise in congestive heart failure. *The American Journal of Cardiology, 84*(9), 1038-1043.

Haskell, W. L., Alderman, E. L., Fair, J. M., Maron, D. J., Mackey, S. F., Superko, H. R., . . . Krauss, R. (1994). Effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease. The Stanford Coronary Risk Intervention Project (SCRIP). *Circulation, 89*(3), 975-990.

Heran, B. S., Chen, J., Ebrahim, S., Moxham, T., Oldridge, N., Rees, K., . . . Taylor, R. S. (2011). Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database of Systematic Reviews, 7*.

Hoffman, R. L. (1999). Effects of Training at the Ventilatory Threshold on the Ventilatory Threshold and Performance in Trained Distance Runners. *The Journal of Strength & Conditioning Research, 13*(2), 118-123.

Holloszy, J. O., & Coyle, E. F. (1984). Adaptations of skeletal muscle to endurance exercise and their metabolic consequences. *Journal of Applied Physiology, 56*(4), 831-838.

Houchen-Wolloff, L., Boyce, S., & Singh, S. (2014). The minimum clinically important improvement in the incremental shuttle walk test following cardiac rehabilitation. *European Journal of Preventive Cardiology*. doi: 10.1177/2047487314540840

Ingle, L., Goode, K., Carroll, S., Sloan, R., Boyes, C., Cleland, J. G. F., & Clark, A. L. (2007). Prognostic value of the VE/VCO2 slope calculated from different time intervals in patients with suspected heart failure. *International Journal of Cardiology, 118*(3), 350-355. doi: 10.1016/j.ijcard.2006.07.105

Jaeschke, R., Singer, J., & Guyatt, G. H. (1989). Measurement of health status: ascertaining the minimal clinically important difference. *Controlled Clinical Trials, 10*(4), 407-415.

Keith, S., Jacobs, I., & McLellan, T. (1992). Adaptations to training at the individual anaerobic threshold. *European Journal of Applied Physiology and Occupational Physiology, 65*(4), 316-323. doi: 10.1007/BF00868134

Keteyian, S. J., Brawner, C. A., Savage, P. D., Ehrman, J. K., Schairer, J., Divine, G., . . . Ades, P. A. (2008). Peak aerobic capacity predicts prognosis in patients with coronary heart disease. *American Heart Journal, 156*(2), 292-300.

Kodama, S., Saito, K., Tanaka, S., & et al. (2009). Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: A meta-analysis. *Journal of the American Medical Association, 301*(19), 2024-2035. doi: 10.1001/jama.2009.681

Lancaster, G. A., Dodd, S., & Williamson, P. R. (2004). Design and analysis of pilot studies: recommendations for good practice. *Journal of Evaluation in Clinical Practice, 10*(2), 307-312. doi: 10.1111/j..2002.384.doc.x

Lavie, C. J., & Milani, R. V. (1996). Effects of Cardiac Rehabilitation and Exercise Training Programs in Patients ≥ 75 Years of Age. *The American Journal of Cardiology, 78*(6), 675-677. doi: 10.1016/S0002-9149(96)00393-1

Lee, E. C., Whitehead, A. L., Jacques, R. M., & Julious, S. A. (2014). The statistical interpretation of pilot trials: should significance thresholds be reconsidered? *BMC Medical Research Methodology, 14*(1), 41.

Lemieux, J., Beaton, D. E., Hogg-Johnson, S., Bordeleau, L. J., & Goodwin, P. J. (2007). Three methods for minimally important difference: no relationship was found with the net proportion of patients improving. *Journal of Clinical Epidemiology, 60*(5), 448-455. doi: 10.1016/j.jclinepi.2006.08.006

Londeree, B. (1997). Effect of training on lactate/ventilatory thresholds: a meta-analysis. *Medicine and Science in Sports and Exercise, 29*(6), 837-843.

McConnell, T. R., Menapace, F. J., Hartley, L. H., & Pfeffer, M. A. (1998). Captopril reduces the VE/VCO2 ratio in myocardial infarction patients with low ejection fraction. *CHEST Journal, 114*(5), 1289-1294.

Miller, N. H., Haskell, W. L., Berra, K., & DeBusk, R. F. (1984). Home versus group exercise training for increasing functional capacity after myocardial infarction. *Circulation, 70*(4), 645-649. doi: 10.1161/01.cir.70.4.645

Myers, J., Prakash, M., Froelicher, V., Do, D., Partington, S., & Atwood, J. E. (2002). Exercise Capacity and Mortality among Men Referred for Exercise Testing. *New England Journal of Medicine, 346*(11), 793-801. doi: doi:10.1056/NEJMoa011858

Page, P. (2014). BEYOND STATISTICAL SIGNIFICANCE: CLINICAL INTERPRETATION OF REHABILITATION RESEARCH LITERATURE. *International Journal of Sports Physical Therapy, 9*(5), 726.

Richardson, J. T. E. (2011). Eta squared and partial eta squared as measures of effect size in educational research. *Educational Research Review, 6*(2), 135-147. doi: 10.1016/j.edurev.2010.12.001

Robbins, M., Francis, G., Pashkow, F. J., Snader, C. E., Hoercher, K., Young, J. B., & Lauer, M. S. (1999). Ventilatory and Heart Rate Responses to Exercise: Better Predictors of Heart Failure Mortality Than Peak Oxygen Consumption. *Circulation, 100*(24), 2411-2417. doi: 10.1161/01.cir.100.24.2411

Rognmo, Ø., Hetland, E., Helgerud, J., Hoff, J., & Slørdahl, S. A. (2004). High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. *European Journal of Cardiovascular Prevention & Rehabilitation, 11*(3), 216-222. doi: 10.1097/01.hjr.0000131677.96762.0c

Sandercock, G., Cardoso, F., Almodhy, M., & Pepera, G. (2013). Cardiorespiratory fitness changes in patients receiving comprehensive outpatient cardiac rehabilitation in the UK: a multicentre study. *Heart, 99*(11), 785-790. doi:10.1136/heartjnl-2012-303055

Sandercock, G., Hurtado, V., & Cardoso, F. (2011). Changes in cardiorespiratory fitness in cardiac rehabilitation patients: A meta-analysis. *International Journal of Cardiology*(0). doi: 10.1016/j.ijcard.2011.11.068

Sheth, S. S., Maxey, D. M., Drain, A. E., & Feinstein, J. A. (2013). Validation of the Innocor device for noninvasive measurement of oxygen consumption in children and adults. *Pediatric Cardiology, 34*(4), 847-852.

Sullivan, M. J., Higginbotham, M. B., & Cobb, F. R. (1989). Exercise training in patients with chronic heart failure delays ventilatory anaerobic threshold and improves submaximal exercise performance. *Circulation, 79*(2), 324-329. doi:10.1161/01.cir.79.2.324

Taylor, R. S., Unal, B., Critchley, J. A., & Capewell, S. (2006). Mortality reductions in patients receiving exercise-based cardiac rehabilitation: how much can be attributed to cardiovascular risk factor improvements? *European Journal of Cardiovascular Prevention & Rehabilitation, 13*(3), 369-374. doi: 10.1097/01.hjr.0000199492.00967.11

Thabane, L., Ma, J., Chu, R., Cheng, J., Ismaila, A., Rios, L. P., . . . Goldsmith, C. H. (2010). A tutorial on pilot studies: the what, why and how. *BMC Medical Research Methodology, 10*, 1. doi: 10.1186/1471-2288-10-1

Tomita, T., Takaki, H., Hara, Y., Sakamaki, F., Satoh, T., Takagi, S., . . . Sunagawa, K. (2003). Attenuation of hypercapnic carbon dioxide chemosensitivity after postinfarction exercise training: possible contribution to the improvement in exercise hyperventilation. *Heart, 89*(4), 404-410.

Tsurugaya, H., Adachi, H., Kurabayashi, M., Ohshima, S., & Taniguchi, K. (2006). Prognostic Impact of Ventilatory Efficiency in Heart Disease Patients With Preserved Exercise Tolerance. *Circulation Journal, 70*(10), 1332-1336. doi:10.1253/circj.70.1332

Van de Veire, N. R., Van Laethem, C., Philippé, J., De Winter, O., De Backer, G., Vanderheyden, M., & De Sutter, J. (2006). VE/Vco2 slope and oxygen uptake efficiency slope in patients with coronary artery disease and intermediate peakVo2. *European Journal of Cardiovascular Prevention & Rehabilitation, 13*(6), 916-923. doi: 10.1097/01.hjr.0000238400.35094.72

Vanhees, L., Fagard, R., Thijs, L., & Amery, A. (1995). Prognostic value of training-induced change in peak exercise capacity in patients with myocardial infarcts and patients with coronary bypass surgery. *The American Journal of Cardiology, 76*(14), 1014-1019.

Wasserman, K., Hansen, J., Sue, D., Stringer, W., Sietsema, K., Sun, X.-G., & Whipp, B. (2012). *Principles of exercise testing and interpretation: Including pathophysiology and clinical applications* (Fifth ed.): Wolters Kluwer Health/Lippincott Williams & Wilkins.

West, R. R., Jones, D. A., & Henderson, A. H. (2012). Rehabilitation after myocardial infarction trial (RAMIT): multi-centre randomised controlled trial of comprehensive cardiac rehabilitation in patients following acute myocardial infarction. *Heart, 98*(8), 637-644. doi: 10.1136/heartjnl-2011-300302

Wilson, R. J. T., Davies, S., Yates, D., Redman, J., & Stone, M. (2010). Impaired functional capacity is associated with all-cause mortality after major elective intra-abdominal surgery. *British Journal of Anaesthesia, 105*(3), 297-303. doi: 10.1093/bja/aeq128

Wisløff, U., Støylen, A., Loennechen, J. P., Bruvold, M., Rognmo, Ø., Haram, P. M., . . . Skjærpe, T. (2007). Superior Cardiovascular Effect of Aerobic Interval Training Versus Moderate Continuous Training in Heart Failure Patients: A Randomized Study. *Circulation, 115*(24), 3086-3094. doi: 10.1161/circulationaha.106.675041

Witt, B. J., Jacobsen, S. J., Weston, S. A., Killian, J. M., Meverden, R. A., Allison, T. G., . . . Roger, V. é. L. (2004). Cardiac rehabilitation after myocardial infarction in the community. *Journal of the American College of Cardiology, 44*(5), 988-996. doi: 10.1016/j.jacc.2004.05.062

World Health Organisation. (1993). Rehabilitation after cardiovascular diseases, with special emphasis on developing countries: a report of a WHO Committee *World Health Organisation Technical Report Series* (pp. 1-122).

Chapter 6 - General Discussion, Recommendations and Limitations

7.1 General Discussion

This thesis investigated the cardiovascular (CV) and cardiorespiratory (CRF) adaptations in response to an eight week (16 session), low to moderate intensity (40-70% heart rate reserve) UK cardiac rehabilitation (CR) exercise training programme (routine practice). Pilot data was subsequently generated to determine whether implementing a higher training dose based on maximal cardiopulmonary exercise test (CPET) data elicited superior CRF improvements. This is the first contemporary controlled study to quantify VO_{2peak} change following routine CR in the UK using 'gold standard' maximal CPET. Furthermore, it is the first UK-based study to investigate the effects of routine CR on carotid intima-media thickness (C-IMT), a surrogate marker of sub-clinical atherosclerosis.

Chapter 3 showed that a CR exercise training programme adhering to national standards (ACPICR, 2015, BACPR, 2012b) did not increase VO_{2peak}. Other key CRF measures including ventilatory anaerobic threshold (VAT), estimated stroke volume (SV) or ventilatory efficiency also did not improve significantly compared to non-exercise controls. Patients undertaking routine CR exercise training may be more likely to experience a VAT increase and, a VE/VCO_2 slope decrease when the minimal clinically important differences (MCID) are used to identify programme efficacy.

