School of Physiotherapy and Exercise Science
Faculty of Health Sciences

The Effects of Left Ventricular Assist Device Implantation on Physical Activity, and the Acute and Chronic Physiological Responses to Exercise

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This thesis is presented for the Degree of
Doctor of Philosophy
of
Curtin University

January 2020

Declaration

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

Human Ethics. The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007) – updated March 2014. The proposed research study received human research ethics approval from the Curtin University Human Research Ethics Committee (EC00262), Approval Number HR13/2016.

Jose Ignacio Moreno Suarez

Date: 21/01/2010

Statement of contributors

The candidate, Jose Ignacio Moreno Suarez, was responsible for all aspects of the research presented in the present project, including obtaining ethics and site approvals, participation in the conception, design, data acquisition, analysis, interpretation and writing. Dr Kurt Smith collaborated with the candidate during the cerebral blood flow assessments and edited the manuscript in Chapters 4 and 5. Anna Scheer contributed in data collection related to brachial artery ultrasound assessment in Chapter 6. Associate Professor Maiorana, as a primary supervisor, contributed to research conception and design, data acquisition, interpretation, editing, critically revised the thesis and gave final approval. Dr Angela Spence, as a secondary supervisor, also contributed to editing and critically revised the thesis.

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Funding disclosure

The candidate, Jose Ignacio Moreno Suarez was supported by an International Postgraduate Research Scholarship from Curtin University and an ad hoc scholarship from the Heart and Lung Transplant Foundation of Western Australia. This research project was funded by a Vanguard Grant from the Heart Foundation of Australia (101040).

Abstract

Left ventricular assist device (LVAD) implantation is now an established treatment option for patients with advanced chronic heart failure (CHF) unresponsive to conventional medical treatment. Despite augmented central haemodynamic support provided by the LVAD, patients still experience an impaired aerobic capacity, which limits their capacity to perform activities of daily living and quality of life (QoL). Reasons behind this remain unclear. Alterations in the vasculature and end-organ function, such as the brain and skeletal muscle may be important factors. Currently, there is a scarcity of data regarding the daily physical activity (PA) levels and the effects of exercise training for this patient population. As LVAD therapy becomes more common, it is important to better understand the effects of physiological and clinical implications of LVAD implantation and responses to exercise. The objectives of the present research thesis were to examine the impact of left ventricular assist device devices in people with advanced CHF on daily PA levels and aerobic fitness; and the effects of acute and chronic responses to exercise on the cardio- and cerebrovascular systems. For these purposes, four experimental studies were conducted.

Study 1. Background: LVADs are associated with increased aerobic capacity in patients with CHF. However, studies evaluating the impact of LVAD implantation on PA are lacking. The aim of this study was to compare daily PA levels in participants with LVADs with well-matched CHF participants. Methods: Sixteen participants with an LVAD (age: 59.1 ± 10.8 yr) were case-matched to 16 participants with advanced CHF (age: 58.3 ± 8.7 yr), who were listed or being considered for cardiac transplantation. Participants underwent a cardiopulmonary exercise test to determine peak oxygen consumption ($\dot{V}O_2$ peak). PA was monitored continuously for at least seven consecutive days with an Actiheart monitor. Results: $\dot{V}O_2$ peak in the CHF group (12.3 ± 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$) was not significantly different to the LVAD group prior to LVAD implantation (10.4 ± 2.1 $mL \cdot kg^{-1} \cdot min^{-1}$), but was lower than in the LVAD group following implantation (15.8 ± 4.3 $mL \cdot kg^{-1} \cdot min^{-1}$; $p < 0.05$). PA was higher in the LVAD (19.7 ± 6.4 $kJ \cdot kg^{-1} \cdot day^{-1}$) compared with the CHF group (11.6 ± 6.9 $kJ \cdot kg^{-1} \cdot day^{-1}$; $p = 0.001$). LVAD participants spent more time performing moderate-intensity PA than their CHF counterparts, 26 (24-40) [median (IQR)] vs. 12

(9-16) min/day ($p < 0.001$). PA was correlated with $\dot{V}O_2$ peak (r = 0.582; $p = 0.001$) across participants in the CHF and LVAD groups. Conclusion: Higher levels of PA were observed in participants with LVAD compared with patients with advanced CHF. This may be due to a higher $\dot{V}O_2$ peak, resulting in an improved capacity to perform activities of daily living with fewer symptoms.

Study 2. Background: Patients with CHF experience cerebral hypoperfusion at rest, but little is known regarding the acute effect of exercise on blood flow (CBF) in patients with CHF, or whether this is effected by LVAD implantation. We hypothesised that patients with CHF would exhibit impaired cerebrovascular responses to incremental exercise when compared to age- and sex-matched healthy control participants (CTRL), but that this would be enhanced by LVAD implantation. Methods: Internal carotid artery (ICA), intra-cranial middle cerebral (MCAv) and posterior cerebral artery velocities (PCAv) were measured continuously using Doppler ultrasound, with concurrent assessment of cardiorespiratory parameters at rest and in response to an incremental cycle ergometer exercise protocol to volitional exhaustion in nine participants with LVADs (57.8 ± 14.6 yr; 87.38 ± 15.98 kg), nine age- and sex-matched participants with CHF (57.6 ± 8.3 yr; 83.6 ± 11.49 kg), and nine healthy control participants (54.8 ± 13.9 yr; 73.80 ± 15.76 kg). Results: At rest, ICA haemodynamics (velocity, shear stress and flow) were greater in the CTRL and LVAD group than the CHF group ($p < 0.05$). Higher levels of MCAv (52.7 ± 14.7 vs. 43.0 ± 15.8 $cm.s^{-1}$; $p < 0.001$) and PCAv (48.8 ± 14.6 vs. 34.9 ± 7.6 $cm.s^{-1}$, $p < 0.001$) were also observed in the LVAD compared with the CHF group, respectively. During exercise, ICA flow increased at all workloads in the CTRL group (Δ63.62 ± 10.8 $ml.min^{-1}$ at 60 W, $p < 0.0001$), whereas no exercise-induced increases were apparent in the either the CHF or LVAD groups. MCAv increased from baseline in both the CHF and CTRL group ($p = 0.0001$), but not in the LVAD group. Despite this, the CTRL and LVAD groups possessed significantly higher MCAv ($p = 0.006$) and PCAv ($p < 0.0001$) values throughout exercise than the CHF group. Conclusion: Our findings indicate that patients with LVADs exhibit higher cerebral blood flow at rest and during exercise than matched CHF subjects, but attenuated brain blood flows during exercise when compared to healthy subjects.

Study 3. Background: Cerebrovascular dysfunction is associated with advanced CHF. While LVAD implantation may improve cerebral perfusion at rest, it remains impaired during exercise. Exercise training is an effective therapy for improving vascular function, but no study has yet assessed its impact on cerebral perfusion. The aim of this study was to determine whether a 12-week exercise training program could mitigate cerebrovascular dysfunction in patients with LVADs. Methods: ICA blood flow and MCAv and PCAv artery velocities were measured continuously using Doppler ultrasound, with concurrent assessment of cardiorespiratory measures at rest and in response to an incremental cycle ergometer exercise protocol in 11 participants with LVADs (53.6 ± 11.8 yr; 84.2 ± 15.7 kg; 1.73 ± 0.08) pre (PreTR) and post (PostTR) completion of a 12-week supervised exercise rehabilitation program. Results: At rest, ICA flow and MCAv remained unchanged after the training program, whereas PCAv was reduced (from 43.0 ± 10.8 to 38.1 ± 10.4 $cm.s^{-1}$; $p < 0.05$). During exercise, the decline observed in PCAv (PreTR) from rest to exercise (5.2 ± 1.8%) was mitigated PostTR ($p < 0.001$). Similarly, exercise training enhanced ICA flow during submaximal exercise (8.6 ± 13.7%), resulting in increased ICA flow PostTR compared to a reduced flow PreTR ($p < 0.001$). Although both end tidal carbon dioxide ($P_{ET}CO_2$) and mean arterial pressure during incremental exercise were greater PostTR than PreTR, only the improved $P_{ET}CO_2$ was related to the improved ICA flow ($r = 0.37$; $p < 0.05$). Conclusion: Our findings suggest that short-term exercise training may improve cerebrovascular function during exercise in patients with LVADs. This preliminary finding should encourage future studies to investigate the effects of longer-term exercise training on cerebral vascular adaptation.

Study 4. Background: Left ventricular assist device (LVAD) implantation is an established treatment for patients with advanced chronic heart failure (CHF). To date, studies evaluating the impact of aerobic training in patients with LVADs have focused on moderate-intensity exercise. Methods: This was a randomised controlled trial comparing the effects of high-intensity interval training (HIIT) versus moderate-intensity continuous training (MICT) on $\dot{V}O_2$ peak in patients with LVADs. Secondary outcomes included 6-minute walk test distance (6MWTD), cardiac function, flow-mediated dilation, body composition and quality of life. Assessments were conducted at baseline and after 12 weeks of supervised training performed 3 times weekly. Participants were randomised to either HIIT (4x4min at 80-90% $\dot{V}O_2$ reserve,

interspersed with 4x3-min at 50-60% $\dot{V}O_2$ reserve) or MICT (28-min continuously at 50-60% $\dot{V}O_2$ reserve). $P<0.05$ was considered statistically significant. Data are expressed as marginal means with 95% confidence intervals. Results: 21 participants (HIIT: 57.7 ± 13.1 years; n=11) and (MICT: 55.6 ± 14.2 years; n=10) were randomised. No major adverse events occurred in response to training in either group. HIIT significantly improved $\dot{V}O_2$ peak (from 15.6 [13.2-17.8] to 18.4 [16.0-20.8] $mL \cdot kg^{-1} \cdot min^{-1}$) compared with MICT (16.2 [13.8-18.7] to 17.2 [14.6-19.7] $mL \cdot kg^{-1} \cdot min^{-1}$); $p<0.05$ between groups. No significant differences were detected in secondary outcomes between groups. Conclusion: HIIT was well tolerated and increased aerobic capacity more than MICT in patients with LVADs. Further studies are required to evaluate the effect of HIIT on a broader range of physiological and clinical outcomes in this cohort.

The work presented in the present thesis expands our current knowledge regarding the impact of LVAD implantation on daily PA levels and how acute and chronic exercise impacts the cerebral and cardiovascular systems. We observed that patients receiving an LVAD engage in higher PA levels compared with well-matched patients without mechanical circulatory support. This seems to be due to a higher aerobic capacity. The improved functional capacity allows patients to engage more vigorously in rehabilitation exercises and activities of daily living with fewer symptoms. In study 2, we showed that patients with LVADs have greater volumetric CBF at rest and during exercise compared to patients with CHF. However, CBF remains attenuated in these clinical cohorts relative to matched healthy controls. In Study 3, we found that CBF during exercise was improved following a short-term exercise training program in patients with LVADs. These findings suggest that exercise rehabilitation may be an effective treatment option for partially reversing the cerebrovascular dysfunction that these patients experience. In Study 4, we found that HIIT may be a safe and more efficient training mode compared to MICT for improving cardiorespiratory fitness in this clinical population. Our findings suggest that higher intensity aerobic exercise may be prescribed in rehabilitation programs for clinically stable patients after an initial lead-in period of moderate intensity is successfully completed.

Note: Some participants partially overlapped between Studies 3 and 4, not all of them. However, outcome measures and assessments were different and reported separately for each study.

Work arising from the thesis

Publications in peer reviewed-journals

1. Moreno-Suarez I, Liew S, Dembo LG, Larbalestier R, Maiorana AJ. Physical activity is higher in patients with left ventricular assist device compared with chronic heart failure. Med Sci Sports Exerc 2020;52:1-7.

2. Smith KJ*, Moreno-Suarez I*, Scheer A, Chasland LC, Thomas HJ, Correia MA, Dembo LG, Naylor LH, Maiorana AJ, Green DJ. Cerebral blood flow during exercise in heart failure: effect of ventricular assist devices. Med Sci Sports Exerc 2019;51:1372-79.

3. Smith KJ*, Moreno-Suarez I*, Scheer A, Dembo L, Naylor LH, Maiorana AJ, Green DJ. Cerebral blood flow responses to exercise are enhanced in left ventricular assist device patients after an exercise rehabilitation program. J Appl Physiol 2020;128:108-16.

4. Moreno-Suarez I, Scheer A, Lam K, Dembo L, Nolan J, Green G, Spence AL, Hayward C, Kaye D, Leet, Fuller L,Naylor L, Green D, Maiorana A. High intensity interval training in patients with left ventricular assist devices: a pilot RCT. J Heart Lung Transplant [in review].

Conference presentations

1. Moreno-Suarez I. The physiological responses to acute and chronic exercise in patients with left ventricular assist devices. Oral presentation at: the Annual Mark Liveris Research Student Seminar. Curtin University; September 1, 2016; Perth, WA, Australia.

2. Moreno-Suarez I. The impact of left ventricular assist device on physical activity levels and aerobic capacity in patients with heart failure. Poster presentation at: Exercise and Sport Science Australia, Research to Practice Conference; March 27, 2018; Brisbane QLD, Australia.

3. Moreno-Suarez I. Ventricular assist device implantation is associated with higher levels of physical activity in patients with advanced heart failure. Oral presentation at: 14th Annual Congress of European Association of Preventive Cardiology, European Society of Cardiology; April 19, 2018; Ljubljana, Slovenia.
4. Moreno-Suarez I. Left ventricular assist device implantation is associated with higher levels of physical activity in patients with advanced heart failure. Oral presentation at: The 24th Annual Meeting of the Japanese Association of Cardiac Rehabilitation; July 15, 2018; Tokyo, Japan.

   At this international conference, the candidate was awarded as the Best Student Oral Presentation.

5. Moreno-Suarez I. The cerebrovascular response to acute exercise in patients with left ventricular assist devices: Inaugural South Metropolitan Health Service Research Showcase; November 29, 2018; Perth, WA, Australia.

6. Moreno-Suarez I. The effects of different intensity exercise training in patients with left ventricular assist devices: A randomised controlled trial. Oral presentation at: Annual Research Symposium 2019; Australian Cardiovascular Health and Rehabilitation Association of Western Australia; July 24, 2019; Perth, WA, Australia.

7. Moreno-Suarez I. The effects of different intensity exercise training in patients with left ventricular assist devices: A randomised controlled trial. Oral presentation at: 29th Annual Scientific Meeting, Australian Cardiovascular Health and Rehabilitation Association; August 6, 2019; Sydney, NSW, Australia.

   At this conference, the candidate, Jose Ignacio Moreno Suarez was awarded as a finalist in the Research Prize Session.

8. Moreno-Suarez I. Effects of different intensity of exercise training in patients with left ventricular assist devices: Podium presentation at: Technology in Research, South Metropolitan Health Service Research Showcase; November 26, 2019; Perth, WA, Australia.

Acknowledgements

Foremost, I would like to express my sincere gratitude to my primary supervisor Associate Professor Andrew Maiorana for providing me with this opportunity to pursue a PhD with an expert like him in the field of exercise physiology. Thanks to his continuous support and guidance, I have been able to achieve a personal and professional goal from conception to completion which has been a life-changing experience. Because of that, I will always be grateful. I also would like to thank Dr Angela Spence for her support, encouragement and technical advice throughout my doctoral journey. Her supervision and motivation helped me in getting this thesis done.

I feel very lucky to have had the partnership of my college Anna Scheer, as well as had established research collaboration with Dr Kurt Smith, Dr Louise Naylor and Winthrop Professor Daniel Green from the University of Western Australia. Our collaborative efforts have been pleasurable and rewarding, and I thank all of you for your contributions.

This research project would not have been possible without the help and support of the staff members at the Advanced Heart Failure and Cardiac Transplant Service of Fiona Stanley Hospital. I have had the great opportunity of conducting my research at the hospital's cardiovascular gymnasium, so I would like to extend my gratitude to Fiona Beeck and Leanne Campbell and the rest of the cardiovascular team for their help, sharing with me their experience and knowledge and making my daily work enjoyable.

I also wish to show gratitude and appreciation to the participants who kindly volunteered to take part in the studies. This thesis would have never been completed without their involvement. The persistent exercise sessions and uncomfortable equipment during the assessments were commonly challenging, so I thank all of you very much for your daily commitment and effort.

Once again, I would like to thank my sponsors for the financial support, Curtin University, the Lung and Heart Transplant Foundation of Western Australia, and the Heart Foundation of Australia, which also made this thesis possible.

Last but not least, I would like to thank my friends from all over the planet that I made along the way at Curtin University and in Perth. Thanks for making my PhD journey such a wonderful experience that I will always remember.

Dedication

This thesis is dedicated to all the patients supported with a left ventricular assist device, and the clinicians of Fiona Stanley Hospital who are dedicated to making a difference to the lives of these patients and their families.

"*I alone cannot change the world, but I can cast a stone across the water to create many ripples*."

– Mother Teresa

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List of abbreviations

Abbreviation	description
1-RM	one-repetition maximum
6MWT	6-minute walk test
6MWTD	6-minute walk test distance
ACE-I	angiotensin-converting enzyme inhibitor
AR	aortic regurgitation
AR VC	aortic regurgitation vena contractor (width of the regurgitating jet)
ARB	angiotensin-receptor blocker
ASE	American society of echocardiography
AV	aortic valve
A-vO_2 diff	arteriovenous oxygen content difference
BiVAD	biventricular assist device
BL	baseline
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
BNP	b-type natriuretic peptide
BP	blood pressure
BSA	body surface area
CBF	cerebral blood flow
CF-LVAD	continuous flow left ventricular assist device
CHF	chronic heart failure
Chol	cholesterol (total)
CIs	confidence intervals
CI	cardiac index
CNS	central nervous system
CO	cardiac output
CO_2	carbon dioxide
CONSORT	consolidated standards of reporting trials
CPET	cardiopulmonary exercise testing

Abbreviation	description
CR	creatinine (serum)
CRP	C-reactive protein
CRTD	cardiac resynchronization therapy defibrillator
CTRL	control group
CVCi	cerebral vascular conductance index
DICOM	digital imaging and communications in medicine
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
EDA	end-diastolic area
EDD	end-diastolic dimension
EF	ejection fraction
ESA	end-systolic area
ET	exercise training
FAC	fractional area change
FMD	flow-mediated dilation
FSH	Fiona Stanley hospital
Hb	haemoglobin
HDL	high-density lipoprotein
HDSE	heart disease self-efficacy
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HIIT	high-intensity interval training
HM	Heartmate (LVAD system)
HR	heart rate
HREC	human ethics research committee
HVAD	Heartware (LVAD system)
ICA	internal carotid artery
INTERMACS	interagency registry for mechanically assisted circulatory support
ITT	intention-to-treat
IVC	inferior vena cava
KCCQ	Kansas city cardiomyopathy questionnaire

Abbreviation	description
LA	left atrium
LDL	low-density lipoprotein cholesterol
LMM	linear mixed models
LV	left ventricular
LVAD	left ventricular assist device
LVEDD	left ventricular end-diastolic diameter
LVEDV	left ventricular end-diastolic volume
LVEF	left ventricular ejection fraction
LVESD	left ventricular end-diastolic diameter
LVESV	left ventricular end-systolic volume
LVO	left ventricular output
MAP	mean arterial pressure
MCAv	middle cerebral artery velocity
MCS	mental component summary
MET	metabolic equivalent of task
MICT	moderate-intensity continuous training
MLHFQ	Minnesota living with heart failure questionnaire
MPAP	mean pulmonary artery pressure
MR	mitral regurgitation
MR VC	mitral regurgitation vena contractor
NIH	national institute of health (USA)
NIRS	near-infrared spectrometry
NO	nitric oxide
NS	non-significant
NYHA	New York heart association
PA	physical activity
PAEE	physical activity energy expenditure
PAWP	pulmonary artery wedge pressure
PCAv	posterior cerebral artery velocity
PCS	physical component summary
$PaCO_2$	Partial pressure of carbon dioxide
$P_{ET}CO_2$	partial pressure of end-tidal carbon dioxide

Abbreviation	description
$P_{ET}O_2$	partial pressure of end-tidal of oxygen
PF-LVAD	pulsatile flow left ventricular assist device
PO	pump output
PostTR	post-training
PP	pump pressure
PreTR	pre-training
QoL	quality of life
RA	right atrium
RAAS	renin-angiotensin-aldosterone system
RCT	randomised controlled trial
RER	respiratory exchange ratio
RPE	rated perceived exertion
RV	right ventricular
RVAD	right ventricular assist device
RVOT VTI	right ventricular outflow track velocity time integral
S'	systolic myocardial velocity
SAE	serious adverse event
SD	standard deviation
SF-36	short form health survey 36-item
SNS	sympathetic nervous system
SR	shear rate
SRauc	shear rate area under the curve
SV	stroke volume
SVR	systemic vascular resistance
TAH	total artificial heart
TCD	transcranial Doppler ultrasound
TCO	total cardiac output
TG	triglycerides (serum)
TGA	therapeutic goods administration
VA	vertebral artery
VAD	ventricular assist device
$\dot{V}E$	minute ventilation volume

Abbreviation	description
$\dot{V}O_2$	oxygen consumption

Chapter 1 General introduction

1.1 Background

Chronic heart failure (CHF) is defined by a reduced capacity of the heart to pump sufficient blood flow to meet the metabolic demands of the body.[1] It is characterised by impaired ventricular function with a resultant decrease in cardiac output, leading to abnormal neurohormonal activation and compensatory mechanisms of peripheral vasoconstriction and fluid retention.[2] Common symptoms of CHF include dyspnoea and muscle fatigue, resulting in exercise intolerance, which becomes progressively more pronounced as the condition progresses.[3]

Chronic heart failure is a global pandemic disease affecting over 26 million in the world people and is a leading cause of morbidity and mortality.[4] In Western countries, the prevalence of CHF ranges between 1–3% of the population[5], increasing to 10% for those aged >75 years[6]. Its economic impact is estimated at 2% of total health-care expenditure.[7] In Australia, the direct and indirect cost of CHF has been estimated at more than one billion a year.[8]

Given the increasing prevalence of CHF secondary to an ageing population and improved management of early-stage CHF, the proportion of patients reaching an advanced phase of the syndrome, class III-IV of the New York Heart Association (NYHA) functional classification system, is constantly increasing.[9] Estimations of the growth of CHF rates into the future are alarming: by 2030, the prevalence of CHF is projected to increase nearly 50%[10] with a subsequent economic burden incremented by 127%.[11]

As a chronic disease, once adverse structural changes occur in the heart, the majority of patients eventually progress to an advanced stage of the disease despite optimal medical therapy. For those refractory to conventional medical management, advanced therapies might be warranted. Historically, heart transplantation was the sole treatment option for patients with advanced CHF. However, due to the limited availability of donor's hearts and strict inclusion criteria for transplant waiting lists, only a small proportion of patients with advanced CHF receive a heart transplant. Even for those

patients who are actively listed for a heart transplant, time on a waiting list may be months or even years[12]. Over the past 25 years, mechanical circulatory support employing ventricular assist devices (VADs) has been an increasingly viable treatment option to complement heart transplantation in the treatment of advanced CHF for a select but broadening cohort of patients with advanced CHF.[12,13] Ventricular assist devices are electromechanical pumps that are surgically implanted into the right (RVAD) or left ventricle (LVAD) of the heart to augment cardiac output and increase blood flow to the lungs (RVAD) and other vital organs and periphery (LVAD).[13,14] LVADs are far more commonly implanted than RVADs in the management of advanced CHF and are the focus of this thesis.

LVADs were initially used predominantly as a bridge to cardiac transplantation, however indications for LVADs now also include a variety of options; such as bridge-to-transplant eligibility, bridge-to-recovery (where the myocardium recovers and the LVAD is removed) and following the seminal REMATCH study,[15] are being implanted increasingly as destination therapy (DT), where the device remains implanted for the rest of the patient's life.[16] Data from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) indicate that the number of patients supported with LVADs has increased dramatically over the past decade, with more than 17,000 LVAD implantations.[17] Survival rates at one-year post-implant are 81%, 59% at five years,[17] with increasing numbers of patients supported with an LVAD surviving to over 10 years,[18,19] highlighting the importance of strategies to support long-term health and wellness in these patients.

An important objective of LVAD implantation is to reduce the exertional symptoms and impaired functional capacity that are characteristic of CHF, to facilitate a more active lifestyle and enable patients to engage in and benefit from structured cardiac rehabilitation. Physical activity (PA) is an important determinant of aerobic capacity in CHF[20] and its beneficial effects on mental and physical health are well documented.[21] Indeed, both PA and aerobic capacity (expressed as $\dot{V}O_2$ peak) correlate with prognosis in patients with CHF.[22,23] However many patients with LVADs continue to experience exercise intolerance and other heart failure-related symptoms,[24-26] which are likely to limit activities of daily living and structured exercise. There remains relatively little research into the effect of LVAD implantation on exercise and PA. In a descriptive study, Hu et al.[27] reported that the majority of

patients with LVADs engage only in low-intensity PA and for a limited period of time. More recent research has shown that while patients augmented their PA levels over the initial phase following LVAD-implantation, this did not differ in comparison to a control group of patients with CHF but without mechanical circulatory support.[28] However, participants in the CHF control group in this study were not well matched for CHF severity to the LVAD group, with a $\dot{V}O_2$ peak that was significantly higher in the CHF group compared with the LVAD group (pre-LVAD). Accordingly, whether LVAD implantation improves PA levels in patients with advanced CHF remains unresolved. Furthermore, the time spent at different intensities of PA, and the relationship between PA and potential mediators such as aerobic capacity physical activity self-efficacy remain to be elucidated.

As highlighted above, one of the hallmark characteristics of advanced CHF is exercise intolerance.[29] The beneficial effect of exercise to improve functional capacity in patients with CHF may result from a range of mechanisms. One under-researched area relates to the growing recognition of the heart and brain interaction in patients with CHF[30] and emerging findings suggest that cerebral signals may contribute to improved sympathovagal balance and attenuated activation of ergo- and metabo-reflexes during exercise.[31,32] In patients with CHF, a 12-week program involving high-intensity interval training (HIIT) was found to improve oxygen uptake efficiency by enhancing cerebral and muscular haemodynamics during exercise.[32] These peripheral factors may be important contributors to exercise capacity, possibly by increasing cardiac efficiency and the delivery and/or utilisation of oxygen during exercise to the skeletal muscle and brain. It is conceivable that these mechanisms would be upregulated by LVAD implantation and evaluating cerebral blood flow (CBF) during exercise provides a novel assessment of the effects of LVAD implantation on systemic blood flow and specifically blood flow to the brain. A comprehensive assessment of the impact of LVAD implantation on CBF will help to provide a more detailed understanding of its effects on the systemic haemodynamic response to exercise. As exercise training (ET) seems to improve arterial vascular function[33] and cerebral haemodynamics,[32] we hypothesised that it may improve cerebrovascular function in patients implanted with LVADs.

A final important consideration in patients with LVADs is how best to deliver exercise rehabilitation to optimise training-induced benefits. Exercise training interventions applied in randomised controlled trials to date have applied a conservative approach of aerobic exercise involving moderate-intensity continuous training (MICT), at an intensity of 50-60% of cardiorespiratory reserve.[34-36] However, training at this intensity has not increased aerobic capacity ($\dot{V}O_2$ peak) above untrained control participants. HIIT has recently been applied in patients with CHF, and resulted in significantly greater improvements in $\dot{V}O_2$ peak, left ventricular ejection fraction and endothelial function than MICT,[37-39] but this form of exercise has not been evaluated to date in patients with LVADs, so it's feasibility and efficacy remain untested.

1.2 Objectives of the research project

The purpose of the present thesis is to address the three outstanding research questions related to physical activity and exercise in patients with LVADs, highlighted in the Introduction. Specifically, the project was designed to accomplish the following objectives:

1. To assess the intensity and duration of physical activity in patients with LVADs versus well-matched patients with CHF without mechanical circulatory support and its relationship with aerobic capacity, quality of life (QoL) and self-efficacy.

2. To assess the impact of LVAD implantation on cerebral haemodynamics at rest and in response to exercise compared with age- and sex-matched CHF and healthy individuals.

3. To examine the impact of exercise training in patients with LVADs on cerebral haemodynamics at rest and during exercise.