UK CR exercise training guidelines appear highly conservative. To maximise the benefits of programmes adhering to these guidelines, CR teams should be encouraged to optimise patients' exercise training regimes. Data from Chapter 3 demonstrated that the CR programme operated to minimum UK standards. However, an analysis of the exercise prescription indicated the potential for increasing patients' total CV exercise duration much earlier in the programme. In addition, rating of perceived exertion (RPE) data suggested that exercise intensity was also sub-optimal. UK CR programmes may wish to implement regular service audit inspections to

ensure that exercise training dose are optimised within current UK guidelines. Increasing the presence of exercise physiologists and integrating regular CPET within CR teams may help to ensure the delivery of high quality exercise prescriptions. Patients should also be encouraged (where appropriate) to exercise at their highest 'tolerable' exercise dose within the constraints of current guidance.

To date, Sandercock et al. (2013b) have presented some of *the* most compelling evidence that UK CR programmes provide sub-optimal CRF improvements, particularly within the context of their previous findings (Sandercock et al., 2011). Compared to international studies (1.55 metabolic equivalents [METs]), CRF changes following a UK CR programme are reported to be modest at best (0.52 METs). As the only recent study to publish findings specifically relating to UK CR outcomes, this report could be ignored by national governing bodies. However, subtle evidence in this regard also exists elsewhere. Houchen-Wolloff et al. (2014) reported (without discussion) that more than half of patients completing their CR programme did not achieve the MCID (70 m) for the incremental shuttle walk test (ISWT). Woolf-May et al. (2005) also reported no CRF change following UK CR (ISWT pre: 43 ± 10.9 shuttles; post: 42.3 ± 11.6 shuttles; VO_2 $ml^{.}kg^{-1.}min^{-1}$: data not reported; p=0.900). Given that exercise training in patients with coronary heart disease (CHD) clearly has the potential to improve CRF (Dugmore et al.,1999, Fukuda et al., 2013), reasons for these negative findings must lie with training modality and broader service delivery issues.

As indicated by others, inadequate exercise dose appears to be implicated for our finding that routine CR does not improve VO_{2peak} (Sandercock et al., 2013a, Ingle and Carroll, 2013). It is reasonable to suggest that the receiver operating characteristics (ROC) curve analysis conducted in Chapter 3 showed no dose-response to routine CR because the cumulative exercise dose was *largely* ineffective. Indeed, similar proportions of patients in the TG (36%) and CG (42%) improved their VO_{2peak}. The mounting evidence that UK CR does not provide the benefits reported in international studies (Sandercock et al., 2013b, Sandercock et al., 2011, Woolf-

May et al., 2005, Houchen-Wolloff et al., 2014) places a burden or responsibility on the National Institute for Health and Care Excellence (NICE), the ACPICR and, the BACPR for improving programme effectiveness. Effective healthcare can only exist when appropriate funding is universally available and, governing bodies accurately interpret evidence from clinical trials, meta-analyses and, systematic reviews.

The lack of efficacy of routine UK CR should be expected in light of the interpretation of scientific literature conducted by the ACPICR (2015). The only original training study cited (in context) in ACPICR (2015) guidelines showed that to improve VO_{2peak}, training intensities similar to those prescribed in the UK (45-55% HRR) required exercise on more than five days per week (30 minutes per session) for six months (Duncan et al., 2005). Whilst the ACPICR (2015) cite the benefits resulting from exercise training on two to three days per week, the study from which they base this guideline (Heran et al., 2011) included numerous studies where patients exercised for four to five days per week and, for more than 30 minutes (or more) per session. Training intensities in many of these studies were also often prescribed at intensities greater than 70% VO_{2peak}, derived from CPET and, conducted for more than 12 weeks. UK CR programmes typically last 11.6 sessions (Brodie et al., 2006). In this context, it is unsurprising that UK CR may not improve CRF or survival (West et al., 2012, Sandercock et al., 2011).

Despite VO_{2peak} remaining unchanged following routine CR, Chapter 3 showed that when METs were used to determine CRF change, both control and training groups experienced a substantial increase in functional capacity; namely, a MET increase two-fold greater than recently reported (Sandercock et al., 2013b). The peak MET change between visit 1 and 2, was 1.08 METS. When converted to estimated VO_{2peak}, the American College of Sports Medicine (2013) formula for MET calculation overestimated VO_{2peak} change by approximately 3.8 $ml.kg^{-1}.min^{-1}$. Because many different equations for estimating METs exist, generalising their predictive value as a whole is limited. However, not only does Wasserman and colleagues' (2011) assertion that METs overestimate VO_{2peak} in patients with CHD appear to be true, but their application for quantifying CRF change also appear to result in overestimated VO_{2peak} improvements. UK CR

interventions showing peak MET changes (Carroll et al., 2011) may not represent VO_{2peak} improvement at all. CR centres that report such improvements may be reporting 'false positive' training responses.

Our patients undergoing routine CR exercise training significantly increased exercise duration, CPET stages, and peak METs without concurrent VO_{2peak} improvement. The MET improvement observed in both training and control groups is likely to be a consequence of the 'placebo effect' as reported by Russell et al. (1998). Peak MET scores may increase as a result of test familiarity. Fowler et al. (2005) demonstrated this phenomenon in patients undertaking repeated ISWT. Whilst functional capacity (i.e. work done) may be useful for risk stratification and CRF categorisation, it may not be sensitive to CRF change, particularly when familiarisation sessions are not performed. The prevalence of familiarisation sessions in clinical practice is not known. Given that practitioner's resources are limited, it is unlikely that this is commonplace.

To the author's knowledge, the only study to report on the validity of METs to estimate VO_{2peak} change in CHD populations found no relationship between MET and VO_{2peak} change (Milani et al., 1995). This may be because in CHD, the linear relationship between VO_2 and work rate cannot always be assumed (Belardinelli et al., 2003, Chaudhry et al., 2009, Hughson, 1984, Poole et al., 2012) or, because the supposition that one MET is equal to 3.5 $ml.kg^{-1}.min^{-1}$ is scientifically flawed (Wasserman et al., 2011, Byrne et al., 2005). Whilst METs are *arguably* widely understood, their application in many circumstances, including the documentation of CRF change may be inappropriate. CPET is the only reliable method of accurately determining the true effect of exercise training on CRF. Many eminent professionals and academics may cite 'practical' and/or 'financial' barriers to the use of CPET and suggest the use of METs is an appropriate alternative. This approach is borne out of the historical view that CR is a 'Cinderella service' (O'Driscoll et al., 2007). It is unlikely that patient's would willingly accept this 'pragmatic' position. Clinical measurements *including* exercise testing parameters must be valid, reliable and affordable. The use of the MET only provides the latter whilst CPET, at the very least, offers validity and reliability.

Despite Chapter 3 demonstrating that routine CR did not improve VO_{2peak}, evidence suggested that patients undertaking exercise training *might* experience slower atherosclerotic progression than those who do not. Chapter 4 showed that C-IMT did not increase amongst patients in the training group whilst controls experienced significant C-IMT progression (in a single angle of insonation). However, previous studies reporting an attenuation of C-IMT progression following exercise training have found that VO_{2peak} and a number of other CV risk factors also improve (Feairheller et al., 2014, Okada et al., 2004). Because our training programme failed to improve CRF, it is unlikely that exercise training itself affected atherosclerosis progression. What these findings could indicate however is that full participation in CR initiates behavioural change that leads to improved CV risk factor profiles and, a reduction in atherogenesis. The reduction in C-IMT at visit 3 (in a single angle of insonation) amongst patients in the training group might also indicate that such behavioural change is sustained in the longer-term. However, only one control patient was available for testing at 12 months limiting the conclusions that can be drawn. Furthermore because the C- IMT changes observed in both groups only occurred at single angles of insonation, consideration should be given to the possibility that differences were a result of a type I error. Studies demonstrating a positive effect of exercise training on C-IMT have shown greater (and uniform) reductions in C-IMT (Kim et al., 2006, Okada et al., 2004). Exercise training regimes in these studies were of greater dose than prescribed in UK CR programmes. Coupled with our findings in Chapter 3, evidence continues to indicate that the format of UK CR programmes requires reviewing. Programmes shown not to elicit VO_{2peak} increases are inadequate and require modification.

In support of data from Chapter 3, Chapter 5 demonstrated that patients enrolled to routine CR did not improve their VO_{2peak}. On this occasion routine CR was not restricted to a single local programme. Patients enrolled to different regional CR programmes failed to increase their VO_{2peak}. By contrast, those using a Guided Exercise (GEx) system to undertake additional exercise training sessions prescribed using maximal CPET and blood lactate sampling significantly improved their VO_{2peak}. However, when compared to patients undertaking CPET

following a treadmill protocol such as that in Chapter 3, patients following a cycle ergometry protocol (Chapter 5) were less likely to achieve peak CPET criteria (48% and 79% respectively). Patients following a cycle ergometry protocol typically experience a VO_{2peak} that is 10 to 20% lower than if they had used a treadmill protocol. This may be due to patients experiencing localised muscle fatigue (Balady et al., 2010) as opposed to cardiorespiratory exhaustion. Failure to achieve peak CPET criteria may mean that patients true 'peak aerobic capacity' was not attained thus compromising the integrity of the VO_{2peak} change data. However, the finding that routine CR does not improve VO_{2peak} is supported by data from Chapter 3, and it seems unlikely that the choice of CPET protocol significantly affected the overall interpretation of Chapter 5. It seems reasonable to conclude that the higher exercise dose delivered as part of the GEx treatment group was responsible for providing superior VO_{2peak} improvements when compared to routine CR. Indeed, correlation and ROC curve analysis indicated an exercise dose-response. Thirteen exercise sessions dichotomised the minimum threshold above which, clinically meaningful improvements to VO_{2peak} were likely. The large treatment group attrition rate clearly demonstrated a need for equipment refinement. However, whilst tele-monitoring represents one possible medium to facilitate additional exercise sessions, it is not essential.

UK CR teams typically perform basic exercise testing protocols prior to commencing CR. Assuming that a patient has a normal physiological response to exercise, simple paper-based prescriptions could be used to deliver additional home exercise sessions. The disadvantage of this system compared to tele-monitoring is the inability to effectively monitor exercise adherence. However, current evidence suggests that traditional home exercise training can be effective (Dalal et al., 2010). Consideration should be given to delivering a*t least* one additional home-based exercise session per week from the onset of CR. Exercising on 5 days per week upon completing CR should be an achievable goal for some. CR teams may wish to consider implementing home-based exercise session in the weeks prior to commencing structured CR, particularly where waiting lists are problematic.

7.2 Summary

- Eight weeks (16 sessions) of routine CR incorporating exercise training of low to moderate intensity does not improve VO_{2peak} in patients with CHD compared to home-based exercising controls.

- Increasing the dose of exercise delivered during an 8 to 12 week exercise training intervention could be a viable way of ensuring CRF improvements in CHD patients.

- The cumulative impact of CR (including exercise training and cardioprotective medications) may slow C-IMT progression during the training period and, reduce C-IMT over the longer-term.

- The American College of Sports Medicine (2013) formula for calculating METs has wide measurement variability and, overestimates VO_{2peak} in CHD patients. The practice of estimating VO_{2peak} from estimated METs should be discouraged.

- Estimated VO_{2peak} measurement bias calculated using the American College of Sports Medicine (2013) formula is reduced if 1 MET is assumed to equal 2.6 $ml^{.}kg^{-1.}min^{-1}$. However, measurement variability remains unacceptably large.