4. To determine the effects of different exercise training intensities in patients with LVADs on $\dot{V}O_2$ peak, submaximal exercise capacity, cardiac function, endothelial function, body composition, biomarkers, QoL and self-efficacy in patients with LVADs.

1.3 Thesis structure

- **Chapter 2** presents the literature review. This chapter provides an overview of the exercise physiology in individuals with CHF and how LVAD implantation affects the cardiovascular system at rest and in response to both acute and chronic exercise exposure.

- **Chapter 3** is presented as a published manuscript entitled "Left ventricular assist device implantation is associated with higher physical activity levels in patients with advanced chronic heart failure" describing Study 1.

- **Chapter 4** is also presented as a published manuscript entitled "Cerebral blood flow velocities during exercise in patients with chronic heart failure: Impact of left ventricular assist devices" describing Study 2.

- **Chapter 5** presents Study 3 which examined the impact of exercise training on cerebrovascular responses during exercise in patients with left ventricular assist devices. This study is also presented as a published manuscript.

- **Chapter 6** presents Study 4 which examined the effects of different intensity exercise training in patients with left ventricular assist devices in a multicentre, randomised, controlled trial. This study evaluated the impact of a 12-week HIIT program versus the usual care exercise rehabilitation (MICT program) on $\dot{V}O_2$ peak, cardiac function, endothelial function, and QoL in patients supported with LVADs.

- **Chapter 7** presents the main findings of the present research project, discusses the overall findings and their clinical implications, acknowledges its limitations, suggests future research considerations and outlines the general conclusion of the thesis by research.

1.4 References

1. de Simone G, Daniels SR, Kimball TR, et al. Evaluation of concentric left ventricular geometry in humans: evidence for age-related systematic underestimation. Hypertension 2005;45:64-8.

2. Hastings PC, Vazir A, Meadows GE, et al. Adaptive servo-ventilation in heart failure patients with sleep apnea: a real world study. Int J Cardiol 2010;139:17-24.

3. Krum H, Jelinek MV, Stewart S, et al. 2011 update to National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand Guidelines for the prevention, detection and management of chronic heart failure in Australia, 2006. Med J Aust 2011;194:405-9.

4. Savarese G, Lund LH. Global Public Health Burden of Heart Failure. Cardiac failure review 2017;3:7-11.

5. Ponikowski P, Anker SD, AlHabib KF, et al. Heart failure: preventing disease and death worldwide. ESC Heart Fail 2014;1:4-25.

6. Sahle BW, Owen AJ, Mutowo MP, Krum H, Reid CM. Prevalence of heart failure in Australia: a systematic review. BMC Cardiovasc Disord 2016;16:32.

7. Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol 2014;63:1123-33.

8. Krum H, Abraham WT. Heart failure. The Lancet 2009;373:941-55.

9. Fitzsimmons GJ, Sadkowsky KR. The Australian Institute of Health and Welfare. Commun Dis Intell Q Rep 2002;26:605-7.

10. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation 2017;135:e146-e603.

11. Writing Group M, Mozaffarian D, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation 2016;133:e38-360.

12. Organ Procurement and Transplantation Network and Scientific Registry of Transplant Recipients 2010 data report. Am J Transplant 2012;12 Suppl 1:1-156.

13. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009;361:2241-51.

14. Weymann A, Patil NP, Sabashnikov A, et al. Continuous-flow left ventricular assist device therapy in patients with preoperative hepatic failure: are we pushing the limits too far? Artif Organs 2015;39:336-42.

15. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-Term Use of a Left Ventricular Assist Device for End-Stage Heart Failure. New England Journal of Medicine 2001;345:1435-43.

16. Kirklin JK, Naftel DC, Kormos RL, et al. Fifth INTERMACS annual report: risk factor analysis from more than 6,000 mechanical circulatory support patients. J Heart Lung Transplant 2013;32:141-56.

17. Kirklin JK, Pagani FD, Kormos RL, et al. Eighth annual INTERMACS report: Special focus on framing the impact of adverse events. J Heart Lung Transplant 2017;36:1080-86.

18. Schmitto JD, Hanke JS, Rojas S, et al. Circulatory support exceeding five years with a continuous-flow left ventricular assist device for advanced heart failure patients. J Cardiothorac Surg 2015;10:107.

19. Willemsen D, Cordes C, Bjarnason-Wehrens B, et al. Rehabilitationsstandards für die Anschlussheilbehandlung und allgemeine Rehabilitation von Patienten mit einem Herzunterstützungssystem (VAD – ventricular assist device). Clinical Research in Cardiology Supplements 2016;11:2-49.

20. Jehn M, Schmidt-Trucksäss A, Schuster T, et al. Daily walking performance as an independent predictor of advanced heart failure: Prediction of exercise capacity in chronic heart failure. American Heart Journal 2009;157:292-98.

21. Pina IL, Apstein CS, Balady GJ, et al. Exercise and heart failure: A statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. Circulation 2003;107:1210-25.

22. Walsh JT, Charlesworth A, Andrews R, Hawkins M, Cowley AJ. Relation of daily activity levels in patients with chronic heart failure to long-term prognosis. Am J Cardiol 1997;79:1364-9.

23. Maiorana AJ, Naylor LH, Dongelmans S, et al. Ventilatory efficiency is a stronger prognostic indicator than peak oxygen uptake or body mass index in heart failure with reduced ejection fraction. European journal of preventive cardiology;0:2047487319862908.

24. Simon MA, Kormos RL, Gorcsan J, 3rd, et al. Differential exercise performance on ventricular assist device support. J Heart Lung Transplant 2005;24:1506-12.

25. Allen JG, Weiss ES, Schaffer JM, et al. Quality of life and functional status in patients surviving 12 months after left ventricular assist device implantation. J Heart Lung Transplant 2010;29:278-85.

26. Jung MH, Gustafsson F. Exercise in heart failure patients supported with a left ventricular assist device. J Heart Lung Transplant 2015;34:489-96.

27. Hu SX, Keogh AM, Macdonald PS, et al. Interaction between physical activity and continuous-flow left ventricular assist device function in outpatients. J Card Fail 2013;19:169-75.

28. Jakovljevic DG, McDiarmid A, Hallsworth K, et al. Effect of Left Ventricular Assist Device Implantation and Heart Transplantation on Habitual Physical Activity and Quality of Life. American Journal of Cardiology 2014;114:88-93.

29. Dunlay SM, Park SJ, Joyce LD, et al. Frailty and outcomes after implantation of left ventricular assist device as destination therapy. J Heart Lung Transplant 2014;33:359-65.

30. Doehner W, Ural D, Haeusler KG, et al. Heart and brain interaction in patients with heart failure: overview and proposal for a taxonomy. A position paper from the Study Group on Heart and Brain Interaction of the Heart Failure Association. Eur J Heart Fail 2018;20:199-215.

31. Antunes-Correa LM, Nobre TS, Groehs RV, et al. Molecular basis for the improvement in muscle metaboreflex and mechanoreflex control in exercise-trained humans with chronic heart failure. Am J Physiol Heart Circ Physiol 2014;307:H1655-66.

32. Fu TC, Wang CH, Lin PS, et al. Aerobic interval training improves oxygen uptake efficiency by enhancing cerebral and muscular hemodynamics in patients with heart failure. Int J Cardiol 2013;167:41-50.

33. Maiorana A, O'Driscoll G, Cheetham C, et al. Combined aerobic and resistance exercise training improves functional capacity and strength in CHF. J Appl Physiol (1985) 2000;88:1565-70.

34. Laoutaris ID, Dritsas A, Adamopoulos S, et al. Benefits of physical training on exercise capacity, inspiratory muscle function, and quality of life in patients with ventricular assist devices long-term postimplantation. European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology 2011;18:33-40.

35. Hayes K, Leet AS, Bradley SJ, Holland AE. Effects of exercise training on exercise capacity and quality of life in patients with a left ventricular assist device: a preliminary randomized controlled trial. J Heart Lung Transplant 2012;31:729-34.

36. Kerrigan DJ, Williams CT, Ehrman JK, et al. Cardiac rehabilitation improves functional capacity and patient-reported health status in patients with

continuous-flow left ventricular assist devices: the Rehab-VAD randomized controlled trial. JACC Heart Fail 2014;2:653-9.

37. Wisloff U, Stoylen A, Loennechen JP, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. Circulation 2007;115:3086-94.

38. Haykowsky MJ, Liang Y, Pechter D, Jones LW, McAlister FA, Clark AM. A meta-analysis of the effect of exercise training on left ventricular remodeling in heart failure patients: the benefit depends on the type of training performed. J Am Coll Cardiol 2007;49:2329-36.

39. Haykowsky MJ, Daniel KM, Bhella PS, Sarma S, Kitzman DW. Heart Failure: Exercise-Based Cardiac Rehabilitation: Who, When, and How Intense? Can J Cardiol 2016;32:S382-S87.

Chapter 2 Review of literature

2.1 Background

Left ventricular assist devices (LVADs) are an increasingly common treatment option for patients with advanced chronic heart failure (CHF), that are used as a bridge to cardiac transplantation, as destination therapy where the patient has the device for the remainder of their life, or in rare cases, as a bridge to myocardial recovery. Following LVAD implantation, and an initial period of post-surgical recovery, patients usually experience a rapid improvement in exercise tolerance,[1] likely due to the increase in 'total cardiac output' resulting from the combination of LVAD flow and cardiac output from the native left ventricle. However, $\dot{V}O_2$ peak remains significantly reduced compared with age- and sex-predicted values,[1,2] which is likely due at least in part to the 'hangover' from the peripheral sequelae and associated physical deconditioning associated with CHF but also an inability of LVADs to generate augmented output in the setting of exercise. Indeed, relatively little is known about peripheral haemodynamics during exercise in patients with LVADs. Furthermore, this limited exercise tolerance may compromise activities of daily living and meeting daily physical activity (PA) recommendations, which may result in further deconditioning. In contemporary clinical practice, it is common for patients with LVADs to undergo exercise rehabilitation as part of multidisciplinary management. However, the literature relating to exercise training (ET) in patients with LVADs is relatively sparse and remains equivocal. Randomised control trials (RCTs)[3-5] performed to date on the effects of ET for patients with continuous-flow LVADs have not found a significant improvement in aerobic capacity compared with untrained controls. Furthermore, there are a lack of evidence-based guidelines for ET in the growing population of LVAD recipients. In view of these limitations to the current literature, optimal training protocols are yet to be determined.

The goals of the present review of the literature are to:

i. Describe how CHF affects the physiology of exercise and factors that influence exercise performance.
ii. Summarise the current knowledge of exercise physiology in LVADs to better understand how exercise affects the cardiovascular system acutely and chronically.
iii. Highlight gaps in the existing knowledge and suggest future research lines.

2.2 The acute haemodynamic response to exercise in healthy individuals

During exercise, there is an increased requirement for blood flow to the active skeletal muscles to supply oxygen and substrates to meet the metabolic demands and facilitate the removal of carbon dioxide and metabolites. This hyperaemia is achieved by an increase in cardiac output (CO) which is proportionate to the increase in metabolic requirements. According to the Fick principle,[6] oxygen consumption ($\dot{V}O_2$) is the product of CO multiplied by the arterial-venous oxygen content difference (a-vO_2 diff); ($\dot{V}O_2$ = CO x a-vO_2 diff). In normal healthy individuals (non-athletes), resting oxygen consumption is ~250 mL/min, increasing up to 10 to 15-fold at maximal effort, depending on age, gender, body mass and level of fitness. During exercise, an increase in $\dot{V}O_2$ is achieved by a 4-6-fold increase in CO and 2-3-fold increase in a-vO_2diff.[7] Augmented CO occurs as a function of increases in both stroke volume (SV) and heart rate (HR). Stroke volume increases up to 50% due to a greater contractile force produced by an elevation in left ventricular end-diastolic volume (LVEDV) and by greater left ventricular emptying leading to a reduced left ventricular end-systolic volume (LVESV). This is facilitated by increased contractibility and peripheral vascular dilation. Increases in LVEDV occur in response to enhanced venous return, mediated by the active skeletal muscles (‘muscle pump’) and the ‘respiratory bellows’ effect of respiration. While SV reaches a plateau at approximately 50% of $\dot{V}O_2$ peak (from ~70 mL at rest to ~110 mL at peak exercise),[8] HR is able to increase up to 4-fold at peak exercise, depending on the age. It is pertinent to note that while HR is initially stimulated through a decreased in parasympathetic activity via vagal withdrawal, at higher exercise intensities, HR is driven by increased levels of

sympathetic activity highlighting the role the central nervous system (CNS) plays in the cardiovascular response to exercise. It is well established that the increase in HR during exercise is closely correlated with $\dot{V}O_2$ in healthy individuals. [9-11]

2.3 The pathophysiological mechanisms of exercise intolerance in chronic heart failure

Chronic heart failure is commonly classified as either heart failure with preserved ejection fraction (HFpEF) or heart failure with reduced ejection fraction (HFrEF). The latter is characterised by systolic dysfunction, whilst the former is characterised by diastolic dysfunction.[12] Mechanical circulatory support has not been systematically evaluated in patients with HFpEF, however, LVADs implanted in patients with restrictive or hypertrophic cardiomyopathies suggested an increased incidence of right ventricular failure after implantation.[13] Accordingly, the focus of the following description of CHF is HFrEF.

By definition, CHF is a progressive syndrome that commonly commences as a result of a myocardial injury that damages the myocardium or weakens its contractile force generation.[14] The aetiology behind the initial injury are complex and multiple, and exceed the scope of the present review, but are most frequently related to an acute myocardial infarction or hypertension. Other causes include valvular disease, viral infection, alcohol/drugs and genetic origin, among others. Regardless of the initial cause, the common feature of CHF is a reduction in CO.[15]

Impaired CO triggers compensatory mechanisms involving neurohormonal activation, in order to maintain hemodynamic homeostasis.[14,15] In brief, the neurohormonal activation includes the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone system (RAAS), and the arginine vasopressin system. These systems preserve CO via salt and water retention, enhanced cardiac contractibility as well as vasoconstriction of peripheral arteries.[16,17] However, while these systems preserve the cardiovascular equilibrium relatively well in the short-term, when they are chronically activated they lead to a detrimental and vicious cycle, causing cardiotoxicity, LV remodelling, cardiac cell necrosis, and excessive fluid retention.[16-18] As such, the neurohormonal response contributes to the progression of the heart failure syndrome

and there exists a relationship between neurohormonal activation levels and the severity of CHF.[19] As a consequence of the increase in systemic vascular resistance, afterload increases resulting in additional load on an already impaired myocardium. These processes contribute to further cardiovascular deterioration, which in turn contributes to worsening of CHF.[18,20]

The clinical presentation of CHF is comprised of several typical symptoms, such as oedema, breathless and fatigue. It is usual medical practice to use the New York Heart Association (NYHA) functional classification[21] to assess and report the severity of symptoms and functional capacity. These are classified as:

- Class I: No limitations to physical activity; ordinary physical activity does not cause symptoms.
- Class II: Slight limitations to physical activity. Comfortable at rest, but ordinary physical activity results in breathlessness, fatigue or palpitations.
- Class III: Marked limitations of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms.
- Class IV: Unable to carry on any physical activity without discomfort. Symptoms at rest can be present.

As such, exercise intolerance is a hallmark of CHF. According to the Fick Principle, the loci of limitation underpinning exercise intolerance in CHF may lie in either of two broad mechanisms; the inability to increase the pumping of oxygenated blood via an increase in CO and/or the ability to improve the utilisation of oxygenated blood (and remove metabolic by-products) from the skeletal muscles. Although initially thought to be exclusively the result of cardiac dysfunction (reduced cardiac output), there has been an increasing recognition over recent years that peripheral mechanisms linked to the pathophysiology of CHF contribute significantly to the exercise intolerance experienced by patients with CHF.[22-24] In this section, the factors contributing to exercise intolerance in patients with CHF are described.

2.3.1 Central mechanisms

Chronic heart failure, by definition, is characterised by an inability of the heart to meet the metabolic demands of the body. This occurs as a result of the two physiological components that contribute to CO:

(1) Failure of the Frank-Starling mechanism to increase SV. In patients with CHF, the heart functions on a portion of the Frank-Starling curve with a decreased slope so that higher end-diastolic volumes (and pressures) are required to maintain adequate contractile force. Over time, this mechanism fails resulting in augmented LVESV. Figure 2.1 illustrates the relationship between LVEDV and SV, according to the Frank-Starling Law in a healthy heart and a heart with heart failure. SV is also lowered at rest and can increase only moderately at peak exercise up to 40-60 mL/beat,[25] whereas healthy individuals reach over 100 mL/beat.[26] This occurs as a dilated LV at rest is pumping relatively close to its maximum volume and thus, some of its contractibility capacity is already consumed.
(2) Incompetence to increase HR proportionally with metabolic demands (chronotropic incompetence),[27] compounded by the fact that patients with CHF often have an elevated resting HR, secondary to an augmented sympathetic activation and parasympathetic inhibition. Moreover, some commonly prescribed medications (such as β-blockers, calcium antagonist, digitalis and amiodarone) for CHF patients are known to further compromise the chronotropic response.

These factors in combination contribute significantly to the impaired aerobic capacity experienced by patients with CHF, with peak oxygen consumption values <50% of predicted in patients with advanced CHF (Figure 2.2).

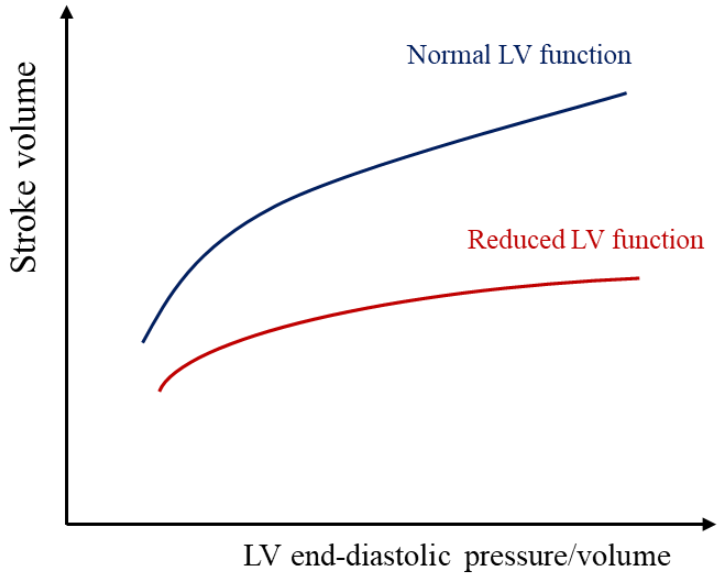

Figure 2.1 Representation of the Frank-Starling mechanism of compensation for CHF. Adapted from Muslin.[14]

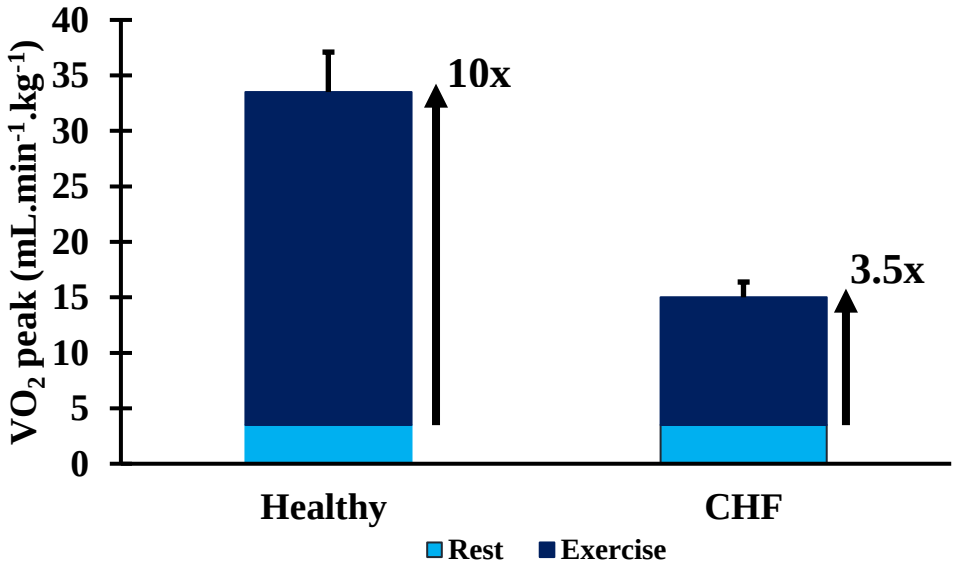

Figure 2.2 Oxygen consumption values at rest and peak exercise capacity in healthy versus people with CHF. Data adapted from Dhakal et al.[26]

2.3.1.1 Role of cardiac output to exercise intolerance: is it mainly a central matter?

Although there is a linear correlation between $\dot{V}O_2$ peak and peak CO in healthy individuals, previous studies have shown that resting left ventricular ejection fraction (LVEF) is a poor predictor of $\dot{V}O_2$ peak in patients with CHF.[28,29] However, a series of acute studies in patients with CHF conducted by Borlaug et al.,[30-32] consistently found similar a-vO2diff at peak exercise between patients with CHF and matched-healthy controls, suggesting that a reduced $\dot{V}O_2$ peak might be mainly due to a lower CO, secondary to chronotropic incompetence. According to Borlaug,[32] there are different lines of evidence supporting the theory that the reduced $\dot{V}O_2$ peak is predominantly caused by a low CO. This notion is supported by the following observations: i) Activation of only half the total body muscle mass is sufficient to achieve $\dot{V}O_2$ peak and additional recruitment of skeletal muscles do not increase CO or $\dot{V}O_2$ any further. ii) When additional muscles are activated during maximal exercise, arterial pressure is preserved by vasoconstriction to the local working muscles; iii) The capacity for oxygen consumption from the skeletal muscle surpasses the CO. However, it is pertinent to highlight that in one of their studies,[31] the healthy control group had a $\dot{V}O_2$ peak of 14.4 $mL.min^{-1}.kg^{-1}$, indicating a severe impairment in aerobic capacity and therefore, raising significant questions about the validity of their methods.

In contrast to Borlaug's theory, there is a large body of research that supports an important role of peripheral factors contributing to exercise intolerance.[26,33-35] Studies of acute exercise response in patients with CHF versus healthy individuals[26,36] have shown that reduced $\dot{V}O_2$ peak in the former was associated with a concurrent decreased peak CO and a-vO_2diff relative to healthy controls. Interestingly, the authors suggested that the drop in peak exercise CO might be secondary to a lower peak HR, rather than an impaired SV.[26] A more recent study performed by Shimiaie et al.[37] compared the cardiopulmonary responses to exercise in three groups: patients with HFpEF, HFrEF, and healthy controls. Both cardiac function (HR and SV) and peripheral (a-vO_2diff) determinants correlated closely with oxygen uptake throughout exercise in all groups. This finding suggests that these factors may be key determinants of exercise capacity irrespective of the phenotype of cardiac insufficiency. An interesting observation was that the HFrEF group showed an increased a-vO_2diff at peak exercise compared with the HFpEF and healthy control groups, which could be interpreted as an improved

peripheral function. An alternative explanation may be that the increase in oxygen extraction during exercise may be a compensatory mechanism as a consequence of a diminished CO, as other investigations have suggested.[38,64] It should be noted that a-vO_2diff was only calculated indirectly according to the Fick equation. In accordance with this finding, an invasive haemodynamic study conducted by Dhakal et al.,[26] found that peak a-vO_2diff was the major determinant of $\dot{V}O_2$ peak in patients with CHF (the degree of a-vO_2diff impairment was greater than the CO), reflecting the significant role of peripheral oxygen extraction and utilisation (Figure 2.3). Likewise, Bhella et al.,[39] observed that CO was not significantly different in patients with CHF compared to age-match healthy subjects, despite having a lower $\dot{V}O_2$ peak. It is worth mentioning the considerable contribution to the field made by Haykowsky and colleagues,[33,34] who have consistently shown the existence of peripheral abnormalities, such as perfusive and diffusive oxygen transport, vascular dysfunction as well as impaired mitochondrial oxidative capacity in patients with CHF.

These aforementioned studies, by conducting acute haemodynamic assessments, have demonstrated the existence of different peripheral factors influencing a-vO_2diff during exercise, and consequently $\dot{V}O_2$ peak. Taken together, these data strongly suggest that a single and dominant determinant of exercise intolerance in CHF seems to be implausible, and rather, it is a multifactorial issue.

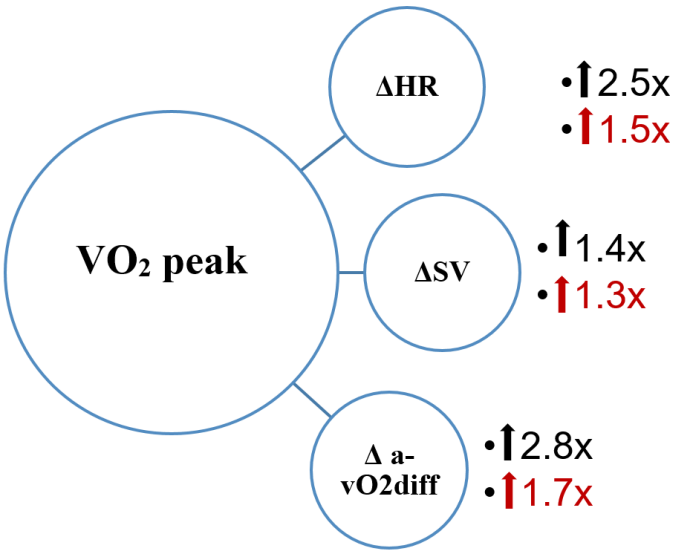

Figure 2.3 Determinants of peak oxygen uptake and its maximum incremental capacity in healthy subjects (black font) compared to matched-individuals with CHF (red font). Data adapted from Dhakal et al.[26]

2.3.2 Peripheral mechanisms

As CO increases during exercise, the vascular system has the capacity to regulate both the volume and flow of blood to ensure it is directed to the working muscles in order to match the metabolic requirements. This redistribution of blood flow supply is achieved by regional vasodilation in the active muscles, combined with vasoconstriction in vessels supplying less metabolically demanding organs, such as inactive muscles, the viscera, liver, and kidneys. The capacity of the vascular system to regulate blood flow during exercise is also vital for blood pressure control, given that without this regional vasoconstriction, hypotension would occur due to the dilation capacity of the conduit arteries in response to increased blood flow. Although reflex increase of the sympathetic system leads the vasoconstriction in less demanded areas, redistribution of blood flow is also regulated at the local level. Among these mechanisms, the endothelium plays a crucial role in maintaining vascular homeostasis.

2.3.2.1 Role of vascular endothelial function

The inner layer of blood vessels is composed of a single layer of squamous cells known as the endothelium. Historically, considered a passive layer of cells which simply separated the circulating blood from the vascular wall,[40] the seminal discovery by Furchgott and Zawadzki[41] in 1980 identified that endothelial cells play an obligatory role of in the relaxation of arterial smooth muscle. It is now understood that the endothelium exerts an influence over vascular tone, and therefore blood flow distribution, by synthesising and releasing an array of vasoactive compounds. This includes vasoconstrictors such as thromboxane A_2, prostaglandin H_2, and endothelin 1 and vasodilators such as hyperpolarizing factor, prostacyclin and nitric oxide (NO).[42,43] Thus, vascular tone is determined by the balance between these vasoconstricting and vasodilating influences. NO is the most extensively studied of these compounds and there is now a wealth of literature supporting its involvement in influencing vasomotor tone in the coronary[44] and peripheral conduit arteries.[45] Endothelium-derived NO production is upregulated by stimuli, such as chemical agents (e.g. acetylcholine) or hemodynamic shear stress occurring during exercise.[40,43] While low levels of NO are released under normal resting conditions, in response to acute exercise, high laminar shear stress is applied to the vascular wall, increasing the

production of NO in order to normalise the shear stress.[43] In addition, endothelium-derived NO inhibits the adhesion and aggregation of platelets and leukocytes, reducing vascular inflammation and atherosclerosis, including the coronary microvascular and endocardial blood vessels.[46] Therefore, NO acts as an important mechanism in preventing plaque accumulation which may ultimately result in an acute coronary thrombosis in a coronary artery and subsequent myocardial infarction.

2.3.2.2 Endothelial dysfunction in chronic heart failure

In healthy individuals, the endothelium preserves vascular homeostasis via vasodilatory, anti-inflammatory and antithrombotic factors thereby counterbalancing vasoconstricting, inflammatory and thrombotic compounds.[47] Whereas in the setting of CHF, reduced shear stress, secondary to impaired CO, combined with neurohormonal activation provoke a breakdown of this equilibrium.[48] The overproduction of reactive oxygen species, proinflammatory cytokines and uncoupled eNOS are not proportionally compensated by the endothelium and bone marrow endothelial progenitor cells, resulting in systemic inflammation.[49] These processes culminate in reduced NO bioavailability. This endothelium-derived vascular response is a major determinant of vasodilation and vasoconstriction imbalance, associated with CHF.[47-49]

Over recent years, a large body of evidence has established a link between endothelial function and cardiovascular pathologies.[40,43,50] Importantly, large sample size research studies[51,52] have demonstrated that brachial artery endothelial function, measured using flow-mediated dilation (FMD), -the gold standard technique for measuring vascular endothelial function non-invasively- is an independent predictor of hospitalisation and death in participants with both ischemic and non-ischaemic CHF. Additionally, an increased activity of the SNS occasioned by elevated plasma levels of catecholamine has also been associated with vasoconstriction and impaired vasodilation response at rest and during exercise in CHF.[53,54] Moreover, a hyperactivated SNS produces an increased sensitivity of the chemoreceptors and ergoreceptors reflexes located in the vasculature and the muscle, along with the suppression of baroreceptors reflex activity[55], which may be contributing factors to fatigue and dyspnoea during exercise in this patient population.[56]

Prior investigations have found that exercise intolerance is associated with impaired vascular endothelial function in patients with CHF.[57,58] Conduit arteries must dilate in response to exercise to enable the transportation of increased blood flow to the working skeletal muscles. It is now understood that the capacity for endothelium-mediated vasodilation of conduit arteries in response to increased laminar shear stress associated with exercise is blunted in patients with CHF, compromising oxygen availability and utilisation in the working muscles. This directly affects exercise performance. For instance, Hundley et al.[59] conducted a cross-sectional study conducted in patients with HFpEF, HFrEF, and healthy age-matched control subjects. They found that femoral artery FMD was significantly decreased in the HFrEF compared to the HFpEF group and the healthy control group. Femoral FMD was associated with $\dot{V}O_2$ peak in patients with HFrEF ($r = 0.9$; $p = 0.02$) as well as in the healthy group ($r = 0.58$, $p = 0.05$), but there was no association in the HFpEF group ($r = 0.07$; $p = 0.6$). This data suggests that while endothelial dysfunction may be an important determinant of exercise intolerance in patients with HFrEF, it may not be as such for patients with HFpEF, a finding supported by follow up research.[60]

2.3.2.2.1 Impact of exercise training on endothelial function in chronic heart failure

A wide body of evidence has shown that ET programs are effective non-pharmacological interventions for improving, or even normalising, endothelial dysfunction in patients with CHF.[61-64] While training intensity is considered a key element in the prescription of exercise rehabilitation for these patients,[65] whether high-intensity interval training (HIIT) provides better outcomes compared to the usual moderate-intensity continuous training (MICT) for patients with CHF remains a topic of debate.

In a systematic review, Vuckvic et al.[64] evaluated the effect of ET on vascular endothelial function in patients with CHF. The authors included 11 studies (n=318) and concluded that collectively, aerobic, resistance and combined ET improved endothelium-dependent function, independently of age, NYHA functional class or aetiology of CHF. However, owing to the heterogeneity of ET protocols used in the literature, the latter review did not resolve whether exercise intensity plays a key role in improving endothelial function. Interestingly, Ashor et al.[66] conducted a meta-analysis evaluating the impact of different exercise modalities (aerobic, resistance or

combined) on endothelial function across studies in different clinical populations, including CHF. In total, 51 RCTs (N=2,260) were included. Authors found that all exercise modalities improved endothelial function up to 2.8% and observed a dose-dependent relation in which a 10% increase of relative aerobic exercise-intensity resulted in 1% unit increment in FMD. However, due to the wide range of populations included, extrapolating these findings to people with CHF is problematic. Specifically in CHF, Wisloff et al.[63] conducted an RCT comparing the effects of HIIT versus MICT and found that 12 weeks of HIIT improved brachial endothelial function significantly more than MICT. Similarly, HIIT was superior to MICT for improving $\dot{V}O_2$ peak (46% vs. 14%; $p < 0.001$), with the increase in $\dot{V}O_2$ peak strongly correlated with the increase in endothelial function ($r = 0.69$; $p < 0.05$). Conversely, a recent systematic review with meta-analysis[62] including 13 studies, showed that both HIIT and MICT improved similarly vascular endothelial function, as measured by brachial FMD, in patients with CHF. The precise mechanism by which exercise training is associated with improved endothelial function remains to be fully elucidated. Several investigations have suggested that changes related to cardiac performance, blood pressure, LDL profile, and improved NO production may be involved.[67] Also, it has been demonstrated that repetitive episodes of acute increases in intra-arterial blood flow promote endothelium-dependent NO-releasing, which in turn, result in enhanced vascular function and structure in the long-term.[43,68]

These experimental studies suggest that any modality of ET (aerobic, resistance and combined) may result in significant improvement in endothelial function in patients with CHF.[69] However, the high degree of heterogeneity among studies, (i.e. different clinical populations and hence difference medication use, couple with different exercise prescription methods and training protocols) may have contributed to the equivocal findings. Overall, findings from the aforementioned studies suggest that factors like frequency, and particularly aerobic exercise-intensity, play a vital role in endothelial function enhancement and should be the focus in future exercise intervention studies.

2.3.2.3 Role of skeletal muscle function

During exercise, the majority of oxygen is consumed by the active muscles, as such, skeletal muscle function likely plays an important role in exercise capacity. In a person

with CHF, diminished blood flow, and subsequently decreased shear stress, is associated with attenuated vasodilation. This affects systemic oxygen delivery to the working muscles,[30] leading to an early reliance on anaerobic metabolism, contributing to the development of symptoms like fatigue and dyspnoea.[20] It is well documented that patients with CHF undergo a range of maladaptations in skeletal muscle morphology and function.[70] In addition to muscle mass loss, other alterations occur including a shift from type I (oxidative) to type II/IIb (fast-switch glycolytic) muscle fibres, and reduced oxidative enzymes,[71,72] mitochondrial volume density[72], and capillary-muscle interface,[73] which have all been associated with decreased aerobic capacity.[71,72]

2.3.2.3.1 Skeletal muscle function during acute exercise in chronic heart failure

In a cross-sectional study, Haykowsky et al.,[74] observed that oxygen uptake during cycling, indexed to leg lean mass, is severely decreased in patients with CHF compared with healthy controls. Similarly, Weiss et al.,[75] recently found that patients with CHF deplete muscular phosphocreatine reserves significantly quicker than healthy controls. This may be an indication that muscular oxygen diffusion capacity and/or oxygen utilization are impaired in patients with CHF, even after correction for skeletal muscle mass; and may explain the shift in fibres type that patients commonly experience and their reliance on anaerobic metabolism and lactate accumulation, leading to early muscle fatigue.

In addition to a blunted connective and diffusive transport of oxygen and utilisation at the local level, patients with CHF also exhibit an impaired functional capacity, associated with muscle wasting[76] and strength in the lower limbs compared with age-matched healthy individuals.[76,77] For example, Panizzolo et al.,[77] compared the passive force in the soleus muscle between 12 participants with CHF and 12 age- and physical activity-matched controls and reported that CHF participants had a 30% reduced passive soleus force at the same relative muscle strength. However, passive force was not different when data were normalised for muscle cross-sectional area, suggesting that muscle size may have a greater effect than muscle intrinsic properties on muscle strength.

These findings in combination suggest that while preservation of skeletal muscle mass may be an important determinant of muscular strength, underlying abnormalities in the oxidative metabolism within the muscular level may compromise exercise tolerance and functional capacity in patients with CHF.

2.3.2.3.2 The impact of exercise training on skeletal muscle metabolism and function in chronic heart failure

Extensive research has demonstrated that ET is an effective approach that specifically targets the skeletal muscle maladaptations evident in patients with CHF.[78,79] In an early study, Hambretch et al.[80] demonstrated that patients with CHF experienced significant improvements in total volume density of mitochondria and volume cytochrome c-oxidase following a training program. ET has also been shown to induce a shift to a greater percentage of type I skeletal muscles fibres[81] and a higher capillary-fibre ratio.[82] Additionally, ET studies have reported improvements in muscular cross-sectional area,[83] mitochondrial ATP production rate[84] and aerobic enzyme activity.[85] Following quadriceps training,[35] changes in skeletal muscle function and structure were correlated with increased oxygen uptake,[35] highlighting the close relationship between muscular metabolism and exercise capacity.

Similarly, trials to date that have combined aerobic and resistance training, have reported significant improvements in mitochondrial size,[86] muscle mass and strength,[65,87,88] which is an independent predictor of survival in CHF.[89] These findings emphasize the importance of incorporating a resistance component in training programs to specifically target cachexia, which becomes increasingly severe as the severity of heart failure increases.[78]

2.3.2.4 Role of cerebrovascular function

The human brain, despite being 3% of the total mass in the body, consumes ~20% of the total oxygen uptake, at rest.[90] As the brain cells lack reserve energy storage, they are fully dependent on adequate blood flow supply to meet the oxygen and glucose requirements as well as to clear metabolic waste to ensure normal function. Functional hyperemia serves hereafter to match cerebral blood flow (CBF) with metabolic requirements to preserve homeostasis. During exercise, the cardiovascular system must increase blood supply to the active muscles, while sustaining sufficient flow to

the rest of the key body organs, including the brain. Research has found that CBF is regulated by a set of different mechanisms, which involve partial pressure of carbon dioxide ($PaCO_2$), arterial blood pressure, cerebral metabolism, neurogenic activity and CO.[91] In healthy individuals, the normal CBF response to acute exercise has been described as biphasic, with a gradual and proportional flow increment as a function of exercise intensity up to ~60-70% of $\dot{V}O_2$ peak, followed by a plateau and decline despite increases in exercise intensity.

Chronic heart failure is a syndrome characterised, but not limited to, reduced CO. The insufficient end-organ perfusion leads to deterioration in other body organs, including the brain.[92] Interestingly, both the heart and the brain suffer common pathophysiological processes caused by atherosclerosis and thrombosis, which eventually leads to chronic organ impairment.[93] Despite the important interconnection that the heart and brain have, not much is known about the role of cerebral haemodynamics in CHF and its clinical implications. In fact, a recent position statement[93] from the European Society of Cardiology has called for further empirical work to address this gap in the literature.

Historically, it was believed that despite the reduced CO, CBF was preserved in patients with CHF due to compensatory mechanisms.[94,95] However, contemporary evidence has revealed that compared with healthy controls, patients with CHF experience significantly decreased cerebral perfusion.[96-98] Indeed, the degree of CBF reduction correlates with NYHA class[47] and left ventricular ejection fraction.[98] It seems logical to assume that a chronically reduced CBF will have neurological consequences. Indeed, the impact of chronically reduced perfusion to the brain has been linked to cognitive decline.[99] A considerable body of evidence has revealed that the prevalence of cognitive impairment is disproportionally high in patients with CHF.[100] However, the association between CHF and cognitive impairment must be interpreted with caution, and a cause-effect relationship cannot be assumed. Firstly because these conditions share common risk factors; and secondly because not everyone with CHF has cognitive impairment, and *vice-versa*. Nevertheless, cerebrovascular alterations seem to be involved.[101]

The precise mechanism underlying the reduction in CBF in CHF remains unclear but may be related to the impaired CO and the neurohormonal activation. Interestingly,

CBF has been demonstrated to normalise following cardiac transplantation,[102] supporting the notion that CBF is reversible and heavily dependent on cardiac function.

2.3.2.4.1 The acute cerebrovascular response to exercise in chronic heart failure

A recent intriguing proposition is that reduced CBF may further contribute to exercise intolerance that patients with CHF normally experience.[103] There may be several mechanisms involved. Although the main cause is probably due to a reduced CO[103] it is unlikely to be the sole reason, as this patient population also exhibit an impaired cerebrovascular reactivity,[104] measured as vasodilation capacity in response to increased levels of carbon dioxide (CO_2). Also, the elevated ventilatory responses ($\dot{V}E/\dot{V}CO_2$) that these patients experience during exercise leads to a diminished $PaCO_2$ and may result in vasoconstriction in the cerebral blood vessels.[103,105] Furthermore, as CHF activates the compensatory neurohormonal responses, the interaction of these factors and neurotransmitters hyperactivates sympathetic nerve activity, which promotes vasoconstriction in the cerebrovasculature, as it does in the conduit arteries.[106] Nonetheless, sympathetic-induced vasoconstriction is also a known mechanism of cerebral autoregulation,[107] which is a protective physiological mechanism to preserve blood pressure stability in the brain despite changes in the rest of the body. As a result of these interactions, CBF may be attenuated during exercise implying a drop in oxygen levels to the brain, and as a consequence, a decline in the central motor drive as well as an increased perception of fatigue.[103]

Moreover, since there is a relationship between aerobic capacity and cerebrovascular function in healthy individuals,[108] it seems plausible that a reduced CBF experienced by patients with CHF may affect their exercise tolerance.[109]

While previous studies have focused on cerebral haemodynamics at rest, there is a surprising scarcity of studies assessing the CBF response to exercise in patients with CHF. The only study investigating this area was conducted by Fu et al.[105] who observed reduced cerebral oxygenation during exercise –measured by near-infrared spectrometry (NIRS)- in patients with CHF compared with healthy controls. To date, it is known that CHF negatively influences CBF at rest, however, whether and to what degree it is diminished during exercise remains to be determined.

2.3.2.4.2 Impact of exercise training on cerebral blood flow in chronic heart failure

To date, only two ET studies have been conducted on cerebral haemodynamics in patients with CHF. Fu et al.,[109] found that a 12-week HIIT program improved ventilatory efficiency, CO and cerebral oxygenation (measured by NIRS) to a greater extent than MICT or a non-exercise control group. In a separate study[110] by the same research group, comparing the impact of a 12-week HIIT on central and peripheral responses in patients with HFrEF versus HFpEF, HIIT improved the cardiac response to exercise in the HFrEF group, while the cerebral haemodynamic and ventilatory efficiency response to exercise was further improved in patients with HFpEF. These findings suggest that HIIT may be superior to the traditional MICT approach for improving cerebral haemodynamic function in people with CHF.

A limitation of these studies relates to the use of near-infrared spectrometry (NIRS), an index of CBF, which only can measure regional relative changes in oxy- and deoxy-haemoglobin, rather than absolute oxygen concentration.[111] According to the recommendations suggested by Brassard and Gustafsson[103] comprehensive assessment of cerebrovascular function, requires an evaluation of both intracranial and extracranial blood flow, cerebrovascular reactivity, and neurovascular coupling.[112] Ideally, the assessment should be done on one artery from the anterior circulation (middle cerebral artery/ internal carotid artery) and on one from the posterior circulation (posterior cerebral artery/vertebral artery), at least. This can be done safely and non-invasively employing a transcranial Doppler ultrasound.

Therefore, employing this optimal assessment technique has yet to be carried out for proper measurements of volumetric CBF during exercise in this patient population.

2.4 Physical activity levels in patients with chronic heart failure

Daily physical activity (PA) is an important determinant of cardiorespiratory fitness in people with CHF[113] and its beneficial effects on mental and physical health are well documented.[114] Indeed, PA levels are associated with better prognosis and survival in

patients with CHF.[115] Thus, promoting PA is a relevant treatment strategy for these patients to improve functional capacity, quality of life (QoL) and prognosis.[116] Current guidelines from the Heart Foundation of Australia[117] and the American Heart Association[114] recommend that people with cardiovascular disease accumulate at least 30 minutes of moderate-intensity PA (i.e., ≥3 METs) on a daily basis for health benefits. However, research has shown that a considerable proportion of patients (34 to 50%) with CHF fail to meet these recommendations,[113,118,119] which ultimately may further impact QoL and prognosis.

In a cross-sectional study, Klompstra et al.[120] found that one-third of patients with CHF did not comply with these PA guidelines and that men were significantly more active than women. Motivation, educational level and self-efficacy were factors positively correlated with PA. Although, this study used a self-reported questionnaire (IPAQ) as a means to measure PA, which is known to be prone to recall bias.[121] Using more objective methods, Dontje et al.[119] found that approximately 50% of patients with CHF have a sedentary lifestyle (i.e., <30 min/day at moderate/vigorous-intensity PA) with an absolute physical activity energy expenditure (PAEE) of 284 ± 302 kcal/day or 1.2 ± 0.2 METs, on average. It was also found that functional classification- as measured by New York Heart Association (NYHA) class- and especially self-efficacy, were associated with PA levels, consistently with previous investigations.[122,123] While daily PA was objectively measured by using an accelerometer, it was only recorded for two days. In an elderly cohort with advanced CHF, none of the patients complied with the PA guidelines performing, on average, only 1 minute per day at moderate/vigorous-intensity.[124] Therefore, in contrast to previous studies that used subjective measures of PA, the latter studies indicate that a high proportion of patients with CHF engaged in low levels of daily PA.

2.4.1 The impact of exercise training on physical activity levels and quality of life in chronic heart failure

As part of cardiac rehabilitation, many patients with CHF benefit from a tailored and structured exercise training program.[125] Once discharged, maintenance of regular PA in the long-term is essential to preserve the benefits associated with training, as they can vanish in a relatively short period if they are not continued. However, whether

participating in structured ET increases the daily PA levels in people with CHF remains unclear.

A recent meta-analysis[126] evaluated this outcome and found that ET participation was associated with higher daily walking (by 1,423 steps/day) and active energy expenditure (by 879 Kcal/week) compared with a control group without structured ET. However, this difference was not considered clinically meaningful,[127] and the time spent (min/day) inactive, performing light-intensity or moderate-to-vigorous-intensity exercise between groups was not statistically significant. This finding suggests that ET participation is not associated with an increase in PA in people with CHF. Limitations of this meta-analysis included the lack of standardisation of PA outcomes and the mix of both subjective and objectives measures. Moreover, 50% of trials were identified as "at risk of bias" and outcomes were reported at different time-points (median of 6-months after intervention). Accordingly, the authors recommended that future studies should assess PA objectively (e.g., using accelerometry), and outcomes should be reported in relation to international guidelines so direct comparisons and interpretation can be made. This is an interesting area to explore, given that increasing daily PA levels as recommended in current guidelines is a key objective of cardiac rehabilitation programs.

With regards to QoL, a recent Cochrane review[128] which included 33 RCTs found that ET participation was associated with a significant improvement in QoL compared with a control group in patients with CHF (effect size = 0.46 [0.26 to 0.66]; $p < 0.001$). In a cohort of patients with predominantly NYHA class II-III symptoms, meta-regression analyses showed that the benefits of ET were independent of age, sex, degree of LV dysfunction and type of exercise (aerobic exercise with or without resistance component). In agreement with this, another meta-analysis[129] in an elderly cohort with CHF, also found a positive impact of ET on QoL (effect size = 0.7 [0.4 to 1.0]; $p < 0.001$). These findings strongly suggest that a structured ET program positively and moderately impacts self-reported QoL, irrespective of patients' characteristics or exercise mode. However, despite the strong evidence provided by these meta-analyses, whether there is a most effective training-intensity on QoL for patients supported with an LVAD remains to be determined.

2.5 Summary of findings

In summary, it is evident that exercise intolerance is not solely due to impaired central haemodynamics mechanisms in patients with CHF and that peripheral mechanisms may play a crucial role in the well-documented impairment in exercise capacity. These factors include vascular endothelial dysfunction, low muscle mass and abnormal muscular metabolism, overstimulated sympathetic nervous system and cerebrovascular dysfunction. Randomised control trials to date have shown that ET is a safe and effective intervention for addressing these factors, resulting in improved aerobic capacity in this patient population. Studies to date suggest that, overall, patients with CHF engage in insufficient daily levels of PA with a significant proportion of them not meeting the minimum doses of exercise according to the guidelines. However, evidence on this topic remains limited. Aerobic capacity and self-efficacy may be important determinants of daily PA that warrant further research. Given that the peripheral sequelae of CHF persist despite optimal medical therapy, it is likely that using ET to target peripheral maladaptations in patients with CHF may be an efficacious management strategy for improving aerobic capacity.

2.6 The physiological impact of left ventricular assist device implantation

2.6.1 The progression of chronic heart failure

As previously described in section 2.3, CHF is a progressive syndrome whereby cardiac structure and function typically deteriorate over time. While there are currently medical therapies available to treat and reduce symptoms of CHF, not much can be done to fully reverse the underlying molecular pathological mechanism driving the disease.[14] Thus, once cardiac dysfunction has occurred, it tends to worsen over time. Following the commencement of medical treatment, most patients experience significant symptomatic improvement in the short-term. Figure 2.4 provides a brief overview of the stages and treatment options for patients with CHF. The main objectives of medical therapy for these patients are: (i) improve prognosis and reduce mortality; and (ii) to alleviate symptoms and reduce morbidity by reversing or, at least, slowing down the cardiac and peripheral dysfunction.

Thanks to appropriate medical treatment, patients usually experience a stabilisation that lasts a variable period, but in the majority of cases, will be followed by recurrent episodes of exacerbation characterised by medical visits, changes in medication or hospitalisations. A typical clinical course of the disease is illustrated in Figure 2.5. Eventually, most patients will develop clinically advanced symptoms (NYHA functional class III-IV), despite optimal medical therapy. For those patients who are refractory to standard medical management, advanced therapies may be considered.

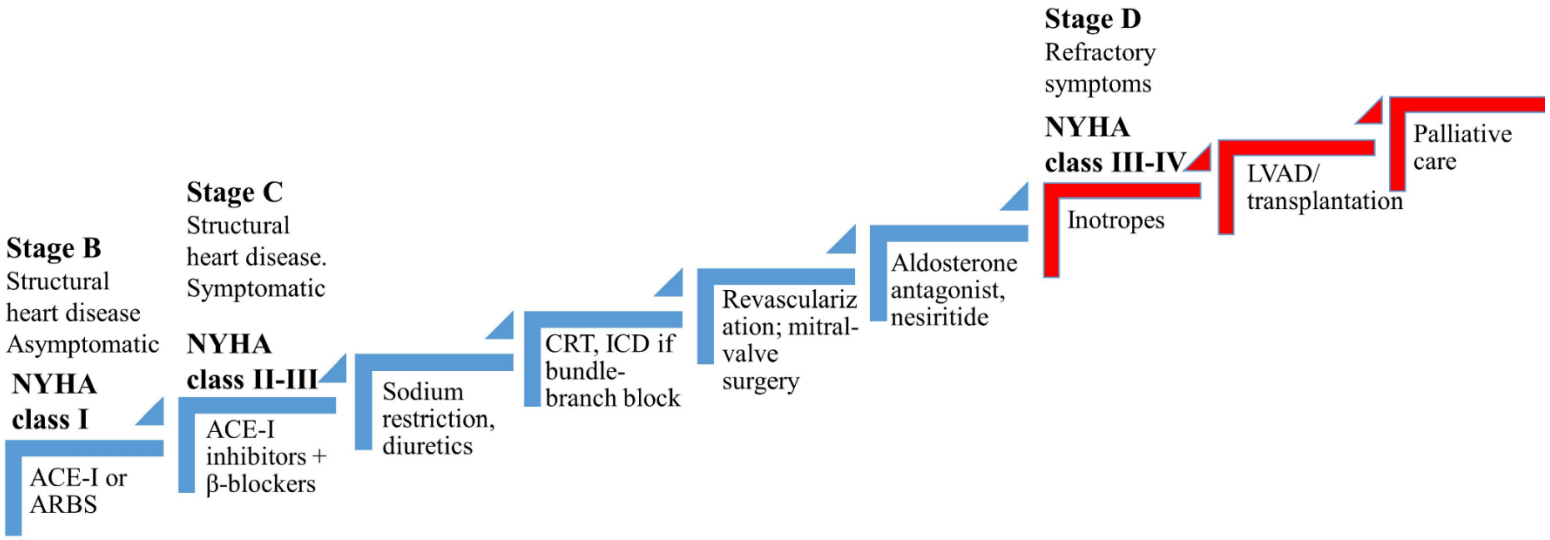

Figure 2.4 Stages of Chronic heart failure and treatment options. Adapted from Jessup et al.[130] ACE-I, angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin receptor blockers (ARBs) are used from an early stage for neuro-hormonal modification, provoking vasodilatation and reduce SVR, which lowers blood pressure. Beta-adrenergic blockers counteract the damaging effects of the hyperactivated sympathetic system, as they promote sodium excretion, arrhythmia prevention and control of ventricular rate. Diuretics and salt restriction are used to reduce the edema by the reduction of blood volume and venous and fluid. For those with advanced CHF, aldosterone levels may become elevated, which promotes salt retention, potassium excretion and myocardial hypertrophy. Aldosterone antagonists, as an adjunct to other drugs for additive diuresis, counteracts these responses and improve heart rate variability, ventricular function and decrease ventricular arrhythmias. For those patients with severe systolic dysfunction that exhibit intraventricular conduction defects (left bundle-branch block), cardiac resynchronisation therapy (CRT) may be indicated. This is a cardiac-pacing device that restores mechanical coordination by electrically activating simultaneously the left and right ventricles. It can be also used in combination with an implantable cardioverter-defibrillator (ICD), which rapidly terminates an abnormal life-threatening cardiac rhythm. Its beneficial effects include reverse remodelling and decreased mitral regurgitation. Revascularization, either through a bypass or angioplasty can be used to increase cardiac perfusion. While patients at any stage of CHF should be screen for myocardial ischemia, those at stage C or D may benefit from vascular bypass surgery to reduce myocardial wall stress. Inotropic agents are normally used at an advance stage for patients with acute decompensation. These drugs improve the contractility of the myocardium, but also affect heart rate and peripheral vascular resistance as a means to restore organ perfusion and reduce congestion.

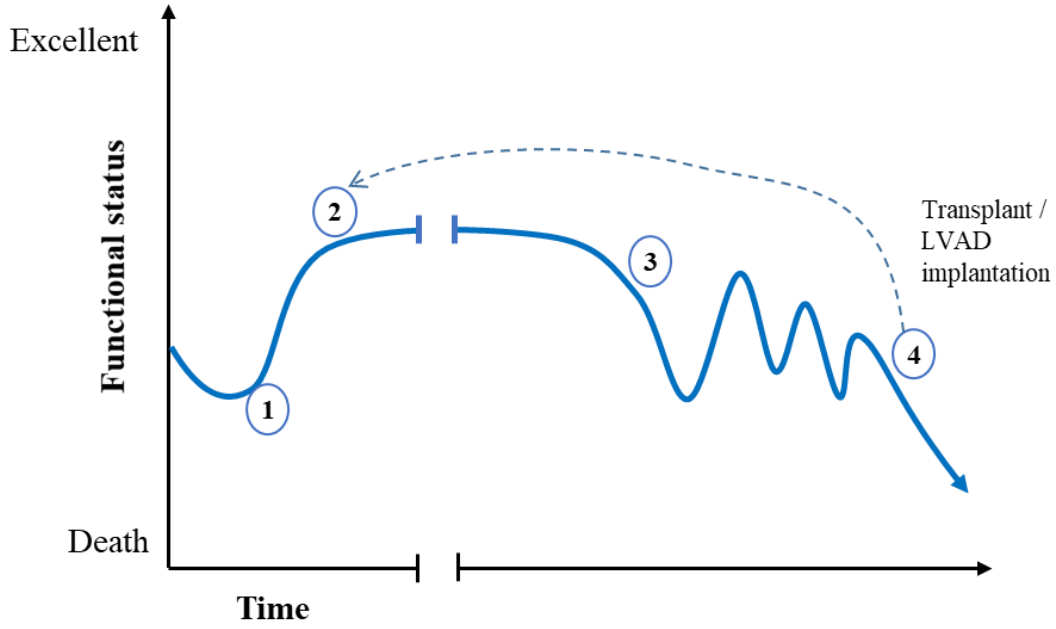

Figure 2.5 Depiction of the functional capacity progression of chronic heart failure: (1) initial presentation and treatment; (2) care for stabilisation; (3) progressive deterioration; (4) advanced therapy needed. Illustration adapted from Goodlin et al.[131]

A major revolution has occurred over the last two decades regarding the treatment of advanced CHF. Due to the scarcity of donor hearts for transplantation, significant resources have been used to foster the development of mechanical circulatory support as a life-saving treatment option for the management of advanced CHF.