- Routine submaximal exercise testing involving Serial measurement of METs using the American College of Sports Medicine (2013) formula leads to substantial overestimations of VO_{2peak} change.

- C-IMT measurement variability is low when obtained by novice operators using the Panasonic CardioHealth Station. Brief training periods (approximately 25 scans) can improve C-IMT measurement variability when taken by novice operators.

7.3 Recommendations for Clinical Practice

- Within the constraints of current CR guidance, UK CR teams should closely monitor patients' CV exercise duration and intensity. Short-term training regimes could be optimised by increasing CV exercise duration and intensity to the highest 'tolerable' dose in the shortest 'reasonable' time frame. Most patients should be capable of achieving 20 minutes of CV exercise at the onset of CR when intensity is appropriately controlled.

- Maximising exercise training dose by increasing the total number of weekly exercise sessions prescribed to patients should be considered. The addition of a home-based exercise prescription may be a viable way of achieving this goal. CR teams should also consider implementing home-based regimes prior to commencing CR programmes *if* patients are clinically stable and have demonstrated normal physiological responses to exercise testing. This should be of particular interest to CR programmes with extensive waiting lists.

- CR teams may wish to routinely exercise patients at intensities of 70% HRR rather than reserving this for 'fitter' patients. Consideration should be given to prescribing marginally higher exercise intensities than this if:

    I.   Patients are willing and able to undertake exercise at these intensities

    II. Cardiovascular exercise duration has been optimised within current recommendations

    III. There is clear evidence that the training intensity provided by the patient's 'optimised' exercise prescription is inadequate (e.g. through symptom monitoring and RPE)

IV.   Patients were asymptomatic during submaximal exercise testing estimated

maximal METs should not be assumed to reliably reflect CRF change following

exercise training.

7.4 Limitations

Whilst the CR programme in Chapter 3 and 4 was developed in accordance with national UK

guidelines, CR provision across the UK is variable (Brodie et al., 2006). Chapters 3 and 4 are

therefore limited by the lack of generalisability across the UK CR network. However, our data

reinforces existing evidence (Woolf-May et al., 2005, Houchen-Wolloff et al., 2014, Sandercock

et al., 2013b, West et al., 2012) that UK CR may be underperforming compared to international

studies (Sandercock et al., 2011).

Whilst this thesis concludes that VO_{2peak} does not change following UK CR, the Modified Bruce

Protocol (Bruce et al., 1973) used in Chapter 3 and, the staged cycle ergometry protocol in

Chapter 5 may lack the sensitivity to detect VO_{2peak} change. Ramp protocols may be superior to

step protocols for identifying VO_{2peak} (and VAT) change amongst cardiac populations, principally

due to the stronger relationship between VO_2 and work rate (Taylor et al., 2015, Balady et al.,

2010, Wasserman et al., 2011). The large work rate increments used in the Modified Bruce

protocol may cause patients to terminate exercise without VO_2 having matched work rate.

Had a ramp protocol been used, VO_{2peak} increases may have been detected. However, the

Modified Bruce protocol is widely accepted within cardiology research. Moreover, the use of

stage-based exercise testing protocols such as the ISWT, BACPR cycle ergometry protocol

(unpublished) and the Chester step tests (Sykes and Roberts, 2004) are widely applied in CR. For

this reason, the Modified Bruce protocol remains relevant to UK CR programmes.

Chapter 4 is principally limited by sample size. Studies showing significant changes to C-IMT

have typically used larger sample sizes (Sato et al., 2008, Kim et al., 2006, Okada et al., 2004). A

further limitation of this chapter was the use of the limits of agreement (LoA) defined by

(Nichols et al., 2014c). Their LoA were not only defined in healthy populations, but also over shorter follow-up periods. It is not known whether these LoA accurately depict C-IMT measurement variability in patients with CHD over longer time periods. However, Nichols et al. (2014c) are the only research group to publish LoA for C-IMT measurement test-retest variability using the Panasonic CardioHealth Station. Applying the LoA from this study is currently the most appropriate way of identifying whether or not C-IMT change exceeded measurement error.

Chapter 5 was limited by the inadequate reporting of exercise training completed by patients both in 'routine care' and treatment groups during the CR period. The study sponsors did not seek ethical approval to liaise with local CR teams and quantify what volume of exercise training had been conducted during routine practice. Furthermore, the pilot software developed for the GEx system did not allow the extraction of exercise training information. No record was kept of how many exercise sessions had been completed by patients using the GEx system. Consequently Chapter 5 assumes that patients using the GEx system completed all prescribed exercise. Irrespective of these limitations, patients in the GEx training group increased their VO_{2peak} to a greater extent than those in routine CR. Given that both sets of patients were tested at approximately the same time point, these findings indicate that patients adhered to the exercise programme outlined in the methods of Chapter 5.

The clear research to practice limitation of Chapter 5 is the viability of implementing tele-monitoring into CR programmes. Initial expense may be the primary barrier to implementing such systems with appropriate staffing and training also likely to be key issues raised. This, however, does not undermine the principle that a greater exercise dose appears to be effective for improving CRF in the short period of time that patients have access to a CR programme. Cost effective alternatives such as a paper-based exercise prescription may prove equally valuable. Mobile phone based software may also have potential as a viable CR tele- monitoring device (Maddison et al., 2014).

7.5 Future Studies

- In Chapter 3, the quantification of exercise dose during routine CR was performed by transcribing paper-based, self-reported data. To accurately determine a true training dose and, whether exercise training guidelines are effectively implemented, studies utilising accelerometers, GPS or other tele-monitoring systems could be used to record patients' exercise habits during CR.

- Future research may wish to investigate whether a simple structured exercise prescription can be integrated into stages zero to two of the CR 'best care pathway'. Facilitating exercise training prior to commencing structured CR may enhance the CRF improvements resulting from short-term exercise training regimes.

- Studies that manipulate training intensity, frequency and type should be conducted with the aim of determining the optimal training modality within the constraints of the UK healthcare system. The development of a 'menu driven' approach may be needed.

- The CV and CRF changes following exercise training and, the time course in which these occur is still poorly understood. Future research may wish to investigate the interaction between central and peripheral adaptations and how one may drive changes to the other.

- There is no contemporary data on the predictive accuracy of serial MET measurement to estimate VO_{2peak} change. Given that many UK CR programmes rely entirely on this metric, a study investigating its sensitivity and accuracy to VO_{2peak} change is warranted.

7.6 Concluding Remarks

This thesis has shown that a review of routine CR guidance (and practice) is warranted. The fact that the efficacy of CR guidance has remained unaddressed may be in part due to the use of METs to assess CRF change improvements. The use of METs may lead to optimistic interpretations of CRF improvements. Additionally, there appears to be reluctance within national governing bodies to address the concerns raised by recent studies (BACPR, 2012a, West et al., 2012). There is sufficient evidence that the recommended dose of exercise for UK CR patients requires revising. A "typical" UK based CR programme may be insufficient to significantly improve CRF in the majority of cardiac patients. Whilst limited evidence indicates that C-IMT progression may be attenuated as a result of participating in CR, this is likely to be a result of collective secondary prevention efforts. Whilst this could be argued as a benefit of participating in CR, the full potential of exercise training regimes is yet to be harnessed. This thesis demonstrates that CRF improvements are achievable in the short window of opportunity that many UK CR programmes operate within. Increasing exercise dose through quality control, innovation, or traditional techniques should not only be considered, but incorporated.

The benefits of exercise training in patients with CHD are not questioned by this thesis. However, the efficacy and rationale of delivering CR programmes designed under current guidelines are worthy of further debate. In principle, the solution to the problem facing CR in the UK is simple; optimising exercise training doses early within the rehabilitation process and, a greater awareness of the role that exercise dose plays are key to improving UK CR programme efficacy. Utilising superior exercise testing techniques such as CPET where possible may provide clinicians with exercise training data that better facilitate the accurate personalisation of exercise prescriptions. Logistically, these challenges are complex. Whilst CR teams must be tenacious in rising to these challenges, national governing bodies including the BACPR, ACPICR, NICE and, clinical commission groups must facilitate change. Until these issues are addressed, UK CR programmes will continue to lag behind our North American and European equivalents.

7.7 References

ACPICR 2015. *Standards for physical activity and exercise in the cardiovascular population*, Association of Chartered Physiotherapists in Cardiac Rehabilitation

ACSM 2013. *ACSM's Guidelines for exercise testing and prescription,* Philadelphia, Wolters Kluwer/Lippincott Williams & Wilkins Health.

BACPR 2012a. RAMIT presents an outdated version of cardiac rehabilitation. *Heart,* 98**,** 672.

BACPR. 2012b. Standards and Core Components for Cardiovascular Disease Prevention and Rehabilitation. Available: http://www.bacpr.com/resources/.

BALADY, G. J., ARENA, R., SIETSEMA, K., MYERS, J., COKE, L., FLETCHER, G. F., FORMAN, D., FRANKLIN, B., GUAZZI, M., GULATI, M., KETEYIAN, S. J., LAVIE, C. J., MACKO, R., MANCINI, D. & MILANI, R. V. 2010. Clinician's Guide to Cardiopulmonary Exercise Testing in Adults: A Scientific Statement From the American Heart Association. *Circulation,* 122**,** 191-225.

BELARDINELLI, R., LACALAPRICE, F., CARLE, F., MINNUCCI, A., CIANCI, G., PERNA, G. & D'EUSANIO, G. 2003. Exercise-induced myocardial ischaemia detected by cardiopulmonary exercise testing. *Eur Heart J,* 24**,** 1304-13.

BRODIE, D., BETHELL, H. & BREEN, S. 2006. Cardiac rehabilitation in England: a detailed national survey. *European Journal of Cardiovascular Prevention & Rehabilitation,* 13**,** 122-128.

BRUCE, R. A., KUSUMI, F. & HOSMER, D. 1973. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *American Heart Journal,* 85**,** 546-562.

BYRNE, N. M., HILLS, A. P., HUNTER, G. R., WEINSIER, R. L. & SCHUTZ, Y. 2005. Metabolic equivalent: one size does not fit all. *Journal of Applied physiology,* 99**,** 1112-1119.

CARROLL, S., TSAKIRIDES, C., HOBKIRK, J., MOXON, J. W. A., MOXON, J. W. D., DUDFIELD, M. & INGLE, L. 2011. Differential Improvements in Lipid Profiles and Framingham Recurrent Risk Score in Patients With and Without Diabetes Mellitus Undergoing Long-Term Cardiac Rehabilitation. *Archives of Physical Medicine and Rehabilitation,* 92**,** 1382- 1387.

CHAUDHRY, S., ARENA, R., WASSERMAN, K., HANSEN, J. E., LEWIS, G. D., MYERS, J., CHRONOS, N. & BODEN, W. E. 2009. Exercise-Induced Myocardial Ischemia Detected by Cardiopulmonary Exercise Testing. *The American Journal of Cardiology,* 103**,** 615-619.

DALAL, H. M., ZAWADA, A., JOLLY, K., MOXHAM, T. & TAYLOR, R. S. 2010. Home based versus centre based cardiac rehabilitation: Cochrane systematic review and meta-analysis. *Bmj,* 340**,** b5631.

DUGMORE, L., TIPSON, R., PHILLIPS, M., FLINT, E., STENTIFORD, N., BONE, M. & LITTLER, W. 1999. Changes in cardiorespiratory fitness, psychological wellbeing, quality of life, and vocational status following a 12 month cardiac exercise rehabilitation programme. *Heart,* 81**,** 359-366.

DUNCAN, G. E., ANTON, S. D., SYDEMAN, S. J., NEWTON, R. L., CORSICA, J. A., DURNING, P. E., KETTERSON, T. U., MARTIN, A. D., LIMACHER, M. C. & PERRI, M. G. 2005. Prescribing

exercise at varied levels of intensity and frequency: a randomized trial. *Archives of internal medicine,* 165**,** 2362-2369.