2.6.2 Evolution of left ventricular assist devices

The history of mechanical circulatory support commenced in 1963 with the first intracorporeal pump implantation by Liotta and Crawford.[132] Although the patient died several days later, this experience provided valuable information for the National Aeronautics and Space Administration (NASA) and the National Institute of Health (NIH) in the USA to support the investigation and development of these devices. In 1971 DeBakey et al.,[133] successfully performed the implantation of a pneumatic ventricular pump system. During the 1970s, DeBakey progressed the development of both LVADs and the total artificial heart (TAH), but due to the large rate of

complication and mortality in the latter, it became apparent that LVADs were a more realistic alternative to support patients in need of a heart transplant.[134]

Significant technological advances continued to occur over the 1980s with the introduction of volume displacement pumps in clinical settings. These first-generation devices used pulsatile-flow and adjusted pump rate based on patient activity, increasing CO during physical exercise.[1] Despite improved cardiac output and enhanced pulsatility from these devices, minimal improvements in survival were reported. Later on, second-generation devices were developed, which employed axial flow to augment blood flow through the systemic circulation.[135]

More recently, a third-generation of devices have been developed which operate using hydrodynamic centrifugal forces.[1,136] The second and third-generation devices are known as continuous-flow left ventricular assist devices (CF-LVADs).[137] While they differ in the way they rotate the blood within the pump, mechanistically they are similar, and trials to date have shown that patients implanted with either axial- or centrifugal-flow have comparable postoperative outcomes, long-term survival,[138] end-organ function,[139] functional capacity and quality of life.[140] They are implanted in the pericardial space, without the need for abdominal surgery in already compromised patients.[141] Figure 2.6 illustrates the components of a modern third-generation CF-LVAD system. Currently, the most commonly used CF-LVADs are HeartMate II, HeartMate 3 (HMII and HM3, Thoratec Corp., Pleasanton, CA,) and HeartWare (HVAD; HeartWare Inc., Framingham, MA) (Table 2.1).[142] These contemporary devices operate at a set pump velocity, independent of patient activity, are non-pulsatile and are capable of delivering up to ten litres per minute of blood flow, depending on the pre- and afterload.[135]

Although both (pulsatile and continuous-flow) systems have been found to provide similar hemodynamic support, in terms of CO, pump flow, mean pulmonary artery and wedge pressures and aerobic capacity (15.4 ± 4.0 vs 15.6 ± 4.7, respectively),[143] modern continuous-flow LVAD systems are quite smaller, more durable and are associated with better clinical outcomes.[144] Consequently, current generation CF-LVADs have replaced pulsatile-flow LVAD systems and are an increasingly common treatment option for patients with advanced CHF.

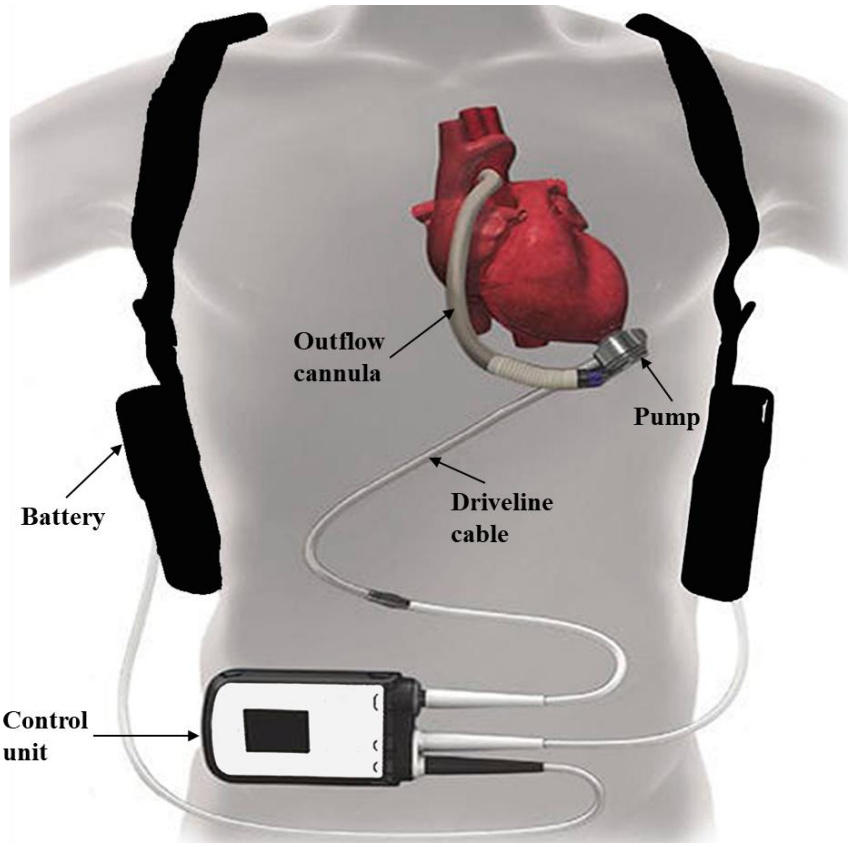

Figure 2.6 Components of a left ventricular assist device. The blood flow enters the pump through an inflow cannula implanted into the apex of the left ventricle or is implanted directly into the left ventricle. A motor inside the pump rotates the blood at high velocity and propels the flow to the ascending aorta via an outflow cannula. An external control unit operates the pump function through a driveline cable, which exits the body via a site in the abdomen. The control unit is connected to two batteries for power supply or can be connected to mains power.

Table 2.1 Main characteristics of the continuous-flow LVADs most commonly implanted.

Brand/model	**Pump type**	**Displaced volume**	**Flow output**	**Pump speed**
HeartWare	Continuous-flow centrifugal rotation	50 cc	10 L/min	1,800 up to 4,000 rpm.
HeartMate II	Continuous-flow axial rotation	160 g	10 L/min	6,000 up to 15,000 rpm

HeartMate 3	Continuous-flow by magnetically levitated centrifugal rotation	281 g	10 L/min	6,000 up to 9,000 rpm

Rpm, revolutions per minute.

2.6.3 Impact of left ventricular assist device implantation on central haemodynamics

The impact of LVAD implantation on the cardiovascular system is complex. The LVAD sets a unique scenario in the central haemodynamic system, in which two pumps work in conjunction to augment total cardiac output (TCO). In this scenario, TCO is then influenced by two determinants: native left ventricular output and pump output (TCO = LVO + PO).[23] While pump output is mostly dependent on pump speed, which is maintained at a constant rotation speed regardless of the exercise metabolic requirements, it is also influenced by differential pump flow pressure (ΔPP: aortic pressure - LV pressure).[22,145,146] If the pump speed increases, so does TCO. However, the differential pump pressure affects TCO in a proportional inverse manner: if the differential pump pressure increases, then pump blood-flow decreases.

While most of the TCO is carried by the pump during the diastolic phase of the cardiac cycle,[147] flow through the pump can be further supplemented to some extent by native cardiac function during the systolic phase, as LV pressure increases during systole making the ΔPP drop. Moreover, it is worth noting the role that blood pressure plays on the cardiovascular system. Higher blood pressure will increase the ΔPP, decreasing the flow through the pump resulting in an elevated differential pump pressure due to high blood pressure and/or low LV pressure.[148,147]

2.6.3.1 Preload-Afterload with an LVAD

The performance of the LVAD is also highly influenced by its preload and afterload sensitivity (this is the ability to change flow based on changes in preload/afterload). In a heart with normal function, CO is augmented with increasing preload but is relatively insensitive to changes in afterload. However, an LVAD is more sensitive to these

changes, as pump output quickly drops with a decrease in preload and afterload. Salamonsen et al.[149] estimated that preload sensitivity in LVADs was approximately 1/3 of a normal heart, whereas the afterload sensitivity was 3-fold higher compared with a normal heart. Although it should be noted that these estimations may differ depending on the type of LVAD implanted. Because LVADs are more susceptible to changes in pressure,[149] the abnormal Frank-Starling ventricular preload and afterload sensitivity may represent a limiting factor for TCO, and subsequently limit exercise capacity.[22]

2.6.3.2 Effect on the left and right ventricles

The LV competes with the pump for the same preload. This is directly determined by RV function, pulmonary vascular resistance and transpulmonary blood flow. Given that the pump speed doesn't decrease as a function of LV filling, poor transpulmonary blood flow may result in emptying and suck-down of the LV. This leads to suction events and reduces flow through the pump,[147] although modern devices have an integrated algorithm that will trigger a transient reduction of pump speed. Suction events are unwanted as they may provoke ventricular arrhythmias. Indeed, suction or ventricular tachycardia tends to be more common patients with poor RV function.[23] LVAD implantation provides an uninterrupted reduction in LV filling pressures and surges in systemic CO. Consequently, RV afterload decrease, and improvement in RV function.[150] Over time, a sustained reduction in LV filling pressures may improve pulmonary hypertension and lead to normalisation of pulmonary vascular resistance and improvements of RV afterload.[151] However, in the presence of a poor RV dysfunction, a sudden increase in venous return may lead to wall stress and tricuspid regurgitation.

2.6.3.3 The impact of continuous-flow on the vasculature

Because modern LVAD systems provide circulatory support in a continuous-flow, it has been perceived that supported individuals lack a pulse. However, it is important to highlight that the LVAD physiology does not necessarily imply a total absence of pulse, as this largely depends on the contractile reserve of the native ventricle. Even with a closed aortic valve, some degree of pulsatility seems to be present.[152] Especially with lower pump speed, where the aortic valve opens more frequently and pulsatility

increases. In contrast, at higher pump speed, the aortic valve tends to open less frequently, and thus, pulsatility decreases.

An important mechanism by which blood pressure is controlled relies on the arterial baroreceptors located in the aortic arch and carotid sinus.[153] These mechanoreceptors respond to stretching of the arterial wall by modifying the firing frequency of actions potentials, and provide information to the brain, which then modulates the SNS on a beat to beat basis by a negative feedback loop.[154] Therefore, with reduced pulsatility there is lesser distension of the baroreceptors, causing less inhibition of the SNA. As previously explained in section 2.3; patients with CHF experience an augmented SNA. This occurs in an attempt to maintain CO by increasing contractility and HR, but another consequence is increased arterial and venous pressure. In patients supported with LVADs, sympathetic tone seems to be even more elevated; this has been attributed to the baroreceptor unloading induced by the low physiological pulse environment.[155] This impairment in baroreflex function may be exacerbated by alterations in the endothelial function in patients with LVADs,[156] as a consequence of a lessened shear-stress and the LVAD-induced haemolysis.[157] As a result, hypertension may be due to these extremes levels of SNA, which in turn, may also predispose to clinical complications that this patient population commonly experience, such as aortic insufficiency, stroke or gastrointestinal bleeding, among others.[158]

2.6.3.4 Impact of left ventricular assist device implantation on skeletal muscle

As discussed in section 2.3.2.2, CHF is associated with metabolic alternations and a catabolic state which contributes to muscle wasting and an early transition to anaerobic metabolism.[70] However, how LVAD impacts the musculoskeletal system has not been systematically investigated. The only study to date which looked at this,[159] found that LVAD implantation increased growth hormone resistance, skeletal muscle cross-sectional area and oxidative capacity. Remarkably, these metabolic and morphologic changes were accompanied by an improvement in muscle strength. These findings suggest that LVAD-induced haemodynamic improvement partially corrects the metabolic and functional impairments occasioned by CHF. In the absence of medical therapy specifically targeting muscle dysfunction in CHF, exercise training is the only

approach to further improve muscular metabolism, structure and function for these patients.

2.6.4 Factors that may influence exercise capacity in patients with left ventricular assist devices

Even though current LVADs have a feedback system incorporated in their settings that decrease the pump speed in case of suction (unbalanced LV emptying), the device does not adjust pump speed in response to increased RV and LV filling.[160] At rest, the majority of TCO is pumped by the LVAD system,[161,162] however during exercise there is an increased reliance on the native cardiac function to meet the increased metabolic demands of skeletal muscle. This is achieved through an increase in HR and LV pressure combined with increased preload through the Frank-Starling mechanism to augment SV. This increases the pressure in the LV, while blood pressure usually remains relatively constant, which in turn gradually lowers the pressure differential across the pump and as a result, blood flow through the pump is slightly augmented.[163,164] Despite the constant pump speed, several studies have shown that pump output increases during aerobic exercise, although the increase is relatively modest and changes in TCO are driven predominantly by native heart function.[162,163,165] In an acute haemodynamic study involving patients implanted with an LVAD, Martina et al.,[163] observed that although pump output augmented slightly at the onset of the exercise, it remained constant during the rest of the exercise test, while TCO gradually increased until the end of the exercise test. Similarly, Schmidt et al.[166] reported that while pump output increased from rest to peak exercise effort by 35%, TCO augmented by 84%, providing further evidence that native LV function is the predominant mechanism for increasing TCO during exercise in patients with LVADs.

2.6.4.1 Native left ventricular function

The contribution of native CO to TCO depends on the extent of LV dysfunction. During exercise, most patients are able to produce an LV filling pressure that exceeds that of the systemic blood pressure, leading to the opening of the aortic valve (Figure 2.7).[167] This requires that the patient has an adequate residual LV function and a

competent aortic valve. While LV output increases, systemic vascular resistance (SVR) decreases due to peripheral vasodilation,[163] allowing more blood flow through the aortic valve. Therefore, during exercise with a competent aortic valve, TCO is gradually increased due to the contribution of native cardiac function. In a small study, Camboni et al.[168] manipulated LVAD speed to facilitate aortic valve opening during a cardiopulmonary exercise testing (CPET) in patients implanted with an INCOR LVAD system and found that aortic valve opening was associated with an impaired $\dot{V}O_2$ peak. However, these results should be interpreted with caution, given the small sample size (n = 8), absence of a control group and maybe device-specific. Conversely, a retrospective study performed by Imamura et al.[169] reported that LVAD patients with a competent aortic valve had a higher $\dot{V}O_2$ peak, lower levels of aortic regurgitation (leaking of the aortic valve causing blood flow in the reverse direction back to the ventricle) and greater LV remodelling compared with patients with aortic insufficiency. Accordingly, some hospitals have adopted a low-speed pump policy in order to allow intermittent aortic valve opening.[170] This policy has gained popularity over recent years given that the number of long-term supported patients is growing and these patients are being supported for a longer duration.[171] However, despite LVAD implantation, many patients continue experiencing aortic insufficiency. To date, there are no data available regarding the impact of ET on the aortic valve function in patients with LVADs, providing an interesting area for future research.

While the relationship between native cardiac function and exercise capacity in patients supported with LVADs is not completely understood, a novel study conducted by Noor et al.[172] found that worse native ventricular function was associated with lower $\dot{V}O_2$ peak and patients were more sensitive to pump speed changes compared with those with better native LV function, highlighting the importance of native cardiac performance during exercise in patients with LVADs. In contrast, other studies have shown a poor correlation between $\dot{V}O_2$ peak and EF.[163,173] For example, Jakovljevic et at.[173] reported that $\dot{V}O_2$ peak was not associated with native cardiac function in LVAD patients. This apparent discrepancy may be attributed to the difficulty in reliably assessing EF in patients with modern LVADs. But also it suggests that aerobic capacity may be limited by other factors apart from the cardiac function.

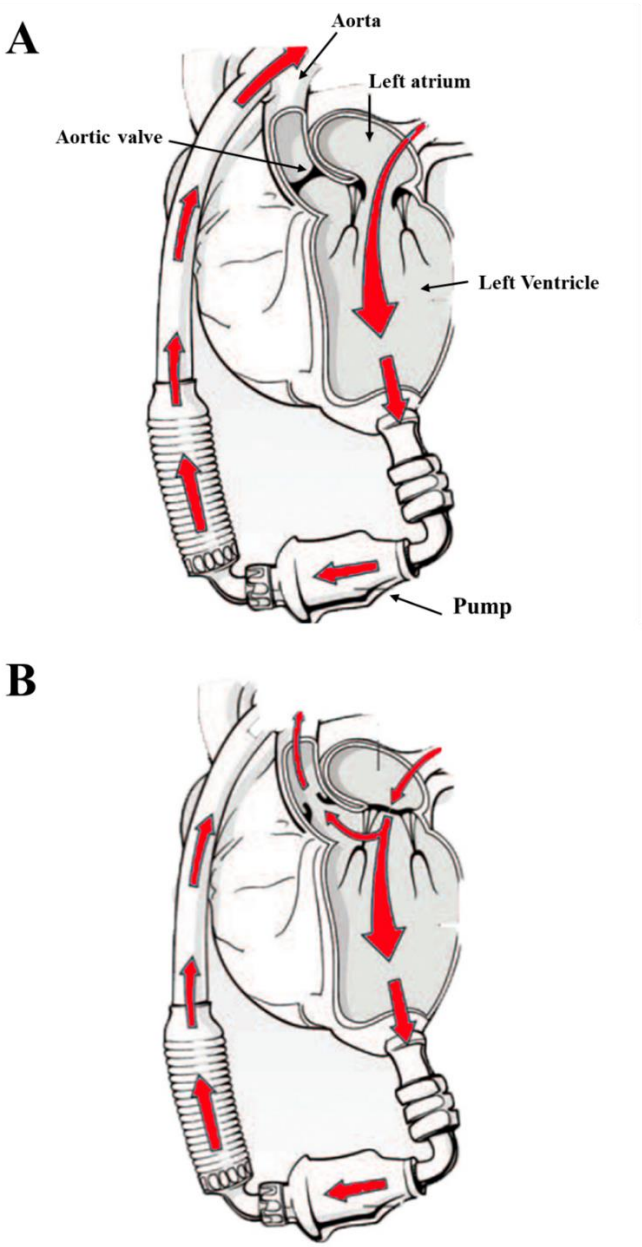

Figure 2.7 Depiction of a heart with a left ventricular assist device system *in situ*. A) At rest, total cardiac output is usually generated only by the pump while the aortic valve is closed. B) During exercise, total cardiac output is generated by the contribution of both the pump and the native left ventricle as the aortic valve opens.

2.6.4.2 Heart rate

The other determinant of CO is HR. The literature contains contradictory results in relation to the specific role of HR on pump flow in LVAD recipients. Exercise studies in patients with early generation of LVADs[24,149,174] showed that augmentation of pump

output during exercise was attributed to an increased HR since the systolic phase gains time while the diastolic phase is compromised. A more recent study conducted by Muthiah et al.[175] did not corroborate the impact of HR to further improve pump output in patients with third-generation LVADs. In this study, HR increases were induced by pacing, which may have provoked a different physiological response to a natural, exercise-induced HR rise. Moreover, the patient's ongoing β-blocker therapy may further affect their chronotropic response negatively and thus CO performance. Furthermore, it has recently been found that LVADs also show a linear relationship between HR and $\dot{V}O_2$ peak during exercise, provided that patients are not being paced.[176] This finding supports the premise that monitoring HR during exercise may be a useful estimate of exercise intensity in patients with LVADs.

2.6.4.3 Right ventricular function

Another potential relevant determinant of exercise intolerance in patients with LVADs is right ventricular (RV) dysfunction. Despite LVAD implantation being associated with a lower RV afterload and decreased pulmonary artery pressure,[177] some patients with LVADs (13-40%) still experience RV failure.[178] Interestingly, preliminary analyses from the RVF-LVAD study[13] has identified three potential predictors of RV failure in patients implanted with modern LVADs: tricuspid regurgitation, poor RV global longitudinal strain, and small LV size. Adequate functioning of the RV is essential to fill the left side of the heart and improving thus CO during exercise. In patients with CHF, studies have shown a positive significant association between right ventricular ejection fraction (RVEF) and $\dot{V}O_2$ peak.[179] However, the literature is scarce in relation to the role of the RV on maximal exercise capacity in patients with LVADs. It has been proposed that RV failure could limit $\dot{V}O_2$ peak, as it does in patients with CHF. Camboni et al.[168] conducted a right heart catheterization in participants implanted with an obsolete 'Incor' LVAD system while they underwent a CPET. At peak exercise, participants had an increased pulmonary artery wedge pressure and pulmonary artery pressure above the normal predicted values. Moreover, participants showed an augmented pulmonary artery resistance, rather than an expected reduction. In line with this finding, Mutiah et al.[180] also reported an elevated right atrial pressure and pulmonary artery wedge pressure in patients with LVADs during exercise. These findings suggest that RV dysfunction may occur as a consequence of LV failure and a

remodelling of the pulmonary artery, and highlight that previous RV failure may further contribute to exercise intolerance in people with LVADs.

2.6.4.4 Vascular endothelial function

As described in section 2.3, vascular endothelial dysfunction has been documented in people with CHF with endothelium function correlating closely with $\dot{V}O_2$ peak.[181] More recently, endothelial dysfunction has been postulated as a significant contributor to exercise intolerance.[182] However, only very limited information exists in relation to endothelial function in people with LVADs *in situ.* While LVAD implantation improves CO at rest, the absence or low physiological pulse has been suggested to further aggravate vascular dysfunction.[156,183]

Following LVAD implantation, the principal vascular changes are seen in the proximal compliance vessels. A study conducted by Ambardekar et al.[183] assessed aortic wall composition and structure in age-matched participants with CF-LVAD (support duration of 6-months) versus CHF and healthy controls and found that the LVAD group had an increase in wall thickness, collagen, and smooth muscle content, accompanied by a reduction in elastin and mucinous ground-substance content. These findings suggest that the low pulsatility contributes to changes in the structure and composition of the aorta.

Keeping with this finding, in a cross-sectional study conducted by Witman et al.,[156] peripheral vascular function, measured as %FMD shear rate, was significantly reduced in LVADs (0.09 ± 0.01 $\%\Delta/s^{-1}$) compared with the CHF group (0.13 ± 0.02 $\% \Delta/s^{-1}$), and this was significantly lower than control subjects (0.24 ± 0.03 $\%\Delta/s^{-1}$). These findings suggest that the already compromised vascular function which exists in patients with advanced CHF is further exacerbated after LVAD implantation (on support duration of 5-7 months). In contrast, in a small experiment, Pitha et al.[184] did not find significant improvement in endothelial function compared with pre-LVAD implantation. In line with the latter study, Lou et al.[185] showed that LVAD implantation did not have an impact on endothelial function. These contradictory results may be explained by the smaller sample size (n=6 and 8, respectively) of the latter studies,[184,185] as well as the short duration of time on LVAD support (1-4 months vs 5-

7 months, respectively). It has also been found that restoration of pulsatility through cardiac transplantation is associated with improvement of %FMD.[186] Therefore, there is evidence indicating that the unique physiology of current LVADs may directly affect endothelial cell function.

To the best of our knowledge, there are currently no studies assessing either the acute or the chronic impact of exercise on endothelial function in people with LVADs.

2.7 The acute haemodynamic response to exercise in left ventricular assist devices

While LVAD implantation restores central haemodynamics to near normal values at rest, preventing low end-organ perfusion, aerobic capacity remains clearly compromised. As previously described in section 2.5, similarly to patients with advanced CHF (but no LVAD), it is likely that there are multiple causes, lying in both centrally and peripherally. However, the acute physiological transition from rest to exercise is not fully understood. In the following section, the current state of the literature regarding the acute haemodynamic impact during exercise in patients with LVADs is addressed.

2.7.1 Aerobic capacity

Although differences in exercise testing mode, participant's gender and age, type of LVAD, as well as support duration, limit the direct comparison of results across studies, general findings can still be summarised (Table 2.2). Overall, patients with LVADs showed an impaired aerobic capacity with $\dot{V}O_2$ peak values that range from 10.6 to 20.3 $mL \cdot kg^{-1} \cdot min^{-1}$ in patients aged from 33 to 63 years old (37-54% of age-predicted values).

2.7.2 Cardiac output

Because pump speed is fixed, patients with LVADs rely predominantly on native cardiac function to increase TCO during exercise, with a smaller contribution from pump output, although the exact contribution share is difficult to distinguish. TCO can

be measured most accurately by assessments methods such as right heart catheter, CO_2 rebreathing or inert gas rebreathing. While differences across studies in terms of CO assessment method, LVAD type, time on support and participants' characteristics limit direct comparisons, an overall overview can be summarised. Taken together, studies report increases in TCO that ranged from 3.4 - 6.3 L/min at rest, to 5.3 - 13.6 L/min at peak exercise in participants aged 39 - 61 years (Table 2). An interesting observation is that younger patients tended to experience a greater increase in TCO during exercise compared with older ones, consistent with previous literature,[24,166] and similar to $\dot{V}O_2$ peak.[22,187]

Jacquet et al.,[24] employing thermodilution, found that LVAD participants had higher TCO peak compared with matched patients with advanced CHF without mechanical circulatory support, at both during rest (5.3 ± 0.7 vs. 3.5 ± 0.4 L/min, $p < 0.05$) and peak exercise (9.2 ± 1.8 vs. 5.6 ± 1.6 L.min^{-1}, $p < 0.05$). Likewise, participants with LVADs also showed a greater aerobic capacity. (LVAD: 15.8 ± 6 vs. CHF: 10.9 ± 3.0 mL·kg^{-1}·min^{-1}; $p < 0.05$). Jakovljevic et al.,[173] reported similar values at rest (LVAD: 5.5 ± 2.1 vs CHF: 4.1 ± 1.3 L/min; $p<0.05$), as well as at peak effort (12.4 ± 2.2 vs. 9.1 ± 2.1 L/min; $p < 0.05$) by using inert gas rebreathing methodology. Again, the LVAD group had a higher $\dot{V}O_2$ peak (19.8 ± 4.1 mL·kg^{-1}·min^{-1}) versus the CHF group (15.8 ± 5.8 mL·kg^{-1}·min^{-1}; $p < 0.05$). While these findings suggest that there is a relationship between CO and $\dot{V}O_2$ peak, the latter study[173] found a moderate correlation (r = 0.55), but this was not statistically significant. These findings support the notion that in addition to CO, peripheral factors account significantly for $\dot{V}O_2$ peak in patients with LVADs.

In agreement with these reported TCO values, Andersen et al.,[160] performed right heart catheterisation simultaneously with echocardiography in 12 patients with an LVAD and found that TCO markedly increased from rest to peak exercise (6.3 ± 2.2 to 13.0 ± 3.0 L/min; $p < 0.001$), while no changes in LV diameters were observed. These results propose that increments in TCO in LVADs may be achieved with minor increases in filling pressures. It has been previously suggested that while LVAD implantation seems to provide sufficient haemodynamic support at rest, this may not be sufficient near peak exercise, given that TCO does not increase proportionately with workload. Likewise, Brassard et al.,[162] reported a peak exercise TCO at 13.6 L/min (in a cohort of mean age 39), which is lower than predicted values of healthy subjects of

similar age (~17 L/min). Similarly, Schmidt et al.,[166] assessed CO by using inert gas rebreathing and found that TCO levels at peak exercise (6.95 ± 1.4 L/min) in patients with LVADs were relatively low in comparison with age-predicted values (~12 L/min). This study observed that while TCO progressively increased during the initial phase of the CPET (from 3.76 to 6.24 L/min), it remained unchanged from moderate to peak effort. Whereas the normal response is to rely more heavily on CO at higher intensities of exercise.[188] This suggests that cardiac performance in LVADs is limited at near maximal exercise, likely due to an impaired residual function coupled with chronotropic inability.

Overall, patients with LVADs seem to be unable to adequately increase TCO during exercise to meet increased metabolic demands. This appears to be due to the combination of impaired residual cardiac function, and the inability of the pump to augment output in response to exercise. However, whether an increasing pump speed during exercise would result in an improved aerobic capacity is unclear. Studies to date have found that increased pump speed provides only modest,[149,189-191] or no improvement [23,172,180,192,193] in aerobic capacity.

Table 2.2 Studies assessing the acute effects of exercise on haemodynamics in patients with LVADs.

Study	Participant's characteristics.	CPET mode	$\dot{V}O_2$peak (mL.min^{-1}.kg^{-1})	Main findings
Haft [143] (2007)	16 P-LVAD vs 18 CF-LVAD at 3 months post-implantation. Age: 51±14 vs 52±14 yr.	Treadmill	15.4±4.0 vs 15.6±4.7 (NS). Precicted: 49.1±13.6	Pulsatile vs. CF LVADs augmented similarly exercise capacity despite better LV unloading of the pulsatile devices.
Andersen[160] (2010)	12 CF-LVAD. Age: 38 (20-65)	Bicycle	Not defined	TCO augmented from 6.3±2.2 to 13.0±3.0 L/min, without LV dimensions nor fractional shortening changes. Right leg blood flow increased from 0.7 to 4.4 L/m.
Jakovljevic[165] (2010)	20 CHF vs 18 CF- LVAD. Age: 45±10 vs 39±14 yr.	Treadmill	11.2±1.9 vs 14.7±4, $p<0.05$	Both resting (5.5±2.1 vs 4.1±1.3 L/min) and peak TCO (9.1±2.1 vs 12.4±2.2 L/min) were greater in LVAD vs CHF. SVR was higher in CHF vs LVAD.
Jakovljevic[173] (2011)	As above		As above	Correlation between peak CPO and $\dot{V}O_2$ peak, CP, VE/VCO_2 is only mild to moderate in LVADs and CHF.
Dimopoulos[194] (2011)	7 LVAD vs 14 CHF vs 7 HC Age: 45±16 vs 50±10 vs 45±7.	Bicycle	13.8±2.8 vs 13.5±2.3 vs 30.3±8.3	LVAD implantation did not improve $\dot{V}O_2$ peak, chronotropic inability or HR reserve in patients with advanced CHF.
Jacquet[24] (2011)	10 HMII vs 10 CHF. Age: 47.3±13.1 and 50.1±13.2 yr, respect.	Bicycle	LVAD: 15.8±6 vs. CHF: 10.9±3.0; $p<0.05$.	LVAD showed significantly higher resting TCO than HF group (5.3±0.7 vs. 3.5±0.4 L/min, $p<0.05$); and peak TCO (9.2±1.8 vs. 5.6±1.6 L/m, $p<0.05$).

Brassard[162] (2011)	8 CF-LVAD. Age: 39±18. CPET at constant (9775 rpm) vs increasing (+400 rpm) pump speed.	Bicycle	Exercise time: 698±270 vs 700±300 seconds, *p*=0.94.	With constant speed, TCO, leg BF increased during exercise but CBF was unchanged. However, increasing pump speed protocol provoke augmented peak CBF (37±12 vs 40±15 cm/s, *p*<0.05) versus constant pump speed.
Noor[172] (2012)	30 CF-LVAD Age: 35±13 yr. CPET at normal (9000 rpm) vs (6000 rpm) pump speed.	Treadmill	Pump speed reduction did not affect $\dot{V}O_2$ peak: 20.3±5.2 vs 19.3±6.1, NS.	Although reducing pump speed did not significantly impact $\dot{V}O_2$ peak in patients with EF≥40%; it made an impact in those with EF<40% (17.2±5.3 to 14.7±5.9 ml/kg/min, *p*=0.02). Also, $\dot{V}O_2$ peak was associated with EF at both normal (r =0.41, *p*=0.03) and reduced pump speed (r =0.50, *p*=0.01).
Kerrigan[195] (2013)	23 CF-LVAD. Age: 55±13 yr.	Treadmill	12.9 ± 3.1	KCCQ score was associated with $\dot{V}O_2$ peak (r=0.51, *p*=0.019) and muscle strength (r=0.58, *p*=0.006). There was no association between $\dot{V}O_2$ peak and 6MWD (r=0.119; NS).
Martina[163] (2013)	30 CF-LVAD. Age: 43±14 y. At 6 months post-implantation. Comparison of resting vs peak exercise haemodynamics.	Bicycle	18.0±6.2 mL/kg/min. (51% of predicted)	TCO increased from rest to peak exercise (4.1±1.1 to 8.5±2.8 L/min; *p*<0.01), while PO augmented from 5.1±0.7 L to 6.4 ±0.6 L/min; *p*<0.01. SVR decreased from baseline to maximal exercise (1766±750 to 1013±383 dynes.s/cm^5).
Compostella[196](2014)	26 CF-LVAD vs 30 CHF. Age: 63.4±7.4 vs 64.6±5.3 y	Bicycle	LVAD: 12.5 ± 3.0 vs CHF: 13.6 ± 2.9, NS.	Within 2 months post-LVAD implantation $\dot{V}O_2$ peak did not improve compared to CHF, the kinetics of $\dot{V}O_2$ recovery after exercise was improved: 212.5±62.5 peak vs CHF: 261.1±80.2

				seconds, $p<0.05$.
Camboni[168] (2014)	8 CF-LVAD. Age: 45 ± 13 y	Bicycle	12.4±2.5 (38% of predicted)	Exercise increased TCO from 4.7 ± 0.5 to 6.2 ± 1.0 L/min (p=0.008); PVR from 117±35.4 to 125±35.1 dyn*sec*cm^{-5} (p=0.58) and PAP from 16±2.4 to 27±2.8 mmHg (p<0.001).
Dumlay[197] (2014)	25 CF-LVAD. Age: 63.4 ± 9.9 y	Treadmill	11.5 ± 2.5 (43% of predicted)	Compared to cardiac transplanted patients, aerobic capacity in LVADs remains significantly lower.
Schmidt[198] (2017)	69 CF-LVADs Age: 55.9± 11.7 yr.	Bicycle	10.6 ± 2.9 (37% of predicted)	Following LVAD implantation (3-months post) aerobic capacity remains restricted, whereas, 6MWD improves significantly.
Schmidt[166] (2018)	20 CF-LVAD. Age: 60.8±7.3 yr.	Bicycle	10.9±3.0 (39% of predicted)	Initially, from rest to light intensity, TCO increases significantly (from 3.8± 0.9 to 5.7±1.2) but did not change significantly beyond that until peak effort (6.9±1.4).

Values presented as mean ± SD.; P-LVAD; pulsatile left ventricular assist device; CF-LVAD, continuous-flow left ventricular assist device; CHF, chronic heart failure; HC, healthy control; TCO, cardiac output; LV, left ventricular; SVR, systemic vascular resistance; HR, heart rate; CPO, cardiac power output; BF, blood flow; CBF, cerebral blood flow; EF; ejection fraction; KCCQ; Kansas city cardiomyopathy questionnaire; PVR; peripheral vascular resistance; PAP, pulmonary artery wedge pressure; 6MWTD, six-minute walk test distance.

2.7.3 Peripheral factors

2.7.3.1 Systemic vascular resistance

In comparison to patients without mechanical circulatory support, those supported with LVADs had a significantly lower SVR during rest (1694 ± 269 vs. 1333 ± 157 dynes.sec.cm^{-5}; $p < 0.05$) and at peak exercise (1144 ± 359 vs. 783 ± 99 dynes.sec.cm^{-5}, $p < 0.05$).[24] Likewise, Camboni et al.,[168] reported a significant decline in SVR from rest (1084 ± 211 to peak exercise 678 ± 27 dynes.sec.cm^{-5}, $p < 0.05$), which was associated with a significant increase in TCO. Of note, these studies determined SVR based on the physiological relationship: SVR = (MAP-CVP)/TCO; where TCO was directly assessed by conducting an invasive right heart catheterisation. By using less rigorous and indirect estimation methods based on oxygen uptake,[199] Martina et al.,[163] reported a similar magnitude change in SVR from rest to peak exercise (1776 ± 750 dynes.sec.cm^{-5} to 1013 ± 383 dynes.sec.cm^{-5}) in patients with LVADs. Interestingly, SVR had the strongest association with TCO (r = −0.72), compared with pump output (r = −0.68), and HR (r = 0.63), which were all significant ($p < 0.01$). These findings suggest that during peak exercise, patients rely more heavily during on exercise-induced vasodilation in reducing SVR and thus, afterload.

2.7.3.2 Arteriovenous oxygen content difference

Using arterial and Swan-Ganz catheters, Jacquet et al.,[24] evaluated a-vO_2diff throughout a CPET in participants with CHF versus LVADs. Arteriovenous oxygen content difference significantly increased from rest to peak exercise in both groups. However, despite having a greater CO at peak exercise, participants with LVADs had a significantly lower a-vO_2diff than those with CHF both at rest (6.2 ± 1.2 vs. 8.6 ± 1.8 mLO_2/ dL, $p < 0.05$) and at peak exercise (12.4 ± 1.1 vs. 14.4 ± 2.3 mLO_2/dL, $p < 0.05$). Given that the LVAD group had a higher $\dot{V}O_2$ peak and TCO peak than the CHF group, this finding suggests that inefficiency in peripheral metabolism may exist. This may be attributed to an impaired oxygen delivery due to attenuated vasodilatory capacity, and/or impaired oxygen utilisation at the muscular level. An alternative explanation may be that patients supported with LVADs lose some compensatory peripheral adaptions due to the increased CO. Interestingly, Schmidt et al.,[166] also found an elevated a-vO_2diff at rest (7.4 ± 1.9 mLO_2/dL or 44% oxygen extraction ratio)

in patients with LVADs, while the normal ratio in healthy individuals is ~33%. This relatively high resting levels of a-vO_2diff are commonly seen in CHF and likely to be attributed to compensatory mechanisms through increased production of hydrons (H^+) within the muscle capillary due to lactic acid, whereby additional oxygen extraction is promoted to balance the low CO.[200]

Another observation which is important to highlight is that while a-vO_2diff and TCO both increased significantly during the initial phase of the CPET (to 9.9 ± 2.3 mLO_2/dL, $p < 0.01$) no further differences were seen with increasing workloads (up to 13.2 ± 3.1 mLO_2/dL, NS). These peak exercise a-vO_2diff values remain relatively low compared to a normal response (15 to 18 mLO_2/dL or 80% of oxygen content).[201,202] This is an indication of oxygen extraction and utilisation impairment in the periphery.

2.7.3.3 Skeletal muscle metabolism

Advanced CHF is associated with muscle wasting and changes in its metabolism and structure. However, there are currently few studies regarding the impact of LVADs on the musculoskeletal system. Andersen et al.,[160] invasively assessed skeletal muscle blood flow via a catheter in the right femoral vein in three participants with LVADs while conducting a CPET on a supine bicycle. A marked increase in muscular blood flow was observed from rest (0.7 L/min) to peak effort (4.4 L/min), in parallel with augmentation of TCO via aortic valve opening. Khawaja et al.,[203] compared 25 patients with CHF pre- versus post-LVAD implantation and found an increase in muscle cross-sectional area (1005 ± 668 vs. 1240 ± 670 μm2, $p < 0.001$). This was associated with an increased number of oxidative type I muscle fibres. This study demonstrated that LVAD implantation improves skeletal muscle mass and function.

2.7.3.4 Cerebrovascular function

The eighth INTERMACS report[204] revealed that from 6 months to 4 years following LVAD implantation, stroke is the major cause of death. Despite this, very little is known t with regards to the role of CBF in patients with CHF, either supported with an LVAD or not. It would be of great interest to elucidate a better understanding of the cerebrovascular function in this patient population. It appears that cerebral autoregulation is preserved in LVAD patients, as shown by recent studies.[205-207] As previously described in section 3.2.2, patients with CHF experience a lowered CBF.

The degree of CBF reduction seems to be associated with disease severity.[94,98] The implications of this may be multiple, including cerebrovascular accidents,[204] cognitive impairment and dementia,[99,208] and may also be a contributory factor to exercise intolerance.[103]

Currently, information is scarce regarding the role of cerebral haemodynamics in patients with LVADs, as only one study to date has been performed. In a novel experiment, Brassard and co-workers.[162] assessed CBF, measured by transcranial Doppler ultrasound, alongside invasive cardiac haemodynamics in eight patients with an LVAD. At rest, middle cerebral artery flow velocity (MCAv) was 39 ± 14 cm/s, which equates to ~80% of that observed in healthy individuals, and remained unchanged throughout the exercise test, while the normal response is to progressively increase up to ~60-70% $\dot{V}O_2$ peak. Interestingly, when pump speed was gradually augmented during exercise, and thus TCO, MCAv was also elevated but the response did not achieve the values observed in healthy individuals. These results suggest that cerebral perfusion may be impaired in patients with LVADs during exercise. However, this study only measured one cerebral artery, did not include a control group, and comparison data was taken from studies in the early 90s, neither were participants matched for characteristics. Therefore, whether LVAD implantation improves cerebral perfusion and to what degree, during rest and exercise remain to be determined.

2.7.4 Summary of findings

At rest, the pumping capacity of LVADs appears to provide sufficient haemodynamic support to meet metabolic demands. In the transition from rest to moderate exercise, patients are able to meet the increasing metabolic demands through an increased in both LVAD output and native CO. This is achieved by a reduction in pump head pressure, which is determined by pump speed (which remains constant), LV contractility and enhanced venous return due to exercise-induced vasodilation and the mechanism of the muscle pump. However, from moderate-intensity to peak exercise, pump output is unable to further increase and patients rely heavily on LV unloading to further augment TCO. If the LV contractibility increases and exerts a pressure superior to that of the systemic blood, the aortic valve will start to open enabling additional

output. This sets out a competing mechanism between the native LV and the LVAD, as mean arterial pressure (and pulse pressure) increase, and subsequently flow through the aorta surges in detriment of the pump output. Concurrent with changes in TCO, oxygen extraction in the skeletal muscles increases gradually during light and moderate exercise but reaches a plateau at high exercise intensity. This is likely due to a limited oxygen extraction reserve capacity (as it is already augmented at rest), secondary to impairments observed in the oxidative metabolism attributed to vascular dysfunction, skeletal muscle wasting and mitochondrial alterations, resulting in a reduced capacity for oxygen delivery and utilisation.

These observations suggest that oxygen uptake in patients with LVADs remains limited with increasing workloads from moderate-intensity upwards as both TCO and a-vO_2diff cannot meet the increasing demands of exercise. Prescribing ET at higher intensities relative to individual exercise capacity may be a potentially effective approach to further improve aerobic fitness in this clinical cohort.

2.8 The effects of exercise training in patients with left ventricular assist devices

2.8.1 Safety of exercise training

While exercise is generally considered to be safe for CHF, very little data is currently available in LVADs. The first RCT[209] considering this outcome reported no adverse events over 168 cardiovascular gymnasium visits. However, Kerrigan et al.,[5] documented a major adverse event due to a syncopal episode precipitated by a wide complex tachycardia after completing an exercise session (one event in 313 sessions). Similarly, Lamotte et al.,[210] reported that two patients suffered pre-syncopal episodes during their sessions, which were managed and solved without further complications. No major adverse events were reported in over 400 training sessions. In a retrospective analysis,[211] only one exercise-related event was found (non-sustained ventricular tachycardia) out of the 1600 training sessions performed by patients.

Since limited studies (only two RCTs) have looked at safety data of ET in patients with LVADs, definitive conclusions cannot be made. Based on the available data, it

seems that ET may be well-tolerated and safe for the vast majority of patients. Remarkably, all studies were conducted in a medically controlled and supervised environment and used training protocols involving only low- to moderate-intensity aerobic exercise. An important question that remains to be answered is whether these patients are able to tolerate and engage safely at higher ET intensities. Future well-powered investigations are needed to elucidate the potential relationship between exercise intensity and rates of serious adverse events.

2.8.2 Aerobic Capacity

Limited but encouraging findings exist in relation to the impact of ET on exercise capacity in LVADs. A small pilot RCT conducted by Adamopoulos et al.[212] reported a beneficial effect of ET on $\dot{V}O_2$ peak in patients with LVADs. However, this study has only been published as a conference abstract so the specific details and results of the trial are unclear (Table 2.3). The remainder of the RCTs[3-5] to date have not found a statistically significant difference in $\dot{V}O_2$ peak between the ET and the control group. The first trial to evaluate the impact of ET in patients with an LVAD was conducted by Laoutaris et al.[3] In patients on LVAD support for a mean of 6 months, there was a within-group improvement by 2.5 $mL \cdot kg^{-1} \cdot min^{-1}$ in the ET group (15%; $p < 0.01$), whereas the control group remained unchanged, but there were no between-group differences. However, this study included patients with an older generation of LVADs, which function in a different manner and are no longer used clinically. A more recent study[4] in which participants were assessed early following CF-LVAD implantation (1 month on support) found that both the training group (Δ4.3 $mL \cdot kg^{-1} \cdot min^{-1}$ or 41%; $p < 0.05$) and the control group (Δ2.9 $mL \cdot kg^{-1} \cdot min^{-1}$ or 23%; $p < 0.05$) experienced significantly improved $\dot{V}O_2$ peak following an 8-week intervention. Although the difference between groups was not significant ($p = 0.43$), it is worth mentioning that the observed increments in aerobic capacity were relatively large in both groups, suggesting that the control group may have engaged in significant exercise over the program duration; control participants underwent a structured mobilisation protocol (Table 6.3). This may partially explain the lack of statistical differences between groups. Similarly, the largest trial thus far, conducted by Kerrigan et al.[5], reported a modest increase in $\dot{V}O_2$ peak of 1.7 $mL \cdot kg^{-1} \cdot min^{-1}$ (12%; $p < 0.01$) in the ET group following 6 weeks of aerobic training, compared with 0.6 $mL \cdot kg^{-1} \cdot min^{-1}$ (5%; NS) in

the control group. Participants in this study were recruited, on average, at 3 months post-LVAD implantation. But again, the change between groups was not statistically significant.

In contrast to these findings, two non-randomised prospective studies in patients with LVADs have found significant between-group differences in $\dot{V}O_2$ peak following ET. In a long-term multimodal intervention (composed of home-based exercise, nutrition and psychological support program), Kugler et al.[213] observed a significant improvement in aerobic capacity (reported as %predicted $\dot{V}O_2$ peak) in the intervention versus the control group (Δ8 % vs Δ3%, respectively; $p < 0.05$). Consistent with this finding, a recent non-randomised prospective trial[210] found that following 6 months of ET, participants with LVADs improved $\dot{V}O_2$ peak by 5 $mL \cdot kg^{-1} \cdot min^{-1}$ (Δ34%) compared with a 2% increase in those who did not attend supervised exercise rehabilitation ($p < 0.01$ for between-group comparison). However, this study included only four participants in the control group. The significant improvement experienced in the ET group may be explained by potential bias inherent to the study design, the relatively long ET period, young age of participants (49 years) and the fact that only one woman was included in the group. While the large disparity between the training and control group highlights the potential of ET rehabilitation in a hospital-based supervised setting, these limitations compromise the interpretation of the study's findings.

It is worth noting that the improvements in $\dot{V}O_2$ peak following training in the abovementioned RCTs, although relatively modest in most cases, surpass the clinically meaningful threshold of 1 $mL \cdot kg^{-1} \cdot min^{-1}$ (or an increase of 10%) for CHF.[214,215] An interesting observation is that those studies with longer program duration and/or higher training intensity seem to result in greater benefit. This suggests that for people with LVADs, a higher intensity of exercise and longer program duration may be required to obtain significant improvements in aerobic capacity.

Although quasi-experimental in nature, several observational retrospective studies have documented significant improvements in aerobic capacity after a period of ET rehabilitation. For instance, Karapolat et al.[216] reported a small but significant improvement in aerobic capacity (14.68 ± 3.63 to 15.13 ± 3.42 $mL \cdot kg^{-1} \cdot min^{-1}$; $p < 0.05$) following an 8-week supervised exercise rehabilitation program involving

aerobic and strength exercises. Similarly, Marko et al.[211] found that a one-month ET regimen was sufficient to detect aerobic capacity gains (11.3 ± 4.1 to 14.5 ± 5.2 mL·kg^{-1}·min^{-1}; p = 0.007) in patients with LVADs. However, these findings warrant caution given the studies' research design.

Current evidence shows conflicting results regarding the impact of ET on $\dot{V}O_2$ peak, assessed by CPET, in patients with LVADs. While findings from low-quality studies suggest that structured and supervised ET may be an effective approach for eliciting aerobic capacity improvements, well-design RCTs have been unable to demonstrate the efficacy of ET. However, these studies were limited by small sample size, short program duration and employed only low- to moderate-intensity of exercise. Therefore, it is conceivable that a longer training period at higher intensities may improve aerobic capacity greater to a greater extent than has been reported to date.

2.8.3 Submaximal exercise capacity

The six-minute walk test (6MWT) is widely used clinically and relatively simple assessment tool that provides a measure of functional capacity as an alternative to CPET. It has been shown that LVAD implantation improves six-minute walk test distance (6MWTD).[1] The MOMENTUM 3 RCT[140] found that implantation of both HMII and HM3 provide similar functional capacity enhancement (assessed by 6MWTD) at 6-month follow up from baseline (HM3: 94 (1–274) vs. HMII: 188 (43–340) m; median and interquartile range). However, the impact of ET on functional capacity is less clear for this patient population.

Consistently with the findings on aerobic capacity, studies to date have been unable to detect a difference comparing ET with the usual care group on submaximal exercise capacity. Although, within-group improvements from baseline to follow up have been reported. For example, Kerrigan et al.[5] observed a 52 m improvement ($p < 0.05$) in the ET rehabilitation group, as opposed to the 19-m increase seen in the control group (NS). However, Hayes et al.[209] observed significant changes on 6MWTD in both the ET training group (Δ180 m), as well as in the control group (Δ122 m). Similarly, Laoutaris et al.[3] observed an increase in 6MWTD by 65 m (p = 0.005) in the training group compared to baseline, whereas the control group only changed by 18 m (NS). It is worth reiterating, that the usual care treatment of the control groups included the

standard recommendation to perform daily walking. This may have reduced the between-group difference in 6MWTD, similar to that observed for $\dot{V}O_2$ peak. Furthermore, despite no trials detecting a significant difference between ET and usual care, the reported values exceeded the minimally clinically important difference for 6MWTD of 45 m for CHF, which has been associated with improvements in QoL.[217]

2.8.4 Muscular strength

Very little information is available on the effect of ET on skeletal muscle strength in patients with LVADs, as only one RCT to date has assessed this outcome.[5] Interestingly, their training intervention did not incorporate a muscle resistance component. It was found that single-leg strength improved (from 85 ± 5 to 100 ± 10 N·m; $p = 0.003$) in the training group, while the control group remained unchanged (at 90 ± 5 N·m) over time. The change between groups was significant ($p = 0.016$). This finding suggests that for LVADs, aerobic training alone may be able to improve skeletal muscle strength. The underlying mechanism of this is not known. One possible explanation is that stimulus provided by aerobic training due to increased muscular blood flow during exercise may have provoked structural and strength improvements on the lower limbs.

While this improvement in muscle function for the training group was relevant, the observed values remained reduced compared with normative data, representing only 51% of age-match individuals.[218] Consequently, incorporating resistance training to ET programs may be a potential option to further improve muscle function and strength in patients with LVADs. This is particularly important given the severe muscle atrophy and wasting[219] that patients with LVADs experience due to the hospitalisation periods (e.g. post-LVAD implantation) and the cachexia induced by CHF. Moreover, muscular strength correlates well with physical disability in CHF patients,[220] and with health-status in LVADs.[195] Therefore, it seems important that further ET studies in LVADs incorporate resistance training component, consistent with best practice, and include muscle strength as an outcome measure to further investigate its potential benefits.

2.8.5 Anthropometry

There is little research in the literature about the impact of ET on body weight or body mass index (BMI) in patients with LVADs. Kugler and colleagues[213] found a significant effect of their multimodal intervention on BMI at 18-month follow-up. While BMI remained unchanged in the intervention group (median: 24.0 to 24.5 kg/m^2), in the control group increased from 23.8 to 29.7 kg/m^2 ($p < 0.02$ for between-group comparison). In contrast, Lamotte et al.,[210] found that BMI increased significantly and to a similar extent in both training (23.2 ± 3.0 to 25.1 ± 3.3 kg/m^2) and control (23.6 ± 2.4 to 25.2 ± 2.7 kg/m^2) groups from baseline to follow-up ($p < 0.01$). However, the interpretation of these results is limited, as BMI does not distinguish between adipose tissue, muscular mass, bone density or oedema, which is a very important component of the medical management of these patients. Accordingly, future studies need to assess the effects of ET on body composition by using more valid and acute methods.

2.8.6 Quality of life

Data from clinical trials suggest that improvement in QoL can be seen post-LVAD implantation from 3 months onwards.[221,222] Of note, female sex and older age are factors that have been associated with a lower score in QoL in this clinical cohort.[223] While results indicate that overall physical function is improved following implantation, likely due to improved functional capacity, many patients continue to experience significant emotional distress.[224] Regular exercise is known to have favourable effects on psychological outcomes in patients with CHF,[225] suggesting that similar benefits may be experienced in LVADs.

Utilising the Kansas City Cardiomyopathy Questionnaire (KCCQ), Kerrigan and co-workers[5] found that the ET group improved QoL (61 ± 8 to 75 ± 5; $p = 0.001$), while the control group remained unchanged (65 ± 5 to 66 ± 5; NS), with a significant difference between groups ($p = 0.005$). Of note, a five-point increment on the KCCQ score is considered clinically meaningful, and it has been found to be a stronger predictor of health-status than 6MWTD.[226] Conversely, Hayes et al.,[209] did not detect differences between the training group (ET: 30.4 ± 10.7 to 59.6 ± 24.2) and the control group (36.7 ± 12.2 to 53.0 ± 6.2; NS) on QoL scores using the SF-36 survey. Although

there were significant improvements only within the training group in several subdomains, such as body pain, vitality, social function, and mental health. Using the same instruments, Kugler et al.,[213] also failed to detect between-group differences in QoL. Laoutaris et al.,[3] using the Minnesota Living with Heart Failure Questionnaire (MLHFQ) found that while the ET group improved QoL (48.9 ± 12.8 to 38.2 ± 11.6 a.u; $p = 0.005$), the control group did not (49.8 ± 9.5 to 50.8 ± 10.3 a.u; $p = 0.3$). But again, there were no between-group differences ($p = 0.3$). The different surveys utilised limits the direct comparison of results across studies. However, it is worth highlighting that all RCT to date have detected within-group improvements in QoL following ET. The only study[5] which detected a significant difference compared with the control group was the one with the biggest sample size. This suggests that the power to detect true differences between groups in the previous trials may have limited the results; and ET may indeed, be able to further improve quality of life following LVAD implantation. Future trials are needed to confirm the impact of ET on QoL for these patient population.

2.8.7 Summary of findings

Studies to date evaluating the effects of ET on maximal and submaximal exercise capacity, strength and QoL in patients with LVADs have been equivocal. Current trials have had a training period ranging from six to ten weeks and used low- to moderate-exercise intensity. It is possible that these training protocols may have been too conservative and applied a suboptimal exercise intervention. The more encouraging findings from several quasi-experimental studies, such as non-randomised prospective, pilot studies documented in conferences and retrospective analysis, suggest that further research is warranted. Compelling evidence is growing in people with cardiovascular disease[227], including CHF[63], that greater improvements can be achieved with higher exercise intensity and with longer training periods. Thus, it is possible that a longer training period, with higher exercise-intensity training, may provide better clinical outcomes without increased risk. Moreover, the RCTs to date have included predominantly males who were supported for ‘bridge-to-transplant’, limiting the generalisability of the findings. Given that the proportion of LVADs indicated as a ‘destination therapy’ has progressively increased over the last decade, and now represents ~50% of total implants, it is important to include a more diverse

clinical population in future trials. As such, finding from these small single-centre RCTs must be interpreted cautiously.

Future research also needs to further assess the safety and efficacy of optimised ET involving training protocols at a higher intensity of aerobic exercise (>80% $\dot{V}O_2$ peak), as well resistance training, as recommended by best practice,[228] and apply longer program duration (at least 12 weeks) in a cohort of patients that better represents the current population.

Table 2.3 Prospective exercise training trials in patients with LVADs.