FEAIRHELLER, D. L., DIAZ, K. M., KASHEM, M. A., THAKKAR, S. R., VEERABHADRAPPA, P., STURGEON, K. M., LING, C., WILLIAMSON, S. T., KRETZSCHMAR, J. & LEE, H. 2014. Effects of moderate aerobic exercise training on vascular health and blood pressure in african americans. *The Journal of Clinical Hypertension,* 16**,** 504-510.

FOWLER, S. J., SINGH, S. J. & REVILL, S. 2005. Reproducibility and validity of the incremental shuttle walking test in patients following coronary artery bypass surgery. *Physiotherapy,* 91**,** 22-27.

FUKUDA, T., KURANO, M., FUKUMURA, K., YASUDA, T., IIDA, H., MORITA, T., YAMAMOTO, Y., TAKANO, N., KOMURO, I. & NAKAJIMA, T. 2013. Cardiac Rehabilitation Increases Exercise Capacity with a Reduction of Oxidative Stress. *Korean circulation journal,* 43**,** 481-487.

HERAN, B. S., CHEN, J., EBRAHIM, S., MOXHAM, T., OLDRIDGE, N., REES, K., THOMPSON, D. R. & TAYLOR, R. S. 2011. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev,* 7.

HOUCHEN-WOLLOFF, L., BOYCE, S. & SINGH, S. 2014. The minimum clinically important improvement in the incremental shuttle walk test following cardiac rehabilitation. *European Journal of Preventive Cardiology*.

HUGHSON, R. L. 1984. Alterations in the oxygen deficit-oxygen debt relationships with beta-adrenergic receptor blockade in man. *The Journal of Physiology,* 349**,** 375-387.

INGLE, L. & CARROLL, S. 2013. Cardiac rehabilitation and exercise training. *Heart*.

KIM, S. H., LEE, S. J., KANG, E. S., KANG, S., HUR, K. Y., LEE, H. J., AHN, C. W., CHA, B. S., YOO, J. S. & LEE, H. C. 2006. Effects of lifestyle modification on metabolic parameters and carotid intima-media thickness in patients with type 2 diabetes mellitus. *Metabolism,* 55**,** 1053-1059.

MADDISON, R., PFAEFFLI, L., WHITTAKER, R., STEWART, R., KERR, A., JIANG, Y., KIRA, G., LEUNG, W., DALLECK, L., CARTER, K. & RAWSTORN, J. 2014. A mobile phone intervention increases physical activity in people with cardiovascular disease: Results from the HEART randomized controlled trial. *European Journal of Preventive Cardiology*.

MILANI, R. V., LAVIE, C. J. & SPIVA, H. 1995. Limitations of estimating metabolic equivalents in exercise assessment in patients with coronary artery disease. *The American journal of cardiology,* 75**,** 940-942.

NICHOLS, S., MILNER, M., MEIJER, R., CARROLL, S. & INGLE, L. 2014. Variability of automated carotid intima-media thickness measurements by novice operators. *Clinical Physiology and Functional Imaging*.

O'DRISCOLL, J. M., SHAVE, R. & CUSHION, C. J. 2007. A National Health Service Hospital's cardiac rehabilitation programme: a qualitative analysis of provision. *Journal of Clinical Nursing,* 16**,** 1908-1918.

OKADA, K., MAEDA, N., TATSUKAWA, M., SHIMIZU, C., SAWAYAMA, Y. & HAYASHI, J. 2004. The influence of lifestyle modification on carotid artery intima-media thickness in a suburban Japanese population. *Atherosclerosis,* 173**,** 327-335.

POOLE, D. C., HIRAI, D. M., COPP, S. W. & MUSCH, T. I. 2012. Muscle oxygen transport and utilization in heart failure: implications for exercise (in) tolerance. *American Journal of Physiology-Heart and Circulatory Physiology,* 302**,** H1050-H1063.

RUSSELL, S. D., MCNEER, F. R., BEERE, P. A., LOGAN, L. J. & HIGGINBOTHAM, M. B. 1998. Improvement in the mechanical efficiency of walking: An explanation for the "placebo effect" seen during repeated exercise testing of patients with heart failure. *American Heart Journal,* 135**,** 107-114.

SANDERCOCK, G., CARDOSO, F. & ALMODHY, M. 2013a. Cardiorespiratory fitness changes in patients receiving comprehensive outpatient cardiac rehabilitation in the UK: a multicentre study. *Heart,* 99**,** 1298-1299.

SANDERCOCK, G., CARDOSO, F., ALMODHY, M. & PEPERA, G. 2013b. Cardiorespiratory fitness changes in patients receiving comprehensive outpatient cardiac rehabilitation in the UK: a multicentre study. *Heart,* 99**,** 785-790.

SANDERCOCK, G., HURTADO, V. & CARDOSO, F. 2011. Changes in cardiorespiratory fitness in cardiac rehabilitation patients: A meta-analysis. *International Journal of Cardiology*.

SATO, S., MAKITA, S., UCHIDA, R., ISHIHARA, S. & MAJIMA, M. 2008. Physical activity and progression of carotid intima-media thickness in patients with coronary heart disease. *Journal of Cardiology,* 51**,** 157-162.

SYKES, K. & ROBERTS, A. 2004. The Chester step test—a simple yet effective tool for the prediction of aerobic capacity. *Physiotherapy,* 90**,** 183-188.

TAYLOR, C., NICHOLS, S. & INGLE, L. 2015. A clinician's guide to cardiopulmonary exercise testing 1: an introduction. *British Journal of Hospital Medicine* 76**,** 192-5.

WASSERMAN, K., HANSEN, J., SUE, D., STRINGER, W., SIETSEMA, K., SUN, X.-G. & WHIPP, B. 2011. *Principles of exercise testing and interpretation: Including pathophysiology and clinical applications,* Philadelphia, Wolters Kluwer Health/Lippincott Williams & Wilkins.

WEST, R. R., JONES, D. A. & HENDERSON, A. H. 2012. Rehabilitation after myocardial infarction trial (RAMIT): multi-centre randomised controlled trial of comprehensive cardiac rehabilitation in patients following acute myocardial infarction. *Heart,* 98**,** 637-644.

WOOLF-MAY, K., BIRD, S. & MACINTYRE, P. 2005. Physical activity levels during phase IV cardiac rehabilitation in a group of male myocardial infarction patients. *British Journal of Sports Medicine,* 39**,** e12-e12.

Appendices

8.1 Appendix 1

NRES Committee Yorkshire & The Humber - Humber Bridge

HRA NRES Centre North West
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0161 625 7816
Facsimile: 0161 625 7299

27 September 2013

Dr Lee Ingle
Senior Lecturer
University of Hull
Sport Health & Exercise Science Dept
Cottingham Road
Hull
HU6 7RX

Dear Dr Ingle

Study title:	Cardiovascular and respiratory adaptations in response to a standard UK exercise based cardiac rehabilitation.
REC reference:	13/YH/0278
Protocol number:	v2
IRAS project ID:	126483

Thank you for your letter of 06 September 2013, 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 NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Manager Miss Diane Catterall, nrescommittee.yorkandhumber-humberbridge@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.

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

Notification(s) of no objection have been received from local assessors for the non-NHS site(s) listed in the table below, following site-specific assessment (SSA).

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
NHS City Health Care Partnership (CHCP) CIC	Dr Lee Ingle
University of Hull, Sport, Health & Exercise Science Department	Dr Lee Ingle

Conditions of the favourable opinion

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

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

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System 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 approvals from host organisations.

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).

Approved documents

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

Document	Version	Date
Covering Letter		23 July 2013
Evidence of insurance or indemnity	University of Hull	02 November 2012
Evidence of insurance or indemnity	City Health care Partnership	
GP/Consultant Information Sheets	1	01 April 2013
GP/Consultant Information Sheets	Without Group Exercise - 1	01 April 2013
Investigator CV	Dr Lee Ingle - 1	01 April 2013
Investigator CV	Professor Sean Carroll	01 November 2012

Investigator CV	Mr Simon Nichols	08 May 2013
Letter of invitation to participant	1	06 September 2013
Other: Patient Support Group Letter from the Chair		27 July 2013
Other: Unfavourable opinion letter		05 July 2013
Other: Ethics Rebuttal Letter	1	29 July 2013
Other: Summary of changes	1	19 July 2013
Other: Power Analysis and Sample Size	1	19 July 2013
Participant Consent Form: Without group exercise	3	06 September 2013
Participant Consent Form: Group exercise	3	06 September 2013
Participant Information Sheet: Without group exercise	3	06 September 2013
Participant Information Sheet: Group exercise	3	06 September 2013
Protocol	2	19 July 2013
REC application	3.5	30 July 2013
Response to Request for Further Information		06 September 2013
Summary/Synopsis	1	19 July 2013

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

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

13/YH/0278	Please quote this number on all correspondence

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

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

Yours sincerely

DM Cattell

Dr Lynn Cawkwell
Chair

Email:nrescommittee.yorkandhumber-humberbridge@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: Mr Gethin Owen
                     Mr James Illingworth, Hull and east Yorkshire NHS Trust
                     Mr Simon Nichols

8.2 Appendix 2

Spirometry

Respiratory function was evaluated from resting spirometry and conducted using an Oxycon Pro. Patients were asked to attach a nose clip to restrict nasal gas exchange before breathing into a mouth piece attached to the metabolic cart's gas flow turbine. Patients were instructed to 'relax' and breathe normally to allow resting tidal volume measurements (litres) to be obtained. A minimum of ten full breathing cycles were observed to allow normalisation of the breathing pattern. Breathing cycles were repeated until consistent values were observed.

Flow volume loops were conducted to obtain forced spirometry measurements. Prior to the manoeuvre being attempted, a demonstration and clear instructions were given. The following terms were used as teaching points:

- Maintaining a 'neutral' head position

- Sitting upright/good posture

- Taking a forced (rapid) deep breath in until their lungs were fully expanded

- Making a forced breath out to breathe out as much air as possible in the first second

- To continue breathing out until they could no longer do so

Up to eight flow-volume loops were conducted to obtain three high quality manoeuvres. Acceptable reproducibility was defined as ≤0.150 L difference between the largest and second largest forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) measurements (American Thoracic Society/European Respiratory Society, 2005). Recorded data included FEV_1, FVC and peak expiratory flow (PEF). Maximum voluntary ventilation (MVV) was estimated (eMVV) using the calculation FEV_1 x 40 (Hansen et al., 1984, Campbell, 1982, Blackie et al., 1991). This was used in all patients to avoid the discomfort and pre-syncopal symptoms commonly associated with direct MVV measurement.