Study	Design	Participants	LVAD type	Exercise intervention	Control group	Duration	CPET mode	$\dot{V}O_2$ peak (mL·kg-1·min-1)	Adverse events
Kerrigan[5] (2014)	RCT	16 Ex vs. 7 C Age: 55±13 y.	CF-LVADs	Treadmill + cycling at 60% HR reserve for 30 min.	Standard recommendations to perform daily walking. Received follow-up calls at weeks 2, 4, and 6 week.	3x/week for 6 weeks.	Treadmill	Ex (13.6 ± 3.3 to 15.3 ± 4.4) vs. C (11.2 ± 2.0 to 11.8 ± 2.0), p=0.222.	1 syncope
Adamopoulos[212] (2013)	RCT	16 Ex vs. 16 C Age: Not defined	Not defined	Aerobic training for 45 min at Borg scale 12-14 + plus inspiratory muscle training.	Not defined	3x/week for 12 weeks.	NA	Ex: 17.0 ± 0.8 vs. C: 12.6 ± 0.7; p<0.05.	Not defined
Hayes[4] (2012)	RCT	7 Ex vs. 7 C Age: 49±15 and 46±15 y	CF-LVADs	Aerobic exercise at 50% $\dot{V}O_2$ reserve + resistance training for an hour.	Mobilization protocol: advised to progressively walk at least 5 days a week for 60 min at intensity level of 13 RPE.	3x/week for 8 weeks	Cycle ergometer	Ex (10.5±2.3 to 14.8±4.9) vs C (12.4±1.7 to 15.3±4.4), p=0.43.	None

Laoutaris [3] (2011)	RCT	10 Ex vs. 5 C Age: 37±18 vs 42±15 y	BiVAD, & pulsatile LVADs	Aerobic training for 45 min + supervised inspiratory muscle training.	Advised to walk every day for 30–45 min	3-5x/ week for 10 weeks.	Tread mill	Ex (from 16.8±3.7 to 19.3±4.5) vs c (from 14.9±4 to 14.8±4.2), p=0.1	None
Lamotte[210] (2018)	Non-radomised	11 Ex vs. 4 C Age: 52.5±12 vs. 46.7±14 y		Aerobic exercise at 13-14 on Borg-scale +strength exercises	Not defined	3x/ week for 18 weeks	Cycle ergometer	Exercise group (from 14.5 ± 4.4 to 19.5 ± 8.6) vs. control (from11 ± 5 to 11 ± 2) $p < 0.01$.	2 lipo-thymic episodes.
Kugler[213] (2012)	Non-radomised	34 Ex vs. 36 C Age: 52±2 vs 51±2 y.	CF-LVADs	Home-based exercise + nutritional & psychological support.	Standard recommendations on healthy diet, to exercise on daily basis and to seek the psychosocial support.	18 months	Cycle ergometer	$\dot{V}O_2$ % pred. in exercise group (61 to 69%) vs control (59 to 62%),$p<0.05$.	None

Values presented as mean ± SD. *p*-value for comparison between groups. RCT, randomized controlled trial; Ex, exercise training group; C, control group; CF-LVAD, continuous-flow left ventricular assist device; BiVAD, Biventricular assist device; HR, hear rate.

2.9 Might high-intensity interval training be a safe option for patients with left ventricular assist devices?

From a historical perspective, significant progress has been achieved over the last few decades in terms of exercise prescription for populations with cardiac conditions. Prior to 1988, exercise was considered an absolute contraindication in patients with severely reduced cardiac function as it was believed this represented an increased risk for cardiac events. Our paradigm and understanding regarding the impact of exercise changed with the landmark paper by Sullivan et al.,[229] in which the beneficial effects on central and peripheral haemodynamics following an ET program were first observed. Their findings marked the commencement of a new era that changed the scientific and clinical approach for the treatment of CHF in relation to exercise. Over the past three decades of research, the effects of exercise in CHF have been extensively studied and consistently yield improvements on functional capacity, CHF-related symptoms, quality of life, morbidity and mortality.[230,116] Accordingly, ET has become a well-established evidence-based medical adjunct for the treatment of CHF.

The aerobic exercise modality of training most commonly being used in clinical settings for CHF involves moderate-intensity continuous training (MICT), in accordance with international guidelines.[231] However, in recent years, high-intensity interval training (HIIT) has gained popularity. Initially designed and applied by athletes, a growing body of evidence is showing in patients with metabolic and cardiovascular diseases,[232] including CHF,[233] that HIIT may be well-tolerated and more beneficial than MICT at eliciting improvements in physiological and functional outcomes. These findings have raised the question of whether HIIT should be considered as an alternative, or complementary option, to the standard approach of MICT that is currently applied in clinical practice. However, a general concern relates to the safety of HIIT. While preliminary evidence in CHF seems to indicate that it may be a safe option for selected patients, no data has been reported yet in patients with LVADs.

High-intensity interval training involves periods of vigorous exercise that are interspersed with periods at a lower intensity, or periods of rest, as a means to recover.

The workload employed is relative to the individual's capacity, so it may vary considerably among participants. The basic principle of HIIT is that during the intervals performed at high-intensity, there is a greater physiological stimulus compared with MICT, and therefore has the potential to invoke greater cardiac, vascular and musculoskeletal adaptations. A recent meta-regression analyses[234] in patients with coronary heart disease and CHF looked at study-related factors which determine improvement in aerobic capacity following ET. Interestingly, only exercise intensity was significantly associated with the magnitude of $\dot{V}O_2$ peak improvement.

HIIT has been applied using a variety of protocols, combining different parameters in relation to work/recovery periods, intensity, timing, duration, number of sets, etc. While different protocols have been studied in patients with CHF, there is one that has been notably widespread. Since the impressive results found in 2007 by Wisloff and colleagues[63] after a 12-week program (46% increase in $\dot{V}O_2$ peak in HIIT vs. 14% in MICT), the protocol of 4-min work at 90-95% HR peak, interspersed with 3-min active recovery at 50-70% HR peak for 4 sets on a treadmill has been most commonly applied. This exercise protocol – the so-called 'Scandinavian HIIT Protocol'- has been replicated in several subsequent studies, although yielding disparate results. For instance, the recent multicentre SMARTEX HF trial[235] did not find significant differences in $\dot{V}O_2$ peak in the HIIT versus the MICT group (8.3% vs. 5%, respectively; $p = 0.70$). Furthermore, there were no significant differences between groups in the number of adverse events. An important limitation of the latter trial was that the intensities at which the groups trained varied somewhat from that intended and partially overlapped; 50% of participants in the HIIT group failed to achieve the prescribed intensity, whereas 80% of participants in the MICT group trained at an intensity higher than prescribed. This may reflect the challenge of closely supervising participants across different sites. Furthermore, the HR method for exercise prescription for these patients may not be ideal due to the frequent chronotropic inability and HR drift that they commonly experience during exercise.[236] Rather, prescribing workload corresponding to a percentage of $\dot{V}O_2$ peak adjusting over time for perceived level of effort has been suggested to be more appropriate.[235,236]

Several meta-analyses in CHF have found the superiority of HIIT over MICT at improving aerobic capacity. Haykowsky et al.[237] reported that HIIT was more effective

than MICT for improving $\dot{V}O_2$ peak (mean difference: 2.1 $mL \cdot kg^{-1} \cdot min^{-1}$). With regards to safety, no serious adverse events in participants carrying out HIIT were encountered. In accordance with this, a more recent meta-analysis[238] found that the improvement with HIIT (mean change: 2.6 $mL \cdot kg^{-1} \cdot min^{-1}$) was significantly superior to the MICT (1.4 $mL \cdot kg^{-1} \cdot min^{-1}$). Another systematic review looking at safety data in patients with coronary heart disease and CHF found only one major adverse event (non-fatal) during a HIIT out of 17083 training sessions.[239] On the basis of these findings from systematic reviews with meta-analyses, there is a strong case to be made that well-implemented HIIT may be more effective at improving aerobic capacity in patients with CHF compared with traditional MICT and the risk of adverse events when performed in a medically controlled environment appears to be relatively low. This is an important finding given the prognostic value of $\dot{V}O_2$ peak in predicting mortality.[240]

In patients with LVADs, data is lacking as no study has yet tested the safety and efficacy of HIIT. There is, however, a case-report that applied the Scandinavian HIIT protocol for 8 weeks in a 61-year old male with severe LV dysfunction implanted with an LVAD.[241] The participant tolerated the training well and $\dot{V}O_2$ peak increased from 13.1 to 17.3 $mL \cdot kg^{-1} \cdot min^{-1}$. This case report suggests that HIIT may be feasible and safe in patients implanted with LVADs for improving aerobic capacity. Considering that HIIT has been shown to be more effective than MICT for improving $\dot{V}O_2$ peak in patients with CHF and appears to be associated with low rates of adverse events, similar to MICT it is timely that HIIT be investigated in patients with LVADs.

2.10 Physical activity levels in patients with left ventricular assist devices

Despite the improved cardiac output associated with LVAD implantation, a sizable number of patients continue experiencing exercise intolerance and other heart failure-related symptoms.[2,22,242] As a consequence, activities of daily living and quality of life may be substantially impacted in this population. Specifically in patients implanted with LVADs, there is a paucity of data available in regards to the patterns and intensity of daily PA, as only three studies have been performed to date.[243,244]

A preliminary study in people with LVADs showed that they continued to have a sedentary lifestyle and engaged only in short-duration and low intensity PA (daily average PA range from 0.75 to 1.53 METs).[245] In a more recent study, Granegger et al.[243] found that similar to aerobic capacity, patients with LVADs achieved half of the PA levels that is undertaken in age-matched healthy individuals. In a longitudinal study, Jakovljevic et al.[246] observed that while patients augmented their PA levels significantly over the initial 3 months of recovery period post-LVAD implantation (from 18±8 to 48±17 min/day at moderate-intensity exercise), PA then plateaued, and did not differ compared with the CHF control group (41±12 min/day at moderate-intensity PA). However, the latter study[246] had some limitations that warrant consideration. Firstly, the CHF control group had a $\dot{V}O_2$ peak above the cut-off point for cardiac transplantation; suggesting that participants may have not been well-matched in terms of disease severity. Moreover, all participants were males and had the same LVAD system (Heartware) indicated as s bridge-to-transplant. Given that these factors may directly affect daily PA levels, whether LVAD implantation allows patients with advanced CHF to achieve higher levels of PA than patients of a similar severity of CHF, but no LVAD, remains unclear.

2.11 Conclusions and implications for research

The pathophysiological mechanisms related to exercise intolerance in patients with CHF are complex and multifactorial, involving both central and peripheral factors.[34,36,37] For patients with advanced CHF implanted with an LVAD, despite improved haemodynamic support, exercise capacity remains significantly reduced.[1] This limits their capacity to perform activities of daily living and quality of life compared with healthy age-matched individuals.[1,2] While the underlying mechanisms behind these limitations remain to be fully elucidated, alterations in the vasculature and end-organ function, such as the brain and skeletal muscle may play an important role and are potential targets for ET interventions.[78,103,187]

During low- to moderate-intensity exercise in patients with LVADs, TCO increases proportionately to exercise intensity, with LVAD output contributing in a significant extent. However, this haemodynamic support reaches a plateau from moderate-

intensity to peak exercise, limiting peak oxygen uptake because further increases in TCO must rely on native LV function in a failing heart.[163,164] Likewise, the abnormalities in the periphery associated with CHF are not resolved by LVAD implantation and continue to adversely impact exercise tolerance. Accordingly, ET that specifically targets the periphery may be an important intervention for augmenting exercise capacity during higher exercise intensities.

Relatively little is known about the effects of ET in patients with LVADs, as only three RCTs have been conducted to date.[3-5] These trials have involved conservative training protocols and have failed to improve cardiorespiratory fitness in the training intervention compared with a control group. Recent studies in patients with CHF have investigated HIIT and found it to be a safe and effective approach for improving exercise capacity,[63,237,239] but this promising intervention has not been tested to date in patients with LVADs, and therefore it remains unresolved whether it is feasible, safe and effective for improving $\dot{V}O_2$ peak for this population.

Finally, it is evident that more research is needed to address significant gaps in the understanding of cerebral haemodynamics in relation to exercise in patients with CHF. For example, whether LVAD implantation and ET have an impact on cerebral perfusion at rest and during exercise remains unknown.

Given the increasing prevalence of people supported with LVADs, either temporarily as a bridge to transplant or for the remainder of their life in the case of destination therapy,[204] it is important to better understand the factors limiting exercise capacity, and to test and implement interventions aimed to optimise exercise tolerance. This is an important clinical outcome, given that even a modest improvement in oxygen uptake has prognostic implications in patients with CHF.[215] Sufficient aerobic capacity is also a fundamental requisite for performing activities of daily living, which ultimately affects patient's quality of life. The studies in the present thesis seek to address these research questions in order to extend what is understood about physical activity and exercise in patients with LVADs.

2.12 References

1. Rogers JG, Aaronson KD, Boyle AJ, et al. Continuous flow left ventricular assist device improves functional capacity and quality of life of advanced heart failure patients. J Am Coll Cardiol 2010;55:1826-34.

2. Simon MA, Kormos RL, Gorcsan J, 3rd, et al. Differential exercise performance on ventricular assist device support. J Heart Lung Transplant 2005;24:1506-12.

3. Laoutaris ID, Dritsas A, Adamopoulos S, et al. Benefits of physical training on exercise capacity, inspiratory muscle function, and quality of life in patients with ventricular assist devices long-term postimplantation. European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology 2011;18:33-40.

4. Hayes K, Leet AS, Bradley SJ, Holland AE. Effects of exercise training on exercise capacity and quality of life in patients with a left ventricular assist device: a preliminary randomized controlled trial. J Heart Lung Transplant 2012;31:729-34.

5. Kerrigan DJ, Williams CT, Ehrman JK, et al. Cardiac rehabilitation improves functional capacity and patient-reported health status in patients with continuous-flow left ventricular assist devices: the Rehab-VAD randomized controlled trial. JACC Heart Fail 2014;2:653-9.

6. Visscher MB, Johnson JA. The Fick principle: analysis of potential errors in its conventional application. J Appl Physiol 1953;5:635-8.

7. Higginbotham MB, Morris KG, Williams RS, McHale PA, Coleman RE, Cobb FR. Regulation of stroke volume during submaximal and maximal upright exercise in normal man. Circ Res 1986;58:281-91.

8. Burton DA, Stokes K, Hall GM. Physiological effects of exercise. Continuing Education in Anaesthesia Critical Care & Pain 2004;4:185-88.

9. Whipp BJ, Wasserman K. Oxygen uptake kinetics for various intensities of constant-load work. Journal of applied physiology 1972;33:351-56.

10. Barstow TJ. Characterization of VO2 kinetics during heavy exercise. Med Sci Sports Exerc 1994;26:1327-34.

11. Beck KC, Randolph LN, Bailey KR, Wood CM, Snyder EM, Johnson BD. Relationship between cardiac output and oxygen consumption during upright cycle exercise in healthy humans. Journal of Applied Physiology 2006;101:1474-80.

12. Komajda M, Lam CSP. Heart failure with preserved ejection fraction: a clinical dilemma. European Heart Journal 2014;35:1022-32.

13. Kalogeropoulos AP, Al-Anbari R, Pekarek A, et al. The Right Ventricular Function After Left Ventricular Assist Device (RVF-LVAD) study: rationale and preliminary results. European heart journal cardiovascular Imaging 2016;17:429-37.

14. Muslin AJ. Chapter 37 - The Pathophysiology of Heart Failure. Muscle. Boston/Waltham: Academic Press; 2012.523-35.

15. Mann DL. Heart failure: beyond practice guidelines. Tex Heart Inst J 2006;33:201-03.

16. Rouleau JL, Moye LA, de Champlain J, et al. Activation of neurohumoral systems following acute myocardial infarction. Am J Cardiol 1991;68:80D-86D.

17. Hartupee J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. Nat Rev Cardiol 2017;14:30-38.

18. Conraads VM, Van Craenenbroeck EM, De Maeyer C, Van Berendoncks AM, Beckers PJ, Vrints CJ. Unraveling new mechanisms of exercise intolerance in chronic heart failure: role of exercise training. Heart Fail Rev 2013;18:65-77.

19. Francis GS, Benedict C, Johnstone DE, et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the Studies of Left Ventricular Dysfunction (SOLVD). Circulation 1990;82:1724-9.

20. Conraads VM, Bosmans JM, Vrints CJ. Chronic heart failure: an example of a systemic chronic inflammatory disease resulting in cachexia. Int J Cardiol 2002;85:33-49.

21. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017;136:e137-e61.

22. Jung MH, Gustafsson F. Exercise in heart failure patients supported with a left ventricular assist device. J Heart Lung Transplant 2015;34:489-96.

23. Hayward CS, Salamonsen R, Keogh AM, et al. Effect of alteration in pump speed on pump output and left ventricular filling with continuous-flow left ventricular assist device. ASAIO J 2011;57:495-500.

24. Jacquet L, Vancaenegem O, Pasquet A, et al. Exercise capacity in patients supported with rotary blood pumps is improved by a spontaneous increase of pump flow at constant pump speed and by a rise in native cardiac output. Artif Organs 2011;35:682-90.

25. Pina IL, Apstein CS, Balady GJ, et al. Exercise and heart failure: A statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. Circulation 2003;107:1210-25.

26. Dhakal BP, Malhotra R, Murphy RM, et al. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction: the role of abnormal peripheral oxygen extraction. Circ Heart Fail 2015;8:286-94.

27. Sullivan MJ, Cobb FR. Central hemodynamic response to exercise in patients with chronic heart failure. Chest 1992;101:340S-46S.

28. Franciosa JA, Park M, Levine TB. Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. Am J Cardiol 1981;47:33-9.

29. Hummel YM, Bugatti S, Damman K, et al. Functional and hemodynamic cardiac determinants of exercise capacity in patients with systolic heart failure. Am J Cardiol 2012;110:1336-41.

30. Borlaug BA, Olson TP, Lam CS, et al. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. J Am Coll Cardiol 2010;56:845-54.

31. Borlaug BA, Melenovsky V, Russell SD, et al. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. Circulation 2006;114:2138-47.

32. Borlaug BA. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction. Circ J 2014;78:20-32.

33. Poole DC, Richardson RS, Haykowsky MJ, Hirai DM, Musch TI. Exercise limitations in heart failure with reduced and preserved ejection fraction. J Appl Physiol (1985) 2018;124:208-24.

34. Haykowsky MJ, Tomczak CR, Scott JM, Paterson DI, Kitzman DW. Determinants of exercise intolerance in patients with heart failure and reduced or preserved ejection fraction. J Appl Physiol (1985) 2015;119:739-44.

35. Esposito F, Reese V, Shabetai R, Wagner PD, Richardson RS. Isolated quadriceps training increases maximal exercise capacity in chronic heart failure: the role of skeletal muscle convective and diffusive oxygen transport. J Am Coll Cardiol 2011;58:1353-62.

36. Haykowsky MJ, Brubaker PH, John JM, Stewart KP, Morgan TM, Kitzman DW. Determinants of exercise intolerance in elderly heart failure patients with preserved ejection fraction. J Am Coll Cardiol 2011;58:265-74.

37. Shimiaie J, Sherez J, Aviram G, et al. Determinants of Effort Intolerance in Patients With Heart Failure: Combined Echocardiography and Cardiopulmonary Stress Protocol. JACC Heart Fail 2015;3:803-14.

38. Nilsson KR, Duscha BD, Hranitzky PM, Kraus WE. Chronic heart failure and exercise intolerance: the hemodynamic paradox. Curr Cardiol Rev 2008;4:92-100.

39. Bhella PS, Prasad A, Heinicke K, et al. Abnormal haemodynamic response to exercise in heart failure with preserved ejection fraction. Eur J Heart Fail 2011;13:1296-304.

40. Feletou M. The Endothelium: Part 1: Multiple Functions of the Endothelial Cells-Focus on Endothelium-Derived Vasoactive Mediators. San Rafael (CA)2011.

41. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980;288:373-6.

42. Brown AA, Hu FB. Dietary modulation of endothelial function: implications for cardiovascular disease. The American Journal of Clinical Nutrition 2001;73:673-86.

43. Maiorana A, O'Driscoll G, Taylor R, Green D. Exercise and the nitric oxide vasodilator system. Sports Med 2003;33:1013-35.

44. Nishikawa Y, Ogawa S. Importance of nitric oxide in the coronary artery at rest and during pacing in humans. J Am Coll Cardiol 1997;29:85-92.

45. Joannides R, Richard V, Haefeli WE, et al. Role of nitric oxide in the regulation of the mechanical properties of peripheral conduit arteries in humans. Hypertension 1997;30:1465-70.

46. Brutsaert DL. Cardiac endothelial-myocardial signaling: its role in cardiac growth, contractile performance, and rhythmicity. Physiol Rev 2003;83:59-115.

47. Gevaert AB, Lemmens K, Vrints CJ, Van Craenenbroeck EM. Targeting Endothelial Function to Treat Heart Failure with Preserved Ejection Fraction: The Promise of Exercise Training. Oxid Med Cell Longev 2017;2017:4865756.

48. Kojda G, Hambrecht R. Molecular mechanisms of vascular adaptations to exercise. Physical activity as an effective antioxidant therapy? Cardiovasc Res 2005;67:187-97.

49. Van Craenenbroeck EM, Conraads VM. Endothelial progenitor cells in vascular health: focus on lifestyle. Microvasc Res 2010;79:184-92.

50. Lerman A, Zeiher AM. Endothelial function: cardiac events. Circulation 2005;111:363-8.

51. Fischer D, Rossa S, Landmesser U, et al. Endothelial dysfunction in patients with chronic heart failure is independently associated with increased incidence of hospitalization, cardiac transplantation, or death. Eur Heart J 2005;26:65-9.

52. Katz SD, Hryniewicz K, Hriljac I, et al. Vascular endothelial dysfunction and mortality risk in patients with chronic heart failure. Circulation 2005;111:310-4.

53. Negrao CE, Rondon MU, Tinucci T, et al. Abnormal neurovascular control during exercise is linked to heart failure severity. Am J Physiol Heart Circ Physiol 2001;280:H1286-92.

54. Shoemaker JK, Naylor HL, Hogeman CS, Sinoway LI. Blood flow dynamics in heart failure. Circulation 1999;99:3002-8.

55. Watson A, G Hood S, May C. *Mechanisms of sympathetic activation in heart failure.* Vol 332007.

56. Kitzman DW, Haykowsky MJ, Tomczak CR. Making the Case for Skeletal Muscle Myopathy and Its Contribution to Exercise Intolerance in Heart Failure With Preserved Ejection Fraction. Circ Heart Fail 2017;10.

57. Drexler H, Hayoz D, Munzel T, et al. Endothelial function in chronic congestive heart failure. Am J Cardiol 1992;69:1596-601.

58. Kubo SH, Rector TS, Bank AJ, Williams RE, Heifetz SM. Endothelium-dependent vasodilation is attenuated in patients with heart failure. Circulation 1991;84:1589-96.

59. Hundley WG, Bayram E, Hamilton CA, et al. Leg flow-mediated arterial dilation in elderly patients with heart failure and normal left ventricular ejection fraction. Am J Physiol Heart Circ Physiol 2007;292:H1427-34.

60. Haykowsky MJ, Herrington DM, Brubaker PH, Morgan TM, Hundley WG, Kitzman DW. Relationship of Flow-Mediated Arterial Dilation and Exercise Capacity in Older Patients With Heart Failure and Preserved Ejection Fraction. The Journals of Gerontology: Series A 2013;68:161-67.

61. Hambrecht R, Gielen S, Linke A, et al. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: A randomized trial. JAMA 2000;283:3095-101.

62. Pearson MJ, Smart NA. Aerobic Training Intensity for Improved Endothelial Function in Heart Failure Patients: A Systematic Review and Meta-Analysis. Cardiol Res Pract 2017;2017:2450202.

63. Wisloff U, Stoylen A, Loennechen JP, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. Circulation 2007;115:3086-94.

64. Vuckovic KM, Piano MR, Phillips SA. Effects of exercise interventions on peripheral vascular endothelial vasoreactivity in patients with heart failure with reduced ejection fraction. Heart Lung Circ 2013;22:328-40.

65. Maiorana A, O'Driscoll G, Cheetham C, et al. Combined aerobic and resistance exercise training improves functional capacity and strength in CHF. J Appl Physiol (1985) 2000;88:1565-70.

66. Ashor AW, Lara J, Siervo M, et al. Exercise modalities and endothelial function: a systematic review and dose-response meta-analysis of randomized controlled trials. Sports Med 2015;45:279-96.

67. Matsumoto A, Hirata Y, Momomura S-i, et al. Increased nitric oxide production during exercise. The lancet 1994;343:849-50.

68. Goto C, Higashi Y, Kimura M, et al. Effect of Different Intensities of Exercise on Endothelium-Dependent Vasodilation in Humans. Circulation 2003;108:530-35.

69. Matsuzawa Y, Kwon TG, Lennon RJ, Lerman LO, Lerman A. Prognostic Value of Flow-Mediated Vasodilation in Brachial Artery and Fingertip Artery for Cardiovascular Events: A Systematic Review and Meta-Analysis. Journal of Vascular Surgery 2017;66:959-60.

70. Fulster S, Tacke M, Sandek A, et al. Muscle wasting in patients with chronic heart failure: results from the studies investigating co-morbidities aggravating heart failure (SICA-HF). Eur Heart J 2013;34:512-9.

71. Massie BM, Simonini A, Sahgal P, Wells L, Dudley GA. Relation of systemic and local muscle exercise capacity to skeletal muscle characteristics in men with congestive heart failure. J Am Coll Cardiol 1996;27:140-5.

72. Drexler H, Riede U, Munzel T, Konig H, Funke E, Just H. Alterations of skeletal muscle in chronic heart failure. Circulation 1992;85:1751-9.

73. Sullivan MJ, Knight JD, Higginbotham MB, Cobb FR. Relation between central and peripheral hemodynamics during exercise in patients with chronic heart failure. Muscle blood flow is reduced with maintenance of arterial perfusion pressure. Circulation 1989;80:769-81.

74. Haykowsky MJ, Brubaker PH, Morgan TM, Kritchevsky S, Eggebeen J, Kitzman DW. Impaired aerobic capacity and physical functional performance in older heart failure patients with preserved ejection fraction: role of lean body mass. J Gerontol A Biol Sci Med Sci 2013;68:968-75.

75. Weiss K, Schar M, Panjrath GS, et al. Fatigability, Exercise Intolerance, and Abnormal Skeletal Muscle Energetics in Heart Failure. Circ Heart Fail 2017;10.

76. Mancini DM, Walter G, Reichek N, et al. Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure. Circulation 1992;85:1364-73.

77. Panizzolo FA, Maiorana AJ, Naylor LH, et al. Is the soleus a sentinel muscle for impaired aerobic capacity in heart failure? Medicine & Science in Sports & Exercise 2015;47:498-508.

78. Iliopoulos F, Mazis N. Exercise training in heart failure patients: effects on skeletal muscle abnormalities and sympathetic nervous activity—a literature review. Sport Sciences for Health 2018;14:217-26.

79. Tucker WJ, Lijauco CC, Hearon CM, et al. Mechanisms of the Improvement in Peak VO2 With Exercise Training in Heart Failure With Reduced or Preserved Ejection Fraction. Heart, Lung and Circulation 2018;27:9-21.

80. Hambrecht R, Niebauer J, Fiehn E, et al. Physical training in patients with stable chronic heart failure: effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. J Am Coll Cardiol 1995;25:1239-49.

81. Tzanis G, Philippou A, Karatzanos E, et al. Effects of High-Intensity Interval Exercise Training on Skeletal Myopathy of Chronic Heart Failure. Journal of cardiac failure 2017;23:36-46.

82. Erbs S, Höllriegel R, Linke A, et al. Exercise Training in Patients With Advanced Chronic Heart Failure (NYHA IIIb) Promotes Restoration of Peripheral Vasomotor Function, Induction of Endogenous Regeneration, and Improvement of Left Ventricular Function. Circulation: Heart Failure 2010;3:486-94.

83. Tzanis G, Dimopoulos S, Agapitou V, Nanas S. Exercise intolerance in chronic heart failure: the role of cortisol and the catabolic state. Curr Heart Fail Rep 2014;11:70-9.

84. Williams AD, Carey MF, Selig S, et al. Circuit resistance training in chronic heart failure improves skeletal muscle mitochondrial ATP production rate--a randomized controlled trial. Journal of cardiac failure 2007;13:79-85.