Variability of automated carotid intima-media thickness measurements by novice operators

S. Nichols[1], M. Milner[1], R. Meijer[2], S. Carroll[1] and L. Ingle[1]

[1]Department of Sport, Health & Exercise Science, University of Hull, Kingston-upon-Hull, UK and [2]Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, The Netherlands

Summary

Correspondence

Simon Nichols, Department of Sport, Health & Exercise Science, University of Hull, Cottingham Road, Kingston-upon-Hull HU7 6RX, UK

E-mail: S.Nichols@hull.ac.uk

Carotid intima-media thickness (C-IMT) measurements provide a non-invasive assessment of subclinical atherosclerosis. The aim of the study was to assess the inter- and intra-observer variability of automated C-IMT measurements undertaken by two novice operators using the Panasonic CardioHealth Station. Participants were free from cardio-metabolic disease, and each underwent serial bilateral C-IMT ultrasound measurements. Immediate interoperator measurement variability was calculated by comparing initial measurements taken by two operators. Immediate retest variability was calculated from two consecutive measurements and longer term variability was assessed by conducting a further scan 1 week later. Fifty apparently healthy participants (n = 20 females), aged $26 \cdot 2 \pm 5 \cdot 0$ years, were recruited. Operator 1 recorded a median (interquartile range) right and left-sided C-IMT of $0 \cdot 471$ mm ($0 \cdot 072$ mm) and $0 \cdot 462$ mm ($0 \cdot 047$ mm). Female's right and left C-IMT were $0 \cdot 442$ mm ($0 \cdot 049$ mm) and $0 \cdot 451$ mm ($0 \cdot 063$ mm), respectively. The limits of agreement (LoA) for immediate interoperator variability were $-0 \cdot 063$ to $0 \cdot 056$ mm (mean bias $-0 \cdot 003$ mm). Operator 1's immediate retest intra-operator LoA were $-0 \cdot 057$ to $0 \cdot 046$ mm (mean bias was $-0 \cdot 005$ mm). One-week LoA were $-0 \cdot 057$ to $0 \cdot 050$ mm (mean bias $-0 \cdot 003$ mm). Operator 2 recorded median right and left-sided C-IMT of $0 \cdot 467$ mm ($0 \cdot 089$ mm) and $0 \cdot 458$ mm ($0 \cdot 046$ mm) for males, respectively, whilst female measurements were $0 \cdot 441$ mm ($0 \cdot 052$ mm) and $0 \cdot 444$ mm ($0 \cdot 054$ mm), respectively. Operator 2's intra-operator immediate retest LoA were $-0 \cdot 056$ to $0 \cdot 056$ (mean bias $<-0 \cdot 001$ mm). Intra-operator LoA at 1 week were $-0 \cdot 052$ to $0 \cdot 068$ mm (mean bias $0 \cdot 008$ mm). Novice operators produce acceptable short-term and 1-week inter- and intra-operator C-IMT measurement variability in healthy, young to middle-aged adults using the Panasonic CardioHealth Station.

Introduction

The process of atherogenesis often occurs in areas of high oscillatory shear stress within human vasculature (Lee et al., 2001; Kolodgie et al., 2007). Early stages of atherosclerosis often present as thickened arterial walls, a phenotype that can be observed using B-mode ultrasound imaging. Pignoli et al. (1986) established that the distance between two parallel echogenic lines observed when imaging human arteries is a valid measurement of combined intima and media thickness of the carotid artery (C-IMT) when compared to histopathological samples. Increased C-IMT has repeatedly been shown to predict cardiovascular disease (CVD), decreased coronary flow reserve and increased risk of mortality (Lorenz et al.,

2007, 2012; Rohani et al., 2005; Salonen & Salonen, 1993; Sonoda et al., 2004; Takiuchi et al., 2003). A thickened intima-media layer in the carotid artery is indicative of long-term exposure to CVD risk factors and is a visually meaningful measurement that can provide important information on the progress of arterial disease. It is now one of the most widely used methods of assessing subclinical atherosclerosis (O'Leary & Bots, 2010) and a valuable surrogate end point for primary and secondary prevention studies. However, the clinical significance of C-IMT measurements is not fully appreciated as its typical measurement variability remains under reported.

Only in recent years have international consensus statements provided guidance on the standardisation of imaging protocols (Stein et al., 2008; Touboul et al., 2012), and equipment

refinement has meant that current systems are more 'user friendly'. Automated edge detection systems may be a way to reduce measurement variability by standardizing image selection and measurement (O'Leary & Bots, 2010). These record measurements based on predefined criteria and may provide opportunities for less-experienced sonographers to reliably measure C-IMT (Vanoli et al., 2013). However, there are few reported data that confirm this technical benefit. The aim of our study was to quantify the variability of C-IMT measurements taken using a specific automated edge detection system (Panasonic CardioHealth Station, Panasonic Biomedical Sales Europe BV, Leicestershire, UK). We hypothesized that novice operators could produce acceptable inter- and intra-operator variability from measurements taken at short-term and 1-week intervals during C-IMT measurements in healthy, young to middle-aged adults.

Methods

Participants

Ethical approval for the study was reviewed and approved by the Department of Sport, Health & Exercise Science Research Ethics Committee and meets the ethical standards of this journal. Participants were recruited from the local community, and written informed consent was taken from each volunteer. All participants were aged 18–40 years and were free from any underlying medical conditions including cardiometabolic disease. Female participants were excluded if they were pregnant. All participants were instructed to attend in a euhydrated state. Participants were asked to refrain from moderate physical activity and to avoid beverages containing caffeine on the day of testing.

Study protocol

Each participant was required to attend on two occasions, 7 days apart. Appointments were scheduled at the same time of day to control for circadian variation. Resting heart rate and blood pressure were taken after 10 min of rest using a sphygmomanometer (Accoson Works, City = Harlow Essex, UK) and a Littman stethoscope (3M Healthcare, St Paul, MN, USA). Body mass was measured using SECA balance scales (Vogel & Halke, Hamburg Germany) and stature was measured using a stadiometer (Holtain Ltd, Crymych, Dyfed UK). Waist and hip circumference measurements were also taken using an inflexible tape measure.

Device specification

The Panasonic CardioHealth Station is a commercially available ultrasound system which uses a broadband probe (5–13 MHz) with a centre frequency of 9 MHz optimized for carotid imaging. When the probe is correctly positioned over the carotid artery, onboard software automatically identifies the far wall with a region of interest (ROI) tool (Fig. 1). The system captures a sequence of near R-wave triggered (end-diastole) images automatically by monitoring the vessel distension characteristics and stops when predefined C-IMT boundary quality criteria are met. A mean, minimum and maximum C-IMT in millimetres are calculated based on real-time raw data over multiple lines in the region of interest and values are displayed to three decimal places. The probe is also fitted with an integrated accelerometer and gyroscope that track its insonation angle relative to ground. The angle of the probe (°) is displayed onscreen (Fig. 1) and recorded with the images to allow the operator to review and reproduce similar angles on repeated scans.

Carotid ultrasound measurement technique

Two right-handed novice operators (<10 practice scans each) performed three C-IMT investigations. At visit 1, operator one (O1) and operator two (O2) scanned the same subject consecutively (initial scan), followed by a second examination by both operators ~10 min later (immediate repeat scan). At 1-week follow-up, O1 and O2 performed a third consecutive scan (1-week scan).

Participants were positioned supine on a 180° examination bed with their head rotated against a gauge angled to 45°. The probe angle was standardized using software that indicated the probe angle (°) relative to ground. All images were taken from the far wall of the distal common carotid artery (CCA), 1 cm proximally from the bifurcation. When the region of interest was correctly identified and software image criteria were met, an image was automatically frozen at end-diastole and C-IMT was calculated over a 10 mm length using automated boundary detection. Each measurement was visually checked for accuracy. Images were taken at four angles following the order: right lateral (125–145°), right anterior (170–190°), left lateral (215–235°) and left anterior (170–190°).

Statistical analysis

SPSS Version 19 (IBM, New York, NY, USA), SigmaPlot Version 12 (Systat Software, San Jose CA, USA) and Microsoft Excel 2007 (Microsoft, Redmond WA, USA) were used for analysis. Continuous variables are presented as mean with 95% confidence intervals (CI) and standard deviation where specified (SD), nonnormally distributed data as medians (interquartile ranges) and categorical data as percentages. Skewness and kurtosis were checked visually with histograms, and Kolmogorov–Smirnov (K-S) tests were used to assess normality. Log_{10} transformations were conducted to attempt to correct for deviations from normality, and where parametric assumptions could not be met, Wilcoxon and Mann–Whitney U-tests were used to identify significant differences between variables. Heteroscedasticity was evaluated using the Breusch-Pagen test. An arbitrary level of 5% statistical significance was used throughout (two-tailed).

Figure 1 A screenshot showing C-IMT investigation where angle of examination is displayed and recorded using an integrated system (Bottom Right). The region of interest (ROI) is located within the white box (centre) and is parallel to a white vertical dotted line (centre -left). The distance between these two features measures 1 cm and allows the operator to measure the distance between the flow divider and the C-IMT measurement site during the scan.

Bland–Altman plots were used to calculate mean bias and limits of agreement (LoA) (Bland & Altman, 1999) and because the CardioHealth Station calculates C-IMT to the nearest micrometre, results were reported as millimetre rounded to three decimal places. The significance of variability shown by LoA and bias depends on whether differences reach clinically meaningful levels. Intraclass correlation coefficients (ICCs) using a two-way mixed effect model for agreement of single measurements were performed. A consensus on ICC strength has not been reached; however, for our purposes, moderate agreement was defined as an ICC of 0·6–0·75, good agreement between 0·75 and 0·9 and excellent >0·9 (Atkinson & Nevill, 1998). Coefficient of variation percentage (CoV%) was calculated as within-subject standard deviation divided by the group mean multiplied by 100 (Atkinson & Nevill, 1998). A CoV% was calculated for each angle interrogated by O1 and O2. Immediate interoperator measurement variability was calculated by directly comparing operator 1's measurement with operators 2's at any given time point, for example O1 initial scan versus O2 initial scan. Longer term interoperator variability was calculated by comparing the initial scans of one operator to the 1-week scan of the other operator. This also allowed a comparison of interoperator measurement variability under conditions similar to those where study participants

return for repeated visits but where scans are conducted by different operators. Short-term and 1-week intra-operator variability was calculated by comparing an operator's initial scan to their immediate repeat scans and initial scan to 1-week scan, respectively.

Results

Fifty participants [60% male; age $26·2 \pm 5·0$ years; BMI $24·6$ Kg m^{-2} (interquartile range $3·2$Kg m^{-2})] were recruited. A significant reduction in resting heart rate and resting systolic blood pressure was noted at the follow-up visit, all other supplementary measurements remained unchanged (Table 1). No scans were excluded due to poor image quality. Both operators noted that males had significantly larger C-IMT than females (table 2); however, all C-IMT measurements were within normal healthy ranges (Simon *et al.*, 2002).

Angle consistency

The CoV% for insonation angle was small for both operators indicating good angle consistency. For O1, right and left anterior measurements were taken at angles of $174 \pm 4°$ and $185 \pm 4°$ with CoV% of $2·1$ and $1·9$, respectively. Right and

Table 1 Baseline and follow-up participant characteristics (mean ± SD and median with interquartile range).

Variable	Visit 1	Visit 2	P value
BMI (Kg m^{-2})	24·6 (3·3)	24·5 (3·4)	0·125[a]
W/H ratio	0·84 ± 0·69	0·83 ± 0·68	0·142[b]
Resting SBP (mmHg)	118 ± 12	114 ± 10	0·002[b],*
Resting DBP (mmHg)	71 ± 9	69 ± 8	0·144[b]
RHR (BPM)	65 (10)	63 (11)	0·032[a],*

BMI, body mass index; W/H, waist to hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; RHR, resting heart rate.
*Significant difference.
[a]Wilcoxon test.
[b]Paired sample t-test.

Table 2 C-IMT for males and females taken by operator 1 & 2 (median with interquartile rage).

	Right (mm)	Left (mm)	P value
Operator 1			
Male	0·471 (0·072)	0·462 (0·047)	0·237
Female	0·442 (0·049)	0·451 (0·063)	0·179
P value	<0·001*	0·033*	
Operator 2			
Male	0·467 (0·089)	0·458 (0·046)	0·021*
Female	0·441 (0·052)	0·444 (0·054)	0·054
P value	<0·001*	0·025*	

Significant difference calculated using Mann–Whitney U-tests and Wilcoxon tests.
*Significant difference.

left lateral measurements were taken at 135 ± 5° (CoV% 3·4) and 222 ± 5° (CoV% 2·4). O2 showed similar results: right anterior 172 ± 3° (CoV% 1·8), left anterior 185 ± 4° (CoV% 2), right lateral 137 ± 5° (CoV% 3·7) and left lateral 219 ± 6° (CoV% 2·5). Statistically significant (P<0·001) differences of ~3° between O1 and O2's measurement angle for right anterior, right lateral and left lateral (mean difference 1·4°, 1·9° and 3·4°, respectively) were recorded.

Immediate interoperator variability

Bland–Altman plots were used to assess the interoperator variability of measurements taken at the same time point. Bland–Altman plots require the differences between two measurements to be normally distributed, an assumption that was not met (P<0·05). Log$_{10}$ transformation did not correct for non-normal distribution, but graphical histograms showed near normality with low kurtosis and skewness, and a Breush-Pagan test showed homoscedasticity (P = 0·0002), so untransformed data were used. The LoA are still useful and are likely to be too wide rather than too narrow when data are not normally distributed (Bland & Altman, 1999). Results from O1 and O2 (Fig. 2) showed low variability from all measurements (mean bias −0·003 mm; LoA −0·063 to 0·056 mm)

and good ICC strength (0·840; 95% CI 0·815–0·862). Similar results were shown when data were binned into separate scans. Initial scan mean bias was −0·009 mm (LoA −0·068 to 0·051 mm; ICC 0·834 95% CI 0·775–0·877), immediate repeat scan mean bias was −0·003 mm (LoA −0·063 to 0·057 mm; ICC 0·840 95% CI 0·794–0·877), and the 1-week follow-up scan had a mean bias of 0·003 mm (LoA −0·054 to 0·060 mm; ICC 0·840 95% CI 0·815–0·926). When measurements were broken down further and analysed by ultrasound view and time point (Table 3), the largest measurement error was from images taken on the left lateral or anterior aspects at the immediate repeat scan; however, all ICCs reached statistical significance (P<0·05).

One-week interoperator variability

One-week variability (initial scan versus 1-week scan) remained similar to immediate variability for both operators. O1's initial measurement had good agreement with O2's 7-day measurement (mean bias −0·001; LoA 0·067–0·066 mm), and O2's initial measurement had good agreement with O1's 7-day measurement (mean bias 0·005; LoA 0·056–0·066 mm) whilst ICCs were 0·815 (95% CI: 0·763–0·857) and 0·814 (95% CI: 0·760–0·856), respectively.

Short-term and 1-week intraoperator variability

O1's short-term mean bias (initial scan versus immediate repeat scan) was −0·005 mm and LoA were −0·057 to 0·046 mm (ICC 0·883; 95% CI: 0·847–0·911). One-week mean bias and LoA (initial scan versus 1-week follow-up scan) were −0·003 mm and −0·057 to 0·050 mm (Fig. 3) with an ICC of 0·868 (95% CI: 0·829–0·899). O2's short-term mean bias and LoA were <−0·001 mm and −0·056 to 0·056 mm, respectively (ICC 0·858; 95% CI: 0·816–0·890), whilst mean bias and LoA for 1-week measurements were 0·008 mm and −0·052 to 0·068 mm (Fig. 4) with an ICC 0·828 (95% CI: 0·771–0·870). All ICC were significant (P<0·001); however, the strength of the ICCs appeared to be dependent on the angle of measurement. For O1, right lateral measurements demonstrated the strongest ICC (0·929; 95% CI 0·890–0·957), whilst left anterior measurements were weakest (ICC: 0·821; 95% CI 0·733–0·888). Right anterior ICC was 0·863 (95% CI: 0·793–0·915), and left lateral was 0·833 (95% CI: 0·749–0·895). O2 also recorded the strongest ICC for right lateral measurements (0·914; 95% CI: 0·867–0·947) however the weakest ICC was for left lateral measurements (0·711; 95% CI: 0·586–0·812). Right anterior ICC was (0·872; 95% CI 0·804–0·921), and left anterior ICC was 0·721 (95% CI: 0·598–0·819).

Learning effect

All C-IMT measurements were chronologically organized and were categorized by the first 25 participants and final 25 scans to examine whether measurement variability improved with
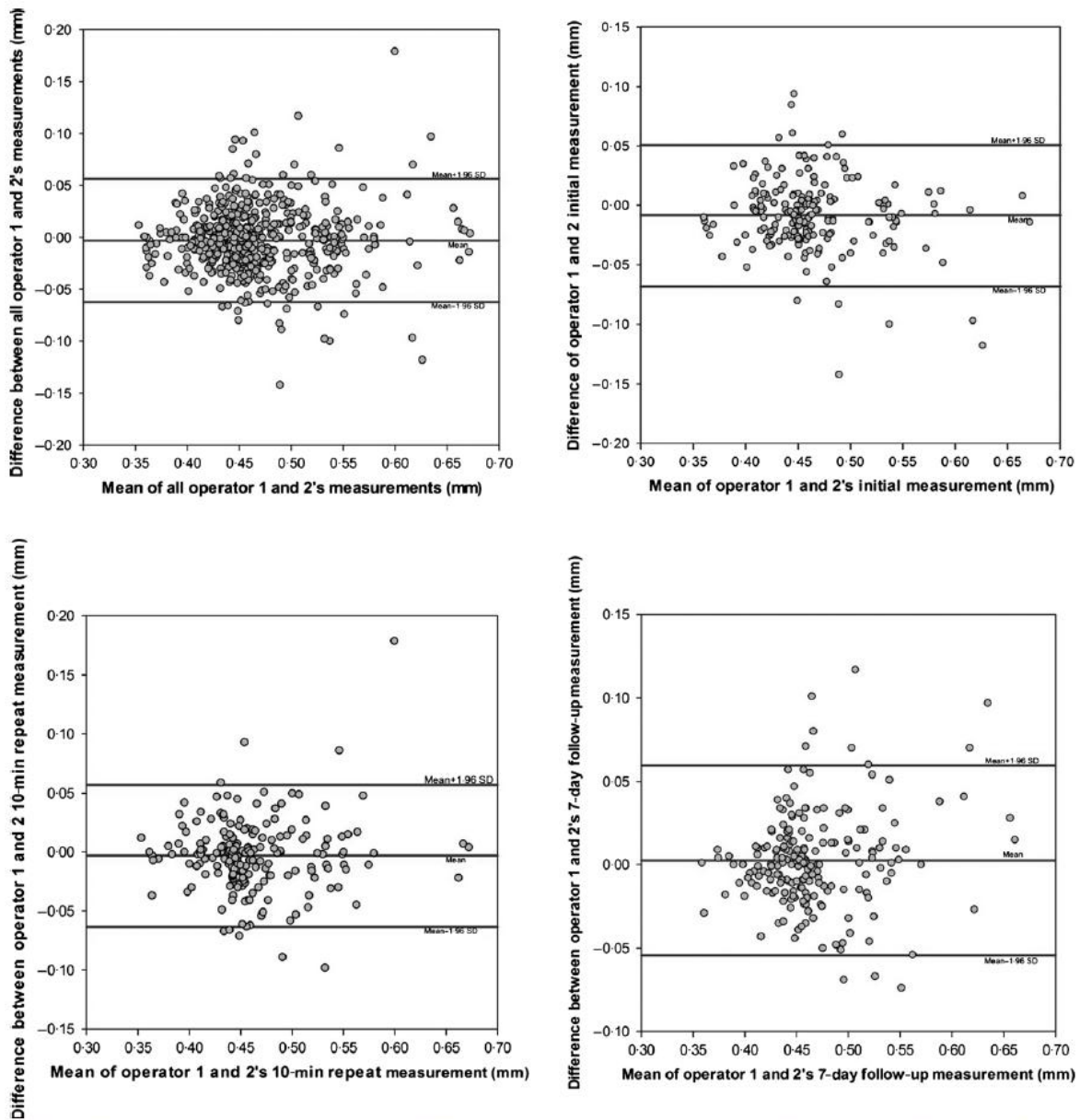
Figure 2 Bland–Altman plots showing mean bias and LOA for immediate interoperator measurements (O1 = operator 1; O2 = operator 2).

experience. Short-term LoA improved after 25 scans for both operators, whereas 1-week LoA only improved for O2 (Table 4). ICC strength decreased with experience for 1-week variability for both operators, but agreement still remained good (O1, ICC = 0·842; O2, ICC = 0·785).

Discussion

We have shown that novice operators produce acceptable short-term and 1-week inter- and intra-operator C-IMT measurement variability in healthy, young to middle-aged adults using the Panasonic CardioHealth Station. We report lower

intra-operator mean bias than previously reported; Kanters *et al.* (1997) stated that mean measurement differences ranging from −0·02 to 0·63 mm in their systematic review, whereas we report a mean bias of −0·011 mm. Intra-operator LoA (O1: −0·049 to 0·039 mm; O2: −0·048 to 0·048) show that novice operators are capable of detecting clinically meaningful C-IMT increases of 0·1 mm (Salonen & Salonen, 1993; Lorenz *et al.*, 2007) using this ultrasound device.

As documented by other investigators, intra-operator variability was lower than interoperator variability (Kanters *et al.*, 1997; Stensland-Bugge *et al.*, 1997; Lundby-Christensen *et al.*, 2010); however, our findings show improved levels of inter-

Table 3 Immediate interoperator variability by time point and angle.

Time point	Ultrasound view	Mean bias (mm)	LoA (mm)	ICC	ICC 95% CI	P value
Initial scan	Right anterior	−0·009	−0·070 to 0·052	0·867	0·773–0·923	<0·001*
	Left anterior	−0·007	−0·066 to 0·052	0·748	0·595–0·848	<0·001*
	Right lateral	−0·011	−0·064 to 0·042	0·894	0·803–0·942	<0·001*
	Left lateral	−0·008	−0·073 to 0·058	0·744	0·590–0·846	<0·001*
Immediate repeat scan	Right anterior	0·001	−0·047 to 0·049	0·908	0·843–0·947	<0·001*
	Left anterior	0·001	−0·061 to 0·063	0·763	0·616–0·858	<0·001*
	Right lateral	−0·004	−0·055 to 0·047	0·920	0·864–0·954	<0·001*
	Left lateral	−0·010	−0·085 to 0·065	0·674	0·488–0·801	<0·001*
1-Week follow-up	Right anterior	0·008	−0·037 to 0·053	0·912	0·841–0·951	<0·001*
	Left anterior	0·010	−0·054 to 0·074	0·719	0·547–0·831	<0·001*
	Right lateral	−0·004	−0·059 to 0·051	0·902	0·835–0·943	<0·001*
	Left lateral	−0·004	−0·062 to 0·054	0·772	0·632–0·864	<0·001*

*Statistically significant.
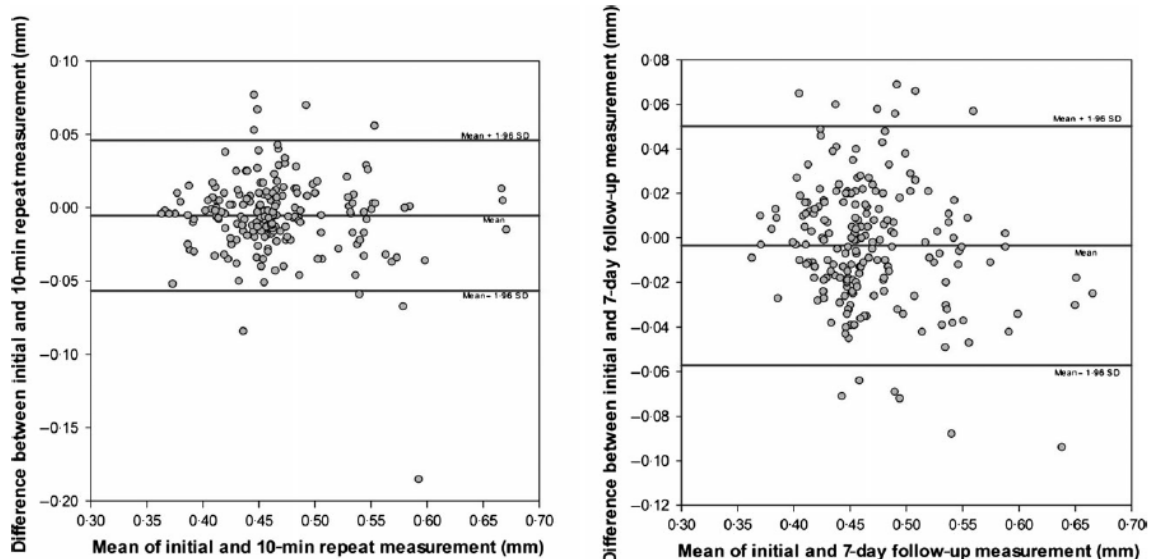
Figure 3 Operator 1's short and longer term measurement variability.

operator agreement in comparison with other investigators (Stensland-Bugge *et al.*, 1997; Lundby-Christensen *et al.*, 2010). A recent study using the CardioHealth Station to evaluate novice user trainability (Vanoli et al., 2013) showed substantially wider interoperator LoA than our study (−0·103 to 0·096 mm versus −0·063 to 0·056 mm). Variable examination angle and the presence of increased IMT (and therefore potentially less homogenous C-IMT) may have contributed to their results and the discrepancy between the study findings. However, this remains speculative as the authors do not provide data on ultrasound probe angle consistency. Future research may wish to focus on the replication of specific angles and artery segments using integrated angle sensors to minimize measurement error.