85. Kiilavuori K, Naveri H, Salmi T, Harkonen M. The effect of physical training on skeletal muscle in patients with chronic heart failure. Eur J Heart Fail 2000;2:53-63.

86. Santoro C, Cosmas A, Forman D, et al. Exercise training alters skeletal muscle mitochondrial morphometry in heart failure patients. Journal of cardiovascular risk 2002;9:377-81.

87. Senden PJ, Sabelis LW, Zonderland ML, Hulzebos EH, Bol E, Mosterd WL. The effect of physical training on workload, upper leg muscle function and muscle areas in patients with chronic heart failure. Int J Cardiol 2005;100:293-300.

88. Mandic S, Tymchak W, Kim D, et al. Effects of aerobic or aerobic and resistance training on cardiorespiratory and skeletal muscle function in heart failure: a randomized controlled pilot trial. Clinical Rehabilitation 2009;23:207-16.

89. Hulsmann M, Quittan M, Berger R, et al. Muscle strength as a predictor of long-term survival in severe congestive heart failure. Eur J Heart Fail 2004;6:101-7.

90. Williams LR, Leggett RW. Reference values for resting blood flow to organs of man. Clinical physics and physiological measurement : an official journal of the Hospital Physicists' Association, Deutsche Gesellschaft fur Medizinische Physik and the European Federation of Organisations for Medical Physics 1989;10:187-217.

91. Smith KJ, Ainslie PN. Regulation of cerebral blood flow and metabolism during exercise. Exp Physiol 2017;102:1356-71.

92. Havakuk O, King KS, Grazette L, et al. Heart Failure-Induced Brain Injury. Journal of the American College of Cardiology 2017;69:1609-16.

93. Doehner W, Ural D, Haeusler KG, et al. Heart and brain interaction in patients with heart failure: overview and proposal for a taxonomy. A position paper from the Study Group on Heart and Brain Interaction of the Heart Failure Association. Eur J Heart Fail 2018;20:199-215.

94. Saxena PR, Schoemaker RG. Organ blood flow protection in hypertension and congestive heart failure. Am J Med 1993;94:4S-12S.

95. Zelis R, Sinoway LI, Musch TI, Davis D, Just H. Regional blood flow in congestive heart failure: concept of compensatory mechanisms with short and long time constants. Am J Cardiol 1988;62:2E-8E.

96. Choi BR, Kim JS, Yang YJ, et al. Factors associated with decreased cerebral blood flow in congestive heart failure secondary to idiopathic dilated cardiomyopathy. Am J Cardiol 2006;97:1365-9.

97. Fraser KS, Heckman GA, McKelvie RS, Harkness K, Middleton LE, Hughson RL. Cerebral hypoperfusion is exaggerated with an upright posture in heart failure: impact of depressed cardiac output. JACC Heart Fail 2015;3:168-75.

98. Loncar G, Bozic B, Lepic T, et al. Relationship of reduced cerebral blood flow and heart failure severity in elderly males. The aging male : the official journal of the International Society for the Study of the Aging Male 2011;14:59-65.

99. Vogels RL, Oosterman JM, Laman DM, et al. Transcranial Doppler blood flow assessment in patients with mild heart failure: correlates with neuroimaging and cognitive performance. Congest Heart Fail 2008;14:61-5.

100. Hammond CA, Blades NJ, Chaudhry SI, et al. Long-Term Cognitive Decline After Newly Diagnosed Heart Failure. Circulation: Heart Failure 2018;11:e004476.

101. Iadecola C, Duering M, Hachinski V, et al. Vascular Cognitive Impairment and Dementia: JACC Scientific Expert Panel. J Am Coll Cardiol 2019;73:3326-44.

102. Gruhn N, Larsen FS, Boesgaard S, et al. Cerebral Blood Flow in Patients With Chronic Heart Failure Before and After Heart Transplantation. Stroke 2001;32:2530-33.

103. Brassard P, Gustafsson F. Exercise Intolerance in Heart Failure: Did We Forget the Brain? Can J Cardiol 2016;32:475-84.

104. Georgiadis D, Sievert M, Cencetti S, et al. Cerebrovascular reactivity is impaired in patients with cardiac failure. Eur Heart J 2000;21:407-13.

105. Fu TC, Wang CH, Hsu CC, Cherng WJ, Huang SC, Wang JS. Suppression of cerebral hemodynamics is associated with reduced functional capacity in patients with heart failure. Am J Physiol Heart Circ Physiol 2011;300:H1545-55.

106. Meng L, Hou W, Chui J, Han R, Gelb AW. Cardiac Output and Cerebral Blood Flow: The Integrated Regulation of Brain Perfusion in Adult Humans. Anesthesiology: The Journal of the American Society of Anesthesiologists 2015;123:1198-208.

107. Tzeng YC, Willie CK, Atkinson G, Lucas SJ, Wong A, Ainslie PN. Cerebrovascular regulation during transient hypotension and hypertension in humans. Hypertension 2010;56:268-73.

108. Ainslie PN, Cotter JD, George KP, et al. Elevation in cerebral blood flow velocity with aerobic fitness throughout healthy human ageing. J Physiol 2008;586:4005-10.

109. Fu TC, Wang CH, Lin PS, et al. Aerobic interval training improves oxygen uptake efficiency by enhancing cerebral and muscular hemodynamics in patients with heart failure. Int J Cardiol 2013;167:41-50.

110. Fu TC, Yang NI, Wang CH, et al. Aerobic Interval Training Elicits Different Hemodynamic Adaptations Between Heart Failure Patients with Preserved and Reduced Ejection Fraction. Am J Phys Med Rehabil 2016;95:15-27.

111. Fantini S, Sassaroli A, Tgavalekos KT, Kornbluth J. Cerebral blood flow and autoregulation: current measurement techniques and prospects for noninvasive optical methods. Neurophotonics 2016;3:031411.

112. Willie CK, Colino FL, Bailey DM, et al. Utility of transcranial Doppler ultrasound for the integrative assessment of cerebrovascular function. J Neurosci Methods 2011;196:221-37.

113. Jehn M, Schmidt-Trucksäss A, Schuster T, et al. Daily walking performance as an independent predictor of advanced heart failure: Prediction of exercise capacity in chronic heart failure. American Heart Journal 2009;157:292-98.

114. Lobelo F, Rohm Young D, Sallis R, et al. Routine Assessment and Promotion of Physical Activity in Healthcare Settings: A Scientific Statement From the American Heart Association. Circulation 2018;137:e495-e522.

115. Walsh JT, Charlesworth A, Andrews R, Hawkins M, Cowley AJ. Relation of daily activity levels in patients with chronic heart failure to long-term prognosis. Am J Cardiol 1997;79:1364-9.

116. Ponikowski P, Voors AA, Anker SD, et al. [2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure]. Kardiol Pol 2016;74:1037-147.

117. Briffa TG, Maiorana A, Sheerin NJ, Stubbs AG, et al. Physical activity for people with cardiovascular disease: recommendations of the National Heart Foundation of Australia. Medical Journal of Australia 2006;184:71-5.

118. Klompstra L, Jaarsma T, Strömberg A. Physical activity in patients with heart failure: barriers and motivations with special focus on sex differences. Patient Prefer Adherence 2015;9:1603-10.

119. Dontje ML, van der Wal MH, Stolk RP, et al. Daily physical activity in stable heart failure patients. J Cardiovasc Nurs 2014;29:218-26.

120. Klompstra L, Jaarsma T, Strömberg A. Physical activity in patients with heart failure: barriers and motivations with special focus on sex differences. Patient preference and adherence 2015;9:1603-10.

121. Lee PH, Macfarlane DJ, Lam TH, Stewart SM. Validity of the International Physical Activity Questionnaire Short Form (IPAQ-SF): a systematic review. Int J Behav Nutr Phys Act 2011;8:115-15.

122. Du H, Everett B, Newton PJ, Salamonson Y, Davidson PM. Self-efficacy: a useful construct to promote physical activity in people with stable chronic heart failure. J Clin Nurs 2012;21:301-10.

123. Tierney S, Elwers H, Sange C, et al. What influences physical activity in people with heart failure?: a qualitative study. International journal of nursing studies 2011;48:1234-43.

124. Yates BC, Pozehl B, Kupzyk K, Epstein CM, Deka P. Are Heart Failure and Coronary Artery Bypass Surgery Patients Meeting Physical Activity Guidelines? Rehabilitation Nursing;n/a.

125. Taylor RS, Sagar VA, Davies EJ, et al. Exercise-based rehabilitation for heart failure. The Cochrane database of systematic reviews 2014:CD003331.

126. Dibben GO, Dalal HM, Taylor RS, Doherty P, Tang LH, Hillsdon M. Cardiac rehabilitation and physical activity: systematic review and meta-analysis. Heart 2018;104:1394-402.

127. Tudor-Locke C, Craig CL, Brown WJ, et al. How many steps/day are enough? For adults. Int J Behav Nutr Phys Act 2011;8:79-79.

128. Taylor RS, Long L, Mordi IR, et al. Exercise-Based Rehabilitation for Heart Failure: Cochrane Systematic Review, Meta-Analysis, and Trial Sequential Analysis. JACC: Heart Failure 2019;7:691-705.

129. Slimani M, Ramirez-Campillo R, Paravlic A, Hayes LD, Bragazzi NL, Sellami M. The Effects of Physical Training on Quality of Life, Aerobic Capacity, and Cardiac Function in Older Patients With Heart Failure: A Meta-Analysis. Frontiers in Physiology 2018;9.

130. Jessup M, Brozena S. Heart failure. N Engl J Med 2003;348:2007-18.

131. Goodlin SJ, Hauptman PJ, Arnold R, et al. Consensus statement: palliative and supportive care in advanced heart failure. Journal of cardiac failure 2004;10:200-09.

132. Liotta D, Hall CW, Henly WS, Cooley DA, Crawford ES, Debakey ME. Prolonged assisted circulation during and after cardiac or aortic surgery. prolonged partial left ventricular bypass by means of intracorporeal circulation. Am J Cardiol 1963;12:399-405.

133. DeBakey ME. Left ventricular bypass pump for cardiac assistance. Clinical experience. Am J Cardiol 1971;27:3-11.

134. DeVries WC, Anderson JL, Joyce LD, et al. Clinical use of the total artificial heart. N Engl J Med 1984;310:273-8.

135. Jakovljevic DG, George RS, Nunan D, et al. The impact of acute reduction of continuous-flow left ventricular assist device support on cardiac and exercise performance. Heart 2010;96:1390-5.

136. Larose JA, Tamez D, Ashenuga M, Reyes C. Design concepts and principle of operation of the HeartWare ventricular assist system. ASAIO J 2010;56:285-9.

137. Woyach JA, Heerema NA, Zhao J, et al. Dic(17;18)(p11.2;p11.2) is a recurring abnormality in chronic lymphocytic leukaemia associated with aggressive disease. Br J Haematol 2010;148:754-9.

138. Sabashnikov A, Mohite PN, Weymann A, et al. Outcomes after implantation of 139 full-support continuous-flow left ventricular assist devices as a bridge to transplantation. Eur J Cardiothorac Surg 2014;46:e59-66.

139. Nadziakiewicz P, Szygula-Jurkiewicz B, Niklewski T, et al. Effects of Left Ventricular Assist Device Support on End-Organ Function in Patients With Heart Failure: Comparison of Pulsatile- and Continuous-Flow Support in a Single-Center Experience. Transplantation Proceedings 2016;48:1775-80.

140. Cowger JA, Naka Y, Aaronson KD, et al. Quality of life and functional capacity outcomes in the MOMENTUM 3 trial at 6 months: A call for new metrics for left ventricular assist device patients. J Heart Lung Transplant 2018;37:15-24.

141. Bekelman DB, Havranek EP, Becker DM, et al. Symptoms, depression, and quality of life in patients with heart failure. J Card Fail 2007;13:643-8.

142. Boruah P, Saqib N, Barooah J, Baruah D, Sharma P. Left Ventricular Assist Device: What the Internist Needs to Know. A Review of the Literature. Cureus 2019;11:e4399-e99.

143. Haft J, Armstrong W, Dyke DB, et al. Hemodynamic and exercise performance with pulsatile and continuous-flow left ventricular assist devices. Circulation 2007;116:I8-15.

144. Dunlay SM, Park SJ, Joyce LD, et al. Frailty and outcomes after implantation of left ventricular assist device as destination therapy. J Heart Lung Transplant 2014;33:359-65.

145. Moazami N, Fukamachi K, Kobayashi M, et al. Axial and centrifugal continuous-flow rotary pumps: a translation from pump mechanics to clinical practice. J Heart Lung Transplant 2013;32:1-11.

146. Pennings KA, Martina JR, Rodermans BF, et al. Pump flow estimation from pressure head and power uptake for the HeartAssist5, HeartMate II, and HeartWare VADs. ASAIO J 2013;59:420-6.

147. Lim HS, Howell N, Ranasinghe A. The Physiology of Continuous-Flow Left Ventricular Assist Devices. Journal of cardiac failure 2017;23:169-80.

148. Pagani FD. Continuous-flow rotary left ventricular assist devices with "3rd generation" design. Semin Thorac Cardiovasc Surg 2008;20:255-63.

149. Salamonsen RF, Pellegrino V, Fraser JF, et al. Exercise studies in patients with rotary blood pumps: cause, effects, and implications for starling-like control of changes in pump flow. Artif Organs 2013;37:695-703.

150. Kukucka M, Potapov E, Stepanenko A, et al. Acute impact of left ventricular unloading by left ventricular assist device on the right ventricle geometry and function: Effect of nitric oxide inhalation. The Journal of Thoracic and Cardiovascular Surgery 2011;141:1009-14.

151. Kutty RS, Parameshwar J, Lewis C, et al. Use of centrifugal left ventricular assist device as a bridge to candidacy in severe heart failure with secondary pulmonary hypertension†. European Journal of Cardio-Thoracic Surgery 2013;43:1237-42.

152. Melisurgo G, De Bonis M, Pieri M, et al. Is flow really continuous in last generation continuous flow Ventricular Assist Devices? A comparison between HeartMate II and HeartWare HVAD. HSR Proc Intensive Care Cardiovasc Anesth 2012;4:268-69.

153. Purohit SN, Cornwell WK, Pal JD, Lindenfeld J, Ambardekar AV. Living Without a Pulse. Circulation: Heart Failure 2018;11:e004670.

154. Cornwell WK, Tarumi T, Stickford A, et al. Restoration of Pulsatile Flow Reduces Sympathetic Nerve Activity Among Individuals With Continuous-Flow Left Ventricular Assist Devices. Circulation 2015;132:2316-22.

155. Markham DW, Fu Q, Palmer MD, et al. Sympathetic neural and hemodynamic responses to upright tilt in patients with pulsatile and nonpulsatile left ventricular assist devices. Circulation: Heart Failure 2013;6:293-99.

156. Witman MA, Garten RS, Gifford JR, et al. Further Peripheral Vascular Dysfunction in Heart Failure Patients With a Continuous-Flow Left Ventricular Assist Device: The Role of Pulsatility. JACC Heart Fail 2015;3:703-11.

157. Sansone R, Stanske B, Keymel S, et al. Macrovascular and microvascular function after implantation of left ventricular assist devices in end-stage heart failure: Role of microparticles. J Heart Lung Transplant 2015;34:921-32.

158. Moazami N, Dembitsky WP, Adamson R, et al. Does pulsatility matter in the era of continuous-flow blood pumps? The Journal of Heart and Lung Transplantation 2015;34:999-1004.

159. Khawaja T, Chokshi A, Ji R, et al. Ventricular assist device implantation improves skeletal muscle function, oxidative capacity, and growth hormone/insulin-like growth factor-1 axis signaling in patients with advanced heart failure. Journal of cachexia, sarcopenia and muscle 2014;5:297-305.

160. Andersen M, Gustafsson F, Madsen PL, et al. Hemodynamic stress echocardiography in patients supported with a continuous-flow left ventricular assist device. JACC Cardiovasc Imaging 2010;3:854-9.

161. Reiss N, Schmidt T, Workowski A, et al. Physical capacity in LVAD patients: hemodynamic principles, diagnostic tools and training control. Int J Artif Organs 2016;39:451-59.

162. Brassard P, Jensen AS, Nordsborg N, et al. Central and peripheral blood flow during exercise with a continuous-flow left ventricular assist device: constant versus increasing pump speed: a pilot study. Circ Heart Fail 2011;4:554-60.

163. Martina J, de Jonge N, Rutten M, et al. Exercise hemodynamics during extended continuous flow left ventricular assist device support: the response of systemic cardiovascular parameters and pump performance. Artif Organs 2013;37:754-62.

164. Levine BD, Cornwell WK, 3rd, Drazner MH. Factors influencing the rate of flow through continuous-flow left ventricular assist devices at rest and with exercise. JACC Heart Fail 2014;2:331-4.

165. Jakovljevic DG, George RS, Donovan G, et al. Comparison of cardiac power output and exercise performance in patients with left ventricular assist devices, explanted (recovered) patients, and those with moderate to severe heart failure. Am J Cardiol 2010;105:1780-5.

166. Schmidt T, Bjarnason-Wehrens B, Mommertz S, et al. Changes in Total Cardiac Output and Oxygen Extraction During Exercise in Patients Supported With an HVAD Left Ventricular Assist Device. Artif Organs 2018;42:686-94.

167. McKellar SH, Deo S, Daly RC, et al. Durability of central aortic valve closure in patients with continuous flow left ventricular assist devices. J Thorac Cardiovasc Surg 2014;147:344-8.

168. Camboni D, Lange TJ, Ganslmeier P, et al. Left ventricular support adjustment to aortic valve opening with analysis of exercise capacity. J Cardiothorac Surg 2014;9:93.

169. Imamura T, Kinugawa K, Nitta D, et al. Opening of native aortic valve accomplished after left ventricular assist device implantation in patients with insufficient preoperative Beta-blocker treatment. Int Heart J 2015;56:303-8.

170. Loyaga-Rendon RY, Plaisance EP, Arena R, Shah K. Exercise physiology, testing, and training in patients supported by a left ventricular assist device. J Heart Lung Transplant 2015;34:1005-16.

171. Pak SW, Uriel N, Takayama H, et al. Prevalence of de novo aortic insufficiency during long-term support with left ventricular assist devices. J Heart Lung Transplant 2010;29:1172-6.

172. Noor MR, Bowles C, Banner NR. Relationship between pump speed and exercise capacity during HeartMate II left ventricular assist device support: influence of residual left ventricular function. Eur J Heart Fail 2012;14:613-20.

173. Jakovljevic DG, Birks EJ, George RS, et al. Relationship between peak cardiac pumping capability and selected exercise-derived prognostic indicators in patients treated with left ventricular assist devices. Eur J Heart Fail 2011;13:992-9.

174. Akimoto T, Yamazaki K, Litwak P, et al. Rotary blood pump flow spontaneously increases during exercise under constant pump speed: results of a chronic study. Artif Organs 1999;23:797-801.

175. Muthiah K, Gupta S, Otton J, et al. Body position and activity, but not heart rate, affect pump flows in patients with continuous-flow left ventricular assist devices. JACC Heart Fail 2014;2:323-30.

176. Kerrigan DJ, Williams CT, Brawner CA, et al. Heart rate and VO2 concordance in continuous-flow left ventricular assist devices. Med Sci Sports Exerc 2016;48:363-7.

177. Morgan JA, Paone G, Nemeh HW, et al. Impact of continuous-flow left ventricular assist device support on right ventricular function. J Heart Lung Transplant 2013;32:398-403.

178. Kavarana MN, Pessin-Minsley MS, Urtecho J, et al. Right ventricular dysfunction and organ failure in left ventricular assist device recipients: a continuing problem. The Annals of thoracic surgery 2002;73:745-50.

179. Murninkas D, Alba AC, Delgado D, et al. Right ventricular function and prognosis in stable heart failure patients. Journal of cardiac failure 2014;20:343-9.

180. Muthiah K, Robson D, Prichard R, et al. Effect of exercise and pump speed modulation on invasive hemodynamics in patients with centrifugal continuous-flow left ventricular assist devices. J Heart Lung Transplant 2015;34:522-9.

181. Nakamura M, Ishikawa M, Funakoshi T, Hashimoto K, Chiba M, Hiramori K. Attenuated endothelium-dependent peripheral vasodilation and clinical characteristics in patients with chronic heart failure. Am Heart J 1994;128:1164-9.

182. Meyer B, Mortl D, Strecker K, et al. Flow-mediated vasodilation predicts outcome in patients with chronic heart failure: comparison with B-type natriuretic peptide. J Am Coll Cardiol 2005;46:1011-8.

183. Ambardekar AV, Hunter KS, Babu AN, Tuder RM, Dodson RB, Lindenfeld J. Changes in Aortic Wall Structure, Composition, and Stiffness With Continuous-Flow Left Ventricular Assist Devices: A Pilot Study. Circ Heart Fail 2015;8:944-52.

184. Pitha J, Dorazilova Z, Melenovsky V, et al. The impact of left ventricle assist device on circulating endothelial microparticles - pilot study. Neuro Endocrinol Lett 2012;33 Suppl 2:68-72.

185. Lou X, Templeton DL, John R, Dengel DR. Effects of continuous flow left ventricular assist device support on microvascular endothelial function. Journal of cardiovascular translational research 2012;5:345-50.

186. Sansone R, Stanske B, Keymel S, et al. Macrovascular and microvascular function after implantation of left ventricular assist devices in end-stage heart failure: role of microparticles. The Journal of Heart and Lung Transplantation 2015;34:921-32.

187. Hayward CS, Fresiello L, Meyns B. Exercise physiology in chronic mechanical circulatory support patients: vascular function and beyond. Curr Opin Cardiol 2016;31:292-8.

188. Brooks GA, Fahey TD, White TP. *Exercise physiology: Human bioenergetics and its applications.* Mayfield publishing company; 1996.

189. Jung MH, Hansen PB, Sander K, et al. Effect of increasing pump speed during exercise on peak oxygen uptake in heart failure patients supported with a continuous-flow left ventricular assist device. A double-blind randomized study. Eur J Heart Fail 2014;16:403-8.

190. A. M, M. P, Corra U, et al. Systemic perfusion at peak incremental exercise in left ventricular assist device recipients: artitioning pump and native left ventricle relative contribution. IJC Heart & Vessels 2014;4:40-45.

191. Vignati C, Apostolo A, Cattadori G, et al. Lvad pump speed increase is associated with increased peak exercise cardiac output and vo2, postponed anaerobic threshold and improved ventilatory efficiency. Int J Cardiol 2017;230:28-32.

192. Hayward CS, Salamonsen R, Keogh AM, et al. Impact of left ventricular assist device speed adjustment on exercise tolerance and markers of wall stress. Int J Artif Organs 2015;38:501-7.

193. Fresiello L, Buys R, Timmermans P, et al. Exercise capacity in ventricular assist device patients: clinical relevance of pump speed and power. Eur J Cardiothorac Surg 2016;50:752-57.

194. Dimopoulos S, Diakos N, Tseliou E, et al. Chronotropic incompetence and abnormal heart rate recovery early after left ventricular assist device implantation. Pacing and clinical electrophysiology : PACE 2011;34:1607-14.

195. Kerrigan DJ, Williams CT, Ehrman JK, et al. Muscular strength and cardiorespiratory fitness are associated with health status in patients with recently implanted continuous-flow LVADs. J Cardiopulm Rehabil Prev 2013;33:396-400.

196. Compostella L, Russo N, Setzu T, Compostella C, Bellotto F. Exercise performance of chronic heart failure patients in the early period of support by an axial-flow left ventricular assist device as destination therapy. Artif Organs 2014;38:366-73.

197. Dunlay SM, Allison TG, Pereira NL. Changes in cardiopulmonary exercise testing parameters following continuous flow left ventricular assist device implantation and heart transplantation. Journal of cardiac failure 2014;20:548-54.

198. Schmidt T, Bjarnason-Wehrens B, Bartsch P, et al. Exercise Capacity and Functional Performance in Heart Failure Patients Supported by a Left Ventricular Assist Device at Discharge From Inpatient Rehabilitation. Artif Organs 2018;42:22-30.

199. Stringer WW, Hansen JE, Wasserman K. Cardiac output estimated noninvasively from oxygen uptake during exercise. J Appl Physiol (1985) 1997;82:908-12.

200. Kisaka T, Stringer WW, Koike A, Agostoni P, Wasserman K. Mechanisms That Modulate Peripheral Oxygen Delivery during Exercise in Heart Failure. Annals of the American Thoracic Society 2017;14:S40-S47.

201. Ehrman JK, Gordon PM, Visich PS, Keteyian SJ. *Clinical exercise physiology.* 2013.

202. Joyner MJ, Casey DP. Regulation of increased blood flow (hyperemia) to muscles during exercise: a hierarchy of competing physiological needs. Physiol Rev 2015;95:549-601.

203. Khawaja T, Chokshi A, Ji R, et al. Ventricular assist device implantation improves skeletal muscle function, oxidative capacity, and growth hormone/insulin-like growth factor-1 axis signaling in patients with advanced heart failure. Journal of cachexia, sarcopenia and muscle 2014;5:297-305.

204. Kirklin JK, Pagani FD, Kormos RL, et al. Eighth annual INTERMACS report: Special focus on framing the impact of adverse events. J Heart Lung Transplant 2017;36:1080-86.

205. Ono M, Joshi B, Brady K, et al. Cerebral blood flow autoregulation is preserved after continuous-flow left ventricular assist device implantation. J Cardiothorac Vasc Anesth 2012;26:1022-8.

206. Cornwell WK, 3rd, Tarumi T, Aengevaeren VL, et al. Effect of pulsatile and nonpulsatile flow on cerebral perfusion in patients with left ventricular assist devices. J Heart Lung Transplant 2014;33:1295-303.

207. Bozkurt S. Effect of Cerebral Flow Autoregulation Function on Cerebral Flow Rate Under Continuous Flow Left Ventricular Assist Device Support. Artif Organs 2018;42:800-13.

208. Hammond Christa A, Blades Natalie J, Chaudhry Sarwat I, et al. Long-Term Cognitive Decline After Newly Diagnosed Heart Failure. Circulation: Heart Failure 2018;11:e004476.

209. Hayes K, Leet AS, Bradley SJ, Holland AE. Effects of exercise training on exercise capacity and quality of life in patients with a left ventricular assist device: A preliminary randomized controlled trial. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 2012;31:729-34.

210. Lamotte MX, Chimenti S, Deboeck G, et al. Left ventricular assist device: exercise capacity evolution and rehabilitation added value. Acta cardiologica 2018;73:248-55.

211. Marko C, Danzinger G, Kaferback M, et al. Safety and efficacy of cardiac rehabilitation for patients with continuous flow left ventricular assist devices. European journal of preventive cardiology 2015;22:1378-84.

212. Adamopoulos S, Gouziouta A, Mantzouratou P, et al. Exercise training up-regulates physiological growth signalling in the myocardium of patients wth mechanical circulatory support: relevance to functional recovery. Journal of the American College of Cardiology 2013;61:E666.

213. Kugler C, Malehsa D, Schrader E, et al. A multi-modal intervention in management of left ventricular assist device outpatients: dietary counselling, controlled exercise and psychosocial support. Eur J Cardiothorac Surg 2012;42:1026-32.

214. Kitzman DW. Exercise training in heart failure with preserved ejection fraction: beyond proof-of-concept. J Am Coll Cardiol 2011;58:1792-4.

215. Swank AM, Horton J, Fleg JL, et al. Modest increase in peak VO2 is related to better clinical outcomes in chronic heart failure patients: results from heart failure and a controlled trial to investigate outcomes of exercise training. Circ Heart Fail 2012;5:579-85.

216. Karapolat H, Engin C, Eroglu M, et al. Efficacy of the cardiac rehabilitation program in patients with end-stage heart failure, heart transplant patients, and left ventricular assist device recipients. Transplant Proc 2013;45:3381-5.

217. Shoemaker MJ, Curtis AB, Vangsnes E, Dickinson MG. Triangulating Clinically Meaningful Change in the Six-minute Walk Test in Individuals with

Chronic Heart Failure: A Systematic Review. Cardiopulm Phys Ther J 2012;23:5-15.