The probe angle that novice operators take images from also appears to affect measurement variability, and right lateral scans provided less measurement variability than other views. This finding indicates that specific angles and hand positions (for right-handed operators) may demand a greater degree of practice before novice operators acquire the same level of measurement accuracy as more experienced operators. The LoA for measurements taken from the right side (LoA ~−0·037 to 0·053 mm) by our novice operators are comparable to recent research (Saba *et al.*, 2012) using sonographers with 3–10 years of experience (~−0·041 to 0·049 mm). However, when all angles of examinations were combined, the LoA for interoperator variability were wider (−0·063 to 0·056 mm) reflecting the higher variability from images acquired at different hand positions.

A learning effect for C-IMT measurements (examined by comparing variability measures among the first 25 participants compared to the remainder of the sample) was also identified.
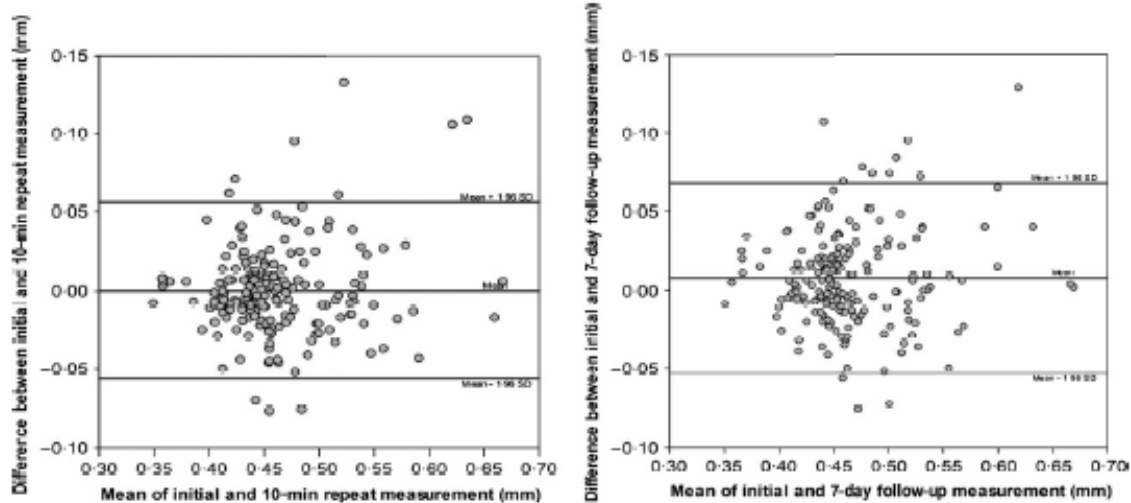
Figure 4 Operator 2's short and longer term measurement variability.

Table 4 The effect of experience on measurement accuracy.

Operator	Scan	First/final scan	Mean bias (mm)	LoA (mm)	ICC	ICC 95% CI	P value
Operator 1	Initial scan versus immediate repeat scan	First 25 patients	−0·006	−0·064 to 0·053	0·875	0·819−0·914	<0·001*
		Final 25 patients	−0·005	−0·049 to 0·039	0·897	0·848−0·930	<0·001*
	Initial scan versus 1-week follow-up scan	First 25 patients	−0·006	−0·060 to 0·047	0·887	0·834−0·923	<0·001*
		Final 25 patients	<−0·001	−0·054 to 0·053	0·842	0·774−0·891	<0·001*
Operator 2	Initial scan versus immediate repeat scan	First 25 patients	<0·001	−0·063 t0 0·064	0·851	0·786−0·897	<0·001*
		Final 25 patients	<0·001	−0·048 to 0·048	0·869	0·812−0·910	<0·001*
	Initial scan versus 1-week follow-up scan	First 25 patients	0·010	−0·050 to 0·071	0·854	0·776−0·904	<0·001*
		Final 25 patients	0·005	−0·054 to 0·064	0·785	0·687−0·850	<0·001*

*Statistically significant.

Although the measurements taken at the start of the study are still within acceptable limits, there is evidence that even limited experience can improve measurement variability. In contrast, measurement variability over 1 week may not improve irrespective of experience, suggesting that the familiarity developed between the short-term scans may influence measurements. To our knowledge, the study by Vanoli et al. (2013) is the only recent study to assess the effect of operator experience on measurement variability. Our results are in concordance with Vanoli et al.'s (2013) findings, confirming that experience does improve short-term measurement variability.

A limitation of our study is that measurement variability was assessed over a relatively short time frame. A longer follow period would help to further assert the variability of C-IMT measurements and may be useful for studies that wish to monitor changes over an extended period. However, studies should bear in mind the dynamic nature of atherosclerosis progression and regression when planning longer term studies, especially if studies involve the use of elderly or clinical cohorts.

Our results will allow researchers and clinicians to monitor clinical changes in C-IMT measurements and appropriately take measurement error into consideration. The applicability of this work is restricted to patient primary prevention due to the effect that vascular remodeling may have on measurement variability. Future work should evaluate the variability of C-IMT in clinical cohorts and attempt to control the angle of investigation between scans. Investigations using C-IMT as an end point should present their own measurement variability data or cite a suitable variability studies to assist with clinical interpretation.

In conclusion, novice operators produce acceptable short-term and 1-week inter- and intra-operator C-IMT measurement variability in healthy, young to middle-aged adults using the Panasonic CardioHealth Station.

Acknowledgment

None.

Conflict of interest

The authors have no conflicts of interest.

References

Atkinson G, Nevill A. Statistical methods for assessing measurement error (reliability) in variables relevant to sports medicine. *Sports Med* (1998); **26**: 217–238.

Bland JM, Altman DG. Measuring agreement in method comparison studies. *Stat Methods Med Res* (1999); **8**: 135–160.

Kanters SDJM, Algra A, van Leeuwen MS, Banga J-D. Reproducibility of in vivo carotid intima-media thickness measurements: a review. *Stroke* (1997); **28**: 665–671.

Kolodgie FD, Burke AP, Nakazawa G, Virmani R. Is pathologic intimal thickening the key to understanding early plaque progression in human atherosclerotic disease? *Arterioscler Thromb Vasc Biol* (2007); **27**: 986–989.

Lee RT, Yamamoto C, Feng Y, Potter-Perigo S, Briggs WH, Landschulz KT, Turi TG, Thompson JF, Libby P, Wight TN. Mechanical strain induces specific changes in the synthesis and organization of proteoglycans by vascular smooth muscle cells. *J Biol Chem* (2001); **276**: 13847–13851.

Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation* (2007); **115**: 459–467.

Lorenz MW, Polak JF, Kavousi M, Mathiesen EB, Völzke H, Tuomainen T-P, Sander D, Plichart M, Catapano AL, Robertson CM, Kiechl S, Rundek T, Desvarieux M, Lind L, Schmid C, DasMahapatra P, Gao L, Ziegelbauer K, Bots ML, Thompson SG. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. *Lancet* (2012); **379**: 2053–2062.

Lundby-Christensen L, Almdal TP, Carstensen B, Tarnow L, Wiinberg N. Carotid intima-media thickness in individuals with and without type 2 diabetes: a reproducibility study. *Cardiovasc Diabetol* (2010); **9**: 40.

O'Leary DH, Bots ML. Imaging of atherosclerosis: carotid intima–media thickness. *Eur Heart J* (2010); **31**: 1682–1689.

Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. *Circulation* (1986); **74**: 1399–1406.

Rohani M, Jogestrand T, Ekberg M, van der Linden J, Källner G, Jussila R, Agewall S. Interrelation between the extent of atherosclerosis in the thoracic aorta, carotid intima-media thickness and the extent of coronary artery disease. *Atherosclerosis* (2005); **179**: 311–316.

Saba L, Mallarini G, Sanfilippo R, Zeng G, Montisci R, Suri J. Intima Media Thickness Variability (IMTV) and its association with cerebrovascular events: a novel marker of carotid therosclerosis? *Cardiovasc Diagn Ther* (2012); **2**: 10.

Salonen J, Salonen R. Ultrasound B-mode imaging in observational studies of atherosclerotic progression. *Circulation* (1993); **87**: II56.

Simon A, Gariepy J, Chironi G, Megnien J-L, Levenson J. Intima-media thickness: a new tool for diagnosis and treatment of cardiovascular risk. *J Hypertens* (2002); **20**: 159–169.

Sonoda M, Yonekura K, Yokoyama I, Takenaka K, Nagai R, Aoyagi T. Common carotid intima–media thickness is correlated with myocardial flow reserve in patients with coronary artery disease: a useful non-invasive indicator of coronary atherosclerosis. *Int J Cardiol* (2004); **93**: 131–136.

Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, Najjar SS, Rembold CM, Post WS. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr* (2008); **21**: 93–111.

Stensland-Bugge E, Bønaa KH, Joakimsen O. Reproducibility of ultrasonographically determined intima-media thickness is dependent on arterial wall thickness: the Tromsø Study. *Stroke* (1997); **28**: 1972–1980.

Takiuchi S, Rakugi H, Fujii H, Kamide K, Horio T, Nakatani S, Kawano Y, Higaki J, Ogihara T. Carotid intima-media thickness is correlated with impairment of coronary flow reserve in hypertensive patients without coronary artery disease. *Hypertens Res* (2003); **26**: 945–951.

Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, Csiba L, Desvarieux M, Ebrahim S, Hernandez Hernandez R, Jaff M, Kownator S, Naqvi T, Prati P, Rundek T, Sitzer M, Schminke U, Tardif JC, Taylor A, Vicaut E, Woo KS. Mannheim carotid intima-media thickness and plaque consensus (2004–2006–2011). *Cerebrovasc Dis* (2012); **34**: 290–296.

Vanoli D, Wiklund U, Lindqvist P, Henein M, Näslund U. Successful novice's training in obtaining accurate assessment of carotid IMT using an automated ultrasound system. *Eur Heart J Cardiovasc Imaging* (2013); **15**: 637–642.

8.4 Appendix 4

Appendix Table 1 – Median Change of Mean C-IMT between Visit 1 and 2 (mm; range)

Insonation Angle	Training Group	Control Group	p-value
Pooled Right Change	-0.004 (-0.320 to 0.160)	0.029 (-0.100 to 0.200)	0.191
Right Anterior Change	-0.014 (-.230 to 0.350)	0.027 (-0.400 to 0.310)	0.249
Right Lateral Change	-0.002 (-0.290 to 0.190)	0.070 (-0.060 to 0.200)	0.312
Right Posterior Change	-0.004 (-0.460 to 0.180)	0.015 (-0.090 to 0.230)	0.387
Pooled Left Change	0.016 (-0.100 to 0.210)	0.022 (-0.100 to 0.160)	0.901
Left Anterior Change	0.011 (-0.110 to 0.400)	-0.017 (-0.140 to 0.290)	0.576
Left Lateral Change	0.043 (-0.210 to 0.350)	-0.038 (-0.280 to 0.260)	0.249
Left Posterior Change	-0.019 (-0.330 to 0.300)	0.085 (-0.150 to 0.300)	0.095

C-IMT = Carotid Intima-Media Thickness; mm = millimetres

Appendix Table 2 – Median Change of Maximum C-IMT between Visit 1 and 2 (mm; range)

Insonation Angle	Training Group	Control Group	p-value
Pooled Right Change	0.001 (-0.270 to 0.170)	0.032 (-0.060 to 0.200)	0.367
Right Anterior Change	-0.025 (-0.780 to 0.190)	-0.045 (-0.190 to 0.160)	0.986
Right Lateral Change	0.039 (-0.380 to 0.360)	0.080 (-0.090 to 0.300)	0.321
Right Posterior Change	0.035 (-0.350 to 0.390)	0.035 (-0.110 to 0.380)	0.815
Pooled Left Change	0.036 (-0.190 to 0.220)	-0.011 (0.-0.140 to 0.200)	0.737
Left Anterior Change	0.040 (-0.230 to 0.430)	0.010 (-0.430 to 0.430)	0.387
Left Lateral Change	0.079 (-0.300 to 0.270)	-0.050 (-0.380 to 0.300)	0.377
Left Posterior Change	0.000 (-0.500 to 0.390)	0.080 (-0.240 to 0.310)	0.151

C-IMT = Carotid Intima-Media Thickness; mm = millimetres

8.5 Appendix 5

Appendix Table 1 – Association (r) between cardiovascular risk factors and mean C-IMT at different insonation angles

Cardiovascular Risk Factor	Angle of Insonation							
	Right Anterior	Right Lateral	Right Posterior	Pooled Right Side C-IMT	Left Anterior	Left Lateral	Left Posterior	Pooled Left Side C-IMT
Age (Years)	0.518 (p=0.002)	0.489 (p=0.004)	0.356 (p=0.039)	0.473 (p=0.005)	0.340 (p=0.049)	0.144 (p=0.415)	0.152 (p=0.405)	0.266 (p=0.128)
BMI (Kg·m^{-2})	-0.306 (p=0.079)	-0.142 (p=0.431)	-0.108 (p=0.543)	0.266 (p=0.266)	-0.073 (p=0.683)	-0.138 (p=0.436)	0.016 (p=0.932)	-0.119 (p=0.501)
Waist Circumference (cm)	-0.195 (p=0.269)	-0.003 (p=0.985)	-0.019 (p=0.915)	-0.075 (p=0.675)	0.023 (p=0.897)	0.059 (p=0.740)	0.104 (p=0.570)	0.017 (p=0.923)
W/H Ratio	-0.044 (p=0.806)	0.076 (p=0.676)	0.163 (p=0.356)	0.070 (p=0.692)	0.137 (p=0.439)	0.018 (p=0.918)	0.077 (p=0.673)	0.046 (p=0.795)
Total Body Fat (%)	-0.165 (p=0.351)	-0.018 (p=0.921)	-0.141 (p=0.425)	-0.126 (p=0.479)	0.083 (p=0.643)	0.104 (p=0.559)	0.242 (p=0.182)	0.098 (p=0.582)
Android Body Fat (%)	-0.306 (p=0.078)	-0.177 (p=0.324)	-0.228 (p=0.195)	-0.257 (p=0.143)	-0.045 (p=0.801)	0.023 (p=0.898)	0.141 (p=0.440)	-0.008 (p=0.965)
VO$_{2peak}$ (ml·kg^{-1}·min^{-1})	-0.188 (p=0.287)	-0.193 (p=0.282)	0.009 (p=0.960)	-0.132 (p=0.456)	-0.313 (p=0.072)	-0.429 (p=0.011)	-0.405 (p=0.021)	-0.393 (p=0.021)
Peak METs	-0.137 (p=0.440)	-0.156 (p=0.385)	-0.108 (p=0.542)	-0.074 (p=0.677)	-0.253 (p=0.149)	-0.277 (p=0.113)	-0.357 (p=0.045)	-0.308 (p=0.077)
SBP (mmHg)	0.150 (p=0.398)	0.287 (p=0.105)	0.177 (p=0.318)	0.226 (p=0.199)	0.072 (p=0.684)	-0.038 (p=0.831)	-0.007 (p=0.968)	0.045 (p=0.802)
DBP (mmHg)	0.099 (p=0.579)	0.130 (p=0.469)	0.138 (p=0.435)	0.122 (p=0.491)	0.115 (p=0.516)	-0.075 (p=0.675)	-0.110 (p=0.551)	-0.010 (p=0.956)

BMI = Body Mass Index; C-IMT= Carotid Intima-Media thickness; Kg·m^{-2}= Kilograms per Meter squared; cm = centimetres; W/H Ratio = Waist to Hip Ratio; VO$_{2peak}$ = Peak O$_2$ uptake; METs = Metabolic Equivalents; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; mmHg = Millimetres of Mercury

* = Significant Correlation

Appendix Table 2 – Association (r) between cardiovascular risk factors and maximum C-IMT at different insonation angles

Cardiovascular Risk Factor	Angle of Insonation							
	Right Anterior	Right Lateral	Right Posterior	Pooled Right Side C-IMT	Left Anterior	Left Lateral	Left Posterior	Pooled Left Side C-IMT
Age (Years)	0.565 (p<0.001)	0.565 (p=0.002)	0.303 (p=0.082)	0.474 (p=0.005)	0.306 (p=0.078)	0.055 (p=0.757)	0.072 (p=0.684)	0.097 (p=0.584)
BMI ($Kg \cdot m^{-2}$)	-0.240 (p=0.171)	-0.133 (p=0.459)	-0.114 (p=0.521)	-0.193 (p=0.274)	-0.015 (p=0.932)	-0.082 (p=0.643)	0.009 (p=0.962)	-0.025 (p=0.889)
Waist Circumference (cm)	-0.165 (p=0.352)	-0.043 (p=0.811)	-0.017 (p=0.925)	-0.093 (p=0.600)	0.138 (p=0.435)	0.100 (p=0.574)	0.141 (p=0.425)	0.177 (p=0.315)
W/H Ratio	-0.003 (p=0.985)	0.011 (p=0.949)	0.148 (p=0.404)	0.060 (p=0.735)	0.171 (p=0.333)	0.017 (p=0.926)	0.106 (p=0.549)	0.157 (p=0.374)
Total Body Fat (%)	-0.168 (p=0.343)	-0.033 (p=0.857)	-0.154 (p=0.384)	-0.140 (p=0.431)	0.098 (p=0.581)	0.116 (p=0.514)	0.177 (p=0.316)	0.133 (p=0.452)
Android Body Fat (%)	-0.310 (p=0.075)	-0.182 (p=0.310)	-0.212 (p=0.228)	0.254 (p=0.146)	-0.006 (p=0.971)	-0.058 (p=0.745)	-0.091 (p=0.608)	0.052 (p=0.771)
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	-0.191 (p=0.279)	-0.166 (p=0.356)	-0.034 (p=0.847)	-0.135 (p=0.059)	-0.290 (p=0.096)	-0.383 (p=0.025)	-0.311 (p=0.073)	-0.327 (p=0.059)
Peak METs	-0.153 (p=0.387)	-0.170 (p=0.343)	0.068 (p=0.703)	-0.071 (p=0.689)	-0.179 (p=0.312)	-0.292 (p=0.094)	-0.283 (p=0.105)	-0.272 (p=0.119)
SBP (mmHg)	0.177 (p=0.316)	0.327 (p=0.063)	0.208 (p=0.239)	0.227 (p=0.197)	0.111 (p=0.532)	0.031 (p=0.860)	-0.031 (p=0.861)	0.013 (p=0.940)
DBP (mmHg)	0.072 (p=0.685)	0.134 (p=0.458)	0.111 (p=0.531)	0.099 (p=0.577)	0.095 (p=0.593)	-0.137 (p=0.440)	-0.164 (p=0.355)	-0.092 (p=0.604)

BMI = Body Mass Index; C-IMT= Carotid Intima-Media thickness; $Kg \cdot m^{-2}$= Kilograms per Meter squared; cm = centimetres; W/H Ratio = Waist to Hip Ratio; VO_{2peak} = Peak O_2 uptake; METs = Metabolic Equivalents; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; mmHg = Millimetres of Mercury

* = Significant Correlation

8.6 Appendix 6

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 Andrew Garrett
Application number	Click here to enter text.
Principal investigator's name	Lee Ingle
Student investigator's name (if applicable)	Simon Nichols

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

Reviewers comments	
Section	**Comment**
Click here to enter text.	This application is acceptable for ethics approval.
Click here to enter text.	Click here to enter text.
Click here to enter text.	Click here to enter text.
Click here to enter text.	Click here to enter text.
Click here to enter text.	Click here to enter text.
Click here to enter text.	Click here to enter text.

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,	■ ☒ ☐

261

	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?	☒	■	☐

262

8.7 Appendix 7

<<hospital headed paper>>
Centre number: Study number:

Patient identification for this trial:

CONSENT FORM

Title of Project: Guided Exercise for CAD patients

Name of researchers: **Please initial box**

1. I confirm that I have read and understood the information sheet dated 8 February 2013 (version 4.0) for this study. I have had the opportunity to consider the information, ask questions & received satisfactory answers.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason, without my care or legal rights being affected.

3. I understand that to enable the study to be properly monitored and regulated, sections of my medical notes relevant to my taking part in this research and data collected during the study may be looked at by members of the research team, the NHS Trust where I will take part in the study, and the regulatory agencies. I give my permission for these individuals to have access to my records.

4. I understand that vital sign measurement will be acquired and stored, and may be sent for analysis to other researchers. Personal details will not be made available but anonymous information on the measurements and other medical information may be shared during the study.

5. I agree that my GP and hospital can be informed of my participation.

6. I agree that information about me can be obtained from the National Office of Statistics and NHS Central Register, Registrar General's Office and Information Division of NHS Scotland as necessary.

7. Should I choose to withdraw consent, I agree that information obtained from me in this study up to that point may still be used.

8. I agree to return all devices, shirts, equipment and accessories I was provided for the study at the end of my participation.

9. I agree to take part in the above study.

_____   _____   _____
Name of Patient   **Date**   **Signature**

_____   _____   _____
Name of Person taking consent   **Date**   **Signature**

Guided Exercise for CAD Patients Consent form version 7.0 dated 8 February 2013

263

8.8 Appendix 8

Results for NT-proBNP

NT-pro BNP was analysed by Castle Hill Hospital's pathology lab. Data was not normally distributed but Log10 transformation succeeded in normalising data. Only 18 patients were eligible for analysis due to assay failure and no results being returned for nine patients. The main effect was not significant (p=0.097; η_p^2=0.162), nor was the interaction (p=0.193; η_p^2=0.103) or group effect (p=0.391; η_p^2=0.046).