218. Harbo T, Brincks J, Andersen H. Maximal isokinetic and isometric muscle strength of major muscle groups related to age, body mass, height, and sex in 178 healthy subjects. Eur J Appl Physiol 2012;112:267-75.

219. Zizola C, Schulze PC. Metabolic and structural impairment of skeletal muscle in heart failure. Heart failure reviews 2013;18:623-30.

220. Savage PA, Shaw AO, Miller MS, et al. Effect of resistance training on physical disability in chronic heart failure. Med Sci Sports Exerc 2011;43:1379-86.

221. Starling RC, Naka Y, Boyle AJ, et al. Results of the post-U.S. Food and Drug Administration-approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation: a prospective study using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). J Am Coll Cardiol 2011;57:1890-8.

222. Miller LW, Pagani FD, Russell SD, et al. Use of a Continuous-Flow Device in Patients Awaiting Heart Transplantation. New England Journal of Medicine 2007;357:885-96.

223. Bogaev RC, Pamboukian SV, Moore SA, et al. Comparison of outcomes in women versus men using a continuous-flow left ventricular assist device as a bridge to transplantation. The Journal of Heart and Lung Transplantation 2011;30:515-22.

224. Maciver J, Ross HJ. Quality of life and left ventricular assist device support. Circulation 2012;126:866-74.

225. Karapolat H, Demir E, Bozkaya YT, et al. Comparison of hospital-based versus home-based exercise training in patients with heart failure: effects on functional capacity, quality of life, psychological symptoms, and hemodynamic parameters. Clinical research in cardiology : official journal of the German Cardiac Society 2009;98:635-42.

226. Flynn KE, Lin L, Moe GW, et al. Relationships between changes in patient-reported health status and functional capacity in outpatients with heart failure. Am Heart J 2012;163:88-94 e3.

227. Ribeiro PA, Boidin M, Juneau M, Nigam A, Gayda M. High-intensity interval training in patients with coronary heart disease: Prescription models and perspectives. Annals of physical and rehabilitation medicine 2017;60:50-57.

228. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Rev Esp Cardiol (Engl Ed) 2016;69:1167.

229. Sullivan MJ, Higginbotham MB, Cobb FR. Exercise training in patients with severe left ventricular dysfunction. Hemodynamic and metabolic effects. Circulation 1988;78:506-15.

230. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1439-50.

231. Selig SE, Levinger I, Williams AD, et al. Exercise & Sports Science Australia Position Statement on exercise training and chronic heart failure. Journal of Science and Medicine in Sport 2010;13:288-94.

232. Levinger I, Shaw CS, Stepto NK, et al. What Doesn't Kill You Makes You Fitter: A Systematic Review of High-Intensity Interval Exercise for Patients with Cardiovascular and Metabolic Diseases. Clinical Medicine Insights Cardiology 2015;9:53-63.

233. Haykowsky MJ, Liang Y, Pechter D, Jones LW, McAlister FA, Clark AM. A meta-analysis of the effect of exercise training on left ventricular remodeling in heart failure patients: the benefit depends on the type of training performed. J Am Coll Cardiol 2007;49:2329-36.

234. Uddin J, Zwisler A-D, Lewinter C, et al. Predictors of exercise capacity following exercise-based rehabilitation in patients with coronary heart disease and heart failure: A meta-regression analysis. European journal of preventive cardiology 2016;23:683-93.

235. Ellingsen O, Halle M, Conraads V, et al. High-Intensity Interval Training in Patients With Heart Failure With Reduced Ejection Fraction. Circulation 2017;135:839-49.

236. Meyer P, Gayda M, Juneau M, Nigam A. High-intensity aerobic interval exercise in chronic heart failure. Curr Heart Fail Rep 2013;10:130-8.

237. Haykowsky MJ, Timmons MP, Kruger C, McNeely M, Taylor DA, Clark AM. Meta-analysis of aerobic interval training on exercise capacity and systolic function in patients with heart failure and reduced ejection fractions. Am J Cardiol 2013;111:1466-9.

238. Gomes-Neto M, Duraes AR, Reis H, Neves VR, Martinez BP, Carvalho VO. High-intensity interval training versus moderate-intensity continuous training on exercise capacity and quality of life in patients with coronary artery disease: A systematic review and meta-analysis. European journal of preventive cardiology 2017;24:1696-707.

239. Wewege Michael A, Ahn D, Yu J, Liou K, Keech A. High-Intensity Interval Training for Patients With Cardiovascular Disease—Is It Safe? A Systematic Review. Journal of the American Heart Association 2018;7:e009305.

240. Ross R, Blair SN, Arena R, et al. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement From the American Heart Association. Circulation 2016;134:e653-e99.

241. Ugata Y, Wada H, Sakakura K, et al. High-Intensity Interval Training for Severe Left Ventricular Dysfunction Treated with Left Ventricular Assist Device. Int Heart J 2018;59:216-19.

242. Allen JG, Weiss ES, Schaffer JM, et al. Quality of life and functional status in patients surviving 12 months after left ventricular assist device implantation. J Heart Lung Transplant 2010;29:278-85.

243. Granegger M, Schloglhofer T, Ober H, Zimpfer D, Schima H, Moscato F. Daily life activity in patients with left ventricular assist devices. Int J Artif Organs 2016;39:22-7.

244. Jakovljevic DG, McDiarmid A, Hallsworth K, et al. Effect of Left Ventricular Assist Device Implantation and Heart Transplantation on Habitual Physical Activity and Quality of Life. American Journal of Cardiology 2014;114:88-93.

245. Hu SX, Keogh AM, Macdonald PS, et al. Interaction between physical activity and continuous-flow left ventricular assist device function in outpatients. J Card Fail 2013;19:169-75.

246. Jakovljevic DG, McDiarmid A, Hallsworth K, et al. Effect of left ventricular assist device implantation and heart transplantation on habitual physical activity and quality of life. Am J Cardiol 2014;114:88-93.

Chapter 3 Experimental study 1

Physical activity levels is higher in patients with left ventricular assist device compared with chronic heart failure

The following chapter has been published as a manuscript in Medicine and Science in Sports and Exercise: Moreno-Suarez I, Liew S, Dembo LG, Larbalestier R, Maiorana A. Physical activity is higher in patients with left ventricular assist device compared with chronic heart failure. Med Sci Sports Exerc 2020;52:1-7.

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Declaration of candidate contribution

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3.1 Introduction

Left ventricular assist devices (LVADs) are implanted to augment cardiac output in patients with advanced chronic heart failure (CHF) which is refractory to conventional medical management. 'Bridging' a patient to cardiac transplantation remains the most common indication for an LVAD, however in recent years LVADs have been used increasingly as 'destination therapy', where the patient has the device for the remainder of their life, resulting in an increasing number of implants occurring worldwide.[1] In addition to improving survival,[2] LVAD implantation is associated with increased exercise tolerance,[3-5] addressing a hallmark symptom of CHF. This provides an opportunity for patients to participate more in cardiac rehabilitation programs, increase walking and engage more in tasks of daily living. However, many patients with LVADs continue to experience impaired exercise tolerance, and peak oxygen consumption ($\dot{V}O_2$) remains well below age-predicted values.[6-8] There are currently only limited data available regarding the patterns and intensity of daily physical activity (PA) in patients with an LVAD *in situ.*[9,10] Recent studies have observed that while PA levels improve over the initial period post-LVAD implantation, they remain markedly below healthy individuals and cardiac transplant patients,[9-11] and were not significantly higher than in patients with CHF without mechanical circulatory support.[10] However, in the latter study, the only longitudinal study to date to compare PA in LVAD directly with patients with CHF, participants in the CHF comparison group were deemed "too well" for cardiac transplantation based on their $\dot{V}O_2$ peak and were therefore not well matched to the LVAD cohort. Furthermore, participants in that study were all males, relatively young (mean age = 49 years), and all had received the one device (Heartware). Accordingly, whether LVAD implantation improves daily PA compared with patients with CHF of similar severity, and in a cohort more representative of the contemporary population of LVAD recipients, remains unresolved. Of particular importance is whether PA is higher in a cohort of patients with LVADs beyond the initial post-implantation period, compared with patients with CHF. The primary objective of the present study was to evaluate daily PA levels in patients with LVAD support compared to well-matched participants with advanced CHF without LVAD support.

3.2 Methods

3.2.1 Participants

This was a case controlled study of PA in patients with LVADs versus well-matched patients with CHF, but no LVAD. Participants were recruited from the Advanced Heart Failure and Cardiac Transplant Service at Royal Perth Hospital/Fiona Stanley Hospital. Participants in the LVAD group had an LVAD *in situ* for at least six weeks and were hemodynamically stable. All patients with an LVAD in situ or receiving an LVAD during the study recruitment period, who met the selection criteria, were invited to participate in the study. Each participant with an LVAD was matched for age (± 5 years), sex and New York Heart Association (NYHA) functional class pre-LVAD implantation with a control participant. The control group was recruited from patients with severe heart failure (NYHA III/IV) who were either wait-listed for cardiac transplantation or had been considered for transplant but excluded for non-cardiac reasons in order to have a control group who were well-matched in terms of clinical severity of CHF. All participants from both groups were enrolled in the hospitals' cardiac rehabilitation program, which included supervised exercise sessions. Potential participants were excluded from the study if they had contraindications to exercise testing[12] (e.g. unstable angina, uncontrolled arrhythmias, hypertension, severe symptomatic aortic valve stenosis, acute systemic infection) or myocardial/skeletal muscle ischaemia, severe musculoskeletal disorders, respiratory disease or other non-heart failure related causes of exercise intolerance likely to influence the ability to undertake PA. Data are provided on aerobic capacity and anthropometry for the CHF group only at the time of PA assessment. For the LVAD group, aerobic capacity and anthropometry are provided at the time of PA assessment, as well as from prior to implantation, for comparison with the CHF group and to allow a pre-post comparison in the LVAD group.

3.2.2 Assessments

3.2.2.1 Aerobic capacity assessment

Cardiopulmonary exercise testing (CPET) was performed using a graded treadmill exercise test to volitional exhaustion with three-minutely increments in grade and/or speed.[13] Prior to the test patients were weighed in light clothing, and for LVAD participants, without the weight of the controller or batteries. Breath-by-breath expired gas analysis was measured by indirect calorimetry using a calibrated metabolic analysis system (Vyntus Jaeger CPX, Carefusion, Hoechberg, Germany) and used to determine ventilatory parameters at rest and during exercise. $\dot{V}O_2$ peak was calculated as the highest $\dot{V}O_2$ recorded during the exercise test averaged over a 30-second period. Twelve-lead electrocardiogram (PC-ECG 1200, Norav Medical Ltd., Yokneam, Israel), pulse oximetry (Oxypleth 520A, Novametrix Medical Systems Inc., Wallingford, Connecticut, USA) were measured continuously at rest and throughout exercise. Mean arterial pressure (MAP) (Dopplex MD2, Huntleigh Healthcare Ltd., Cardiff, UK) and rating of perceived exertion (Borg Category Scale)[14] were recorded during the final 30 seconds of each three-minute stage and at peak exercise.[15,16] Serial cardiopulmonary exercise testing is employed in the service where the study was conducted. All patients in the CHF group had at least one cardiopulmonary exercise test prior to the test employed for the study. In the LVAD group, three participants did not have a cardiopulmonary exercise test prior to LVAD implantation due to the device being implanted as an emergency intervention, soon after referral to the service. The pre-LVAD cardiopulmonary exercise test was routinely conducted in the fortnight preceding LVAD implantation, while post LVAD implantation cardiopulmonary exercise tests were conducted at the time of PA activity assessment (Table 3.1).

3.2.2.2 Physical activity assessment

Physical activity energy expenditure (PAEE) was monitored for at least seven consecutive days. Participants were fitted with the Actiheart device immediately following the CPET, but data was analysed from the following to ensure a full day of recording. Participants were instructed not to alter their usual PA during the week of monitoring, including maintaining their scheduled cardiac rehabilitation sessions. Follow-up phone calls from an investigator were made to participants to address any issues that they were experiencing with the monitoring device. Daily PAEE was

measured as active energy expenditure ($kJ \cdot kg^{-1} \cdot day^{-1}$) by using an Actiheart monitoring device (Cambridge Neurotechology Ltd., Cambridge, U.K.) which combines accelerometry and heart rate (HR) monitoring simultaneously. Heart rate response have previously been found to be a reliable indicator of PA intensity in patients with LVADs.[17] The Actiheart monitor was attached to participants' upper chest horizontally, via two ECG electrodes, positioned at the level of third intercostal space. The device was individually calibrated and set up to collect data over one minute epochs. The Actiheart has been validated against doubly labelled water for measuring energy expenditure under free-living conditions and during different conditions such as at rest, walking and running.[18-20] At the end of the Actiheart monitoring period, participants returned the device to the researchers and data were downloaded for subsequent data analysis. PAEE was calculated using the branched equation model for adults described by Brage et al.,[21] and converted to metabolic equivalent of task (MET) to determine minutes of sedentary time (< 1.5 METs), and activity performed at conventional levels of low (1.5 - 3.0 METs), moderate (> 3.0 – 6.0 METs) and vigorous (METs > 6.0) intensity.

3.2.2.3 Self-efficacy and quality of life assessment

A 16-item Heart Disease Self-Efficacy (HDSE) Scale, modified slightly from a previously validated PA scale[22,23] to make it more appropriate for patients with heart disease, was administered to all participants prior to the commencement of the PAEE monitoring period. This scale was used to rate the perceived ability of the participants to begin, continue and complete PA under a range of specific circumstances. The scale measures the strength of efficacy beliefs against a 100-point scale, ranging in 10-unit intervals from '0' (cannot do), through '50' (moderately certain can do), to 100 (absolutely certain can do).

Health-related quality of life (QoL) was measured using the SF-36 questionnaire. This tool measures a variety of health domains and gives two aggregate summary measures: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). These scores rank in a scale from 0-100, where the higher the score, the less disability.[24]

The study was approved by the Royal Perth Hospital Research Ethics & Governance Unit (REG13-122) and reciprocal ethics was granted by Curtin University Human Ethics Research Committee (HR147/2013). The study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12614000233628). All participants provided written informed consent prior to enrolment in the study.

3.2.3 Data analysis

A statistical power test was performed assuming a between group difference on PAEE of 12 $kJ \cdot kg^{-1} \cdot day^{-1}$ with a standard deviation (SD) of 8 $kJ \cdot kg^{-1} \cdot day^{-1}$,[10] with a p-value of 5% for significance at a power of 80%. Factoring in a conservative dropout rate of 15%, we aimed to recruit a total sample size of 32 participants. Statistical analysis was performed using Windows SPSS 25 software (SPSS, Chicago, IL, USA). Student's paired *t*-test was used to assess the within-group changes from pre- to post-implantation in the LVAD group. Between groups comparison was performed using unpaired Student's *t*-test for normally distributed data or the Mann-Whitney *U*-test for nonparametric data, as appropriate. For nominal data, the chi-squared was used. To determine the associations between continuous variables either Pearson's or Spearman's rank correlation coefficient was applied, depending on whether the data were parametric or not. Data are presented as mean ± SD for normally distributed data and median and interquartile range for nonparametric data. All statistical analysis were two-tailed with statistical significance set at $p < 0.05$.

3.3 Results

3.3.1 Participants' characteristics

Thirty-two participants were recruited and completed the study (16 LVAD and 16 CHF). Detailed participant characteristic are described in Table 3.1. Of the available LVAD patients during the recruitment period, we excluded one patient due to severe back pain who was bed bound and one patient with severe respiratory disease. Two other patients were invited to take part in the study but declined. No significant differences were observed for age, weight, or NYHA functional class between the LVAD and CHF groups. Weight and BMI were higher in the LVAD group post

implantation compared with pre implantation ($p < 0.001$). Male sex was predominant (82%). No participants in either group were receiving intravenous inotropes at the time of testing. All participants in the LVAD group were implanted with a continuous-flow LVAD: HeartWare (HeartWare Inc, Framingham, Massachusetts) (25%), HeartMate II (56%) and HeartMate 3 (19%) (Thoratec Corporation, Pleasanton, CA).

Table 3.1 Characteristics of participants in the LVAD and CHF groups

Parameter	LVAD group (n=16)		CHF group (n=16)	
	Pre-LVAD implantation	Post-LVAD implantation		*p*-value
Age (years)	59.1 ± 10.8	-	58.3 ± 8.7	0.808
Female sex	3 (19%)	-	3 (19%)	
Weight (kg)	78.7 ± 11.6	84.8 ± 15.3*	79.1 ± 12.9	0.234
BMI ($kg \cdot m^{-2}$)	26.9 ± 3.3	28.1 ± 4.2*	25.8 ± 3.2	0.353
Ischemic cardiomyopathy	7 (44%)	-	8 (50%)	
Duration of HF diagnosis (years)		7.7 ± 7.5 (0-24)	5.9 ± 6.2 (0–19)	0.662
NYHA functional class, n (%)				0.710
III	5 (31%)		6 (38%)	
IV	11 (69%)		10 (63%)	
INTERMACS profile, n (%)				
3	5 (31%)			
4	3 (19%)			
5	4 (25%)			
6	4 (25%)			
LVEF (%)	22.2 ± 9.2	-	25.3 ± 7.5	0.321
Days on LVAD support	-	154 ± 138 (82-580)	-	

Indication for LVAD, n (%)				
Bridge-to-transplant	9 (16%)			
Bridge-to-candidacy	2 (13%)			
Bridge-to-recovery	1 (6%)			
Destination therapy	4 (25%)			
MAP (mmHg)	80.3 ± 7.9	87.3 ± 9.8	78.8 ± 6.8	0.663
CRT/CRTD, n (%)		3 (19%)	2 (13%)	0.122
Medication, n (%)				
Levosimendan infusion		11 (69%)	9 (56%)	0.455
ACE-I or ARB		15 (94%)	13 (81%)	0.274
β-blockers		13 (81%)	12 (75%)	0.687
Aldosterone antagonist		6 (38%)	6 (50%)	0.501
Warfarin		16 (100%)	3 (19%)	0.001
Diuretics		14 (88%)	13 (81%)	0.590
Amiodarone		3 (19%)	7 (44%)	0.134
Antiplatelet agents		14 (88%)	9 (56%)	0.051
Phosphodiesterase inhibitor (PDE-5)		9 (56%)	5 (31%)	0.150

Data are presented as mean ± standard deviation and (range) or number of participants (percentage); LVAD, left ventricular assist device; CHF, chronic heart failure; BMI, body mass index; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; CRTD; cardiac resynchronization therapy defibrillator; ACE-I, angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; *p*-values in the table are for comparison between pre-LVAD implantation and CHF group. "levosimendan infusion" reflects an infusion at any time prior to the physical activity assessment. *denotes significant within-group difference (from pre- to post-LVAD) by paired *t*-test.

3.3.2 Aerobic capacity

Pre-implantation $\dot{V}O_2$ peak was not significantly different in the LVAD group compared with the CHF group (Table 3.2). Following LVAD implantation $\dot{V}O_2$ peak was significantly higher in the LVAD compared with the CHF group ($p < 0.025$) and

in the LVAD group post- versus pre-LVAD ($p < 0.001$). The ventilatory efficiency slope ($\dot{V}E/\dot{V}CO_2$) was significantly steeper in the CHF compared with the LVAD group. Peak MAP was higher in the LVAD compared with the CHF group. There were no statistical significant differences between groups on test duration, peak respiratory exchange ratio, peak rating of perceived exertion or peak heart rate.

Table 3.2 Results of the cardiopulmonary exercise testing of participants in the LVAD and CHF groups

Parameter	LVAD group (n=16)		CHF group (n=16)	
	Pre-LVAD	Post-LVAD		*p*-value
$\dot{V}O_2$ peak ($mL \cdot kg^{-1} \cdot min^{-1}$)	10.4 ± 2.1	15.8 ± 4.3**	12.3 ± 3.5	0.021
% of age-predicted	36.2 ± 9.6	53.4 ± 15**	38.8 ± 10.1	0.012
$\dot{V}O_2$ peak ($L \cdot min^{-1}$)	0.82 ± 0.2	1.35 ± 0.5**	0.97 ± 0.4	0.042
$\dot{V}E/\dot{V}CO_2$ slope	44.3 ± 8.5	32.4 ± 3.5*	43.7 ± 9.6**	< 0.001
Test duration (s)	521 ± 147	616 ± 205	578 ± 190	0.705
Peak RER	1.18 ± 0.2	1.20 ± 0.1	1.16 ± 0.1	0.858
Peak RPE	18.1 ± 0.9	17.0 ± 0.9	16.6 ± 0.8	0.243
Peak MAP (mmHg)	103.9 ± 10.1	111.2 ± 11.5	95.9 ± 18.9	0.019
Peak HR (bpm)	122.3 ± 18	128.6 ± 21.9	126.7 ± 25	0.833

Data are presented as mean ± SD; LVAD, left ventricular assist device; CHF, chronic heart failure; $\dot{V}E/\dot{V}CO_2$, minute ventilation/carbon dioxide production; RER, respiratory exchange ratio; RPE, rating of perceived exertion; MAP, mean arterial pressure; HR, heart rate; $^{**}p < 0.001$ and $^{*}p < 0.05$ for LVAD within-group comparison; *p*-value for comparison between groups (post-LVAD implantation versus CHF group).

3.3.3 Physical activity

Mean daily PAEE levels in the LVAD group were significant higher compared with the CHF group (Figure 3.1). The LVAD group spent more time performing moderate intensity PA than their CHF counterparts, but there was no difference in light or vigorous intensity PA. However, brief bouts of vigorous intensity PA were more common in the LVAD group (44% of participants) compared with the CHF group (19% of participants). Sedentary time was significantly higher in the CHF cohort compared to the LVAD group (Table 3.3).

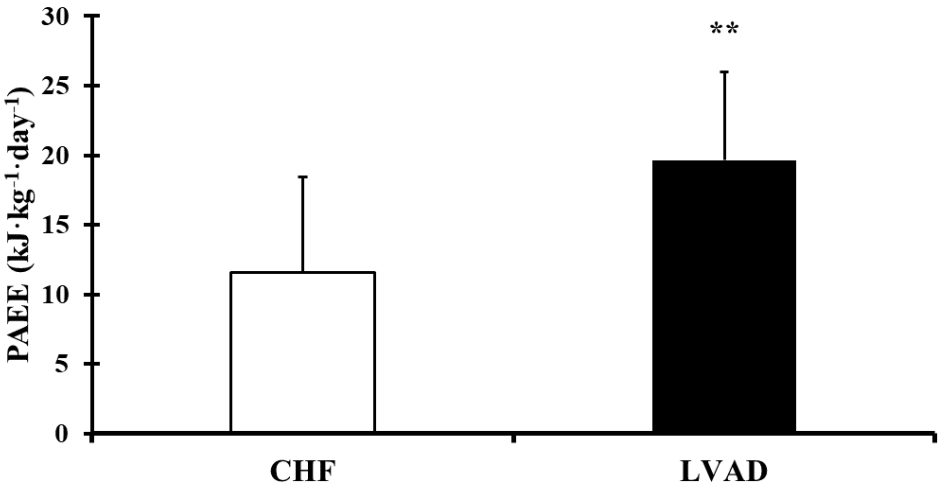

Figure 3.1 Comparison of mean PA levels in the LVAD group versus the CHF group. PAEE, physical activity energy expenditure; CHF, chronic heart failure; LVAD, left ventricular assist device. ** for $p = 0.001$ by independent samples *t*-test.

Table 3.3 Physical activity duration at different intensities in the LVAD and CHF groups.

Physical activity intensity (METs)	LVAD group (min/day)	CHF group (min/day)	*p*-value
Sedentary, including sleeping (< 1.5)	1294 (1265 - 1317)	1329 (1305 - 1360)	0.015*
Light (1.5 - 3)	116 (99 - 148)	99 (73 - 125)	0.136
Moderate (> 3 - 6)	26 (24 - 40)	12 (9 - 16)	<0.001*
Vigorous (> 6.0)	0.5 (0 - 1)	0 (0 - 0.3)	0.126

Values are presented as median (interquartile range); MET, metabolic equivalent of task; LVAD, left ventricular assist device; CHF, chronic heart failure.* *p*-value for between-groups comparison by Mann-Whitney *U* test.

3.3.4 Self-efficacy and quality of life

Table 3.4 presents the results of QoL derived from the SF-36, and self-efficacy from the HDSE scale. There was a significantly higher physical role score, and physical health summary component score in the LVAD group compared with the CHF group. There were no significant differences between groups in the scores from the physical function, pain, general health, vitality, social function and emotional role domains. HDSE score was not significantly different between groups.

Table 3.4 Scores from the SF-36 and Heart Disease Self-Efficacy Scale in the LVAD and CHF groups

Domain	LVAD group	CHF group	*p*-value
SF-36			
Physical Function	56.3 ± 16.1	43.3 ± 23.8	0.080
Physical role	72.4 ± 30.2	44.9 ± 35.2	0.025*
Pain	60.8 ± 21.1	66.8 ± 25.1	0.466
General Health	53.6 ± 24.3	46.6 ± 21.9	0.387
Vitality	55.1 ± 19.7	49.0 ± 18.9	0.381
Social Function	68.3 ± 29.8	69.2 ± 19.7	0.917
Emotional role	79.6 ± 26.1	60.4 ± 37.3	0.101
Mental Health	72.7 ± 18.5	77.6 ± 17.8	0.448
Summary scores			
Physical Health	48.6 ± 13.1	40.5 ± 8.1	0.045*
Mental Health	52.2 ± 11.2	49.3 ± 9.4	0.429

Heart Disease Self-efficacy score	73.8 ± 15.7	68.4 ± 18.7	0.381

Data are presented as mean ± SD; LVAD, left ventricular assist device; CHF, chronic heart failure. * for *p*-value for between groups comparison by independent *t*-test.

3.3.5 Relationship between physical activity and aerobic capacity, quality of life and exercise self-efficacy

There was a significant correlation between PAEE and $\dot{V}O_2$ peak (r = 0.582; $p = 0.001$) across participants in the CHF and LVAD groups (Figure 3.2). Similarly, a negative moderate correlation was detected between PAEE and $\dot{V}E/\dot{V}CO_2$ slope (r = -0.569; $p = 0.001$). Likewise, there was a modest positive correlation between the HDSE Scale score and PA level, which approached statistical significance (r = 0.343; $p = 0.055$). No significant relationship was evident between time on LVAD support (days post-implant) and PAEE (r = 0.306, $p = 0.249$).

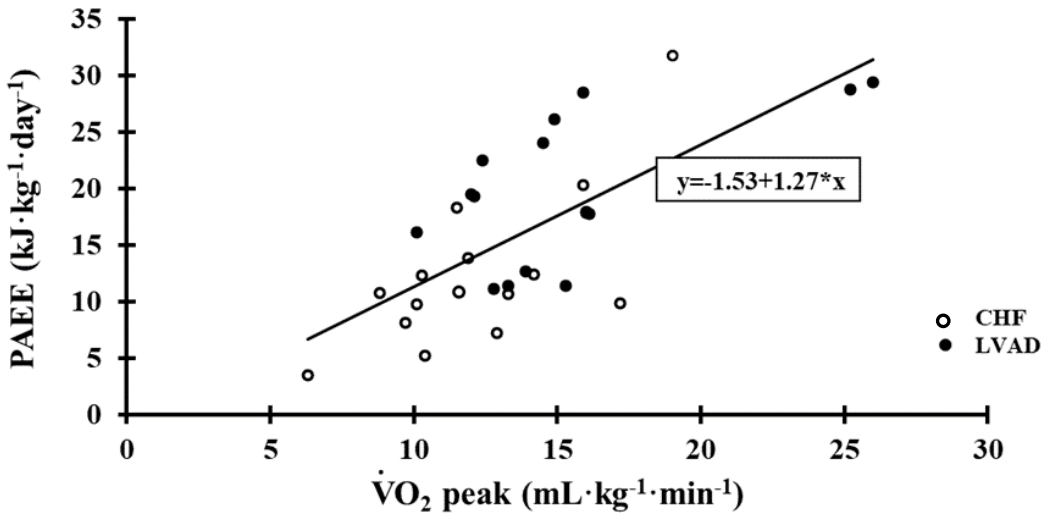

Figure 3.2. Relationship between physical activity and $\dot{V}O_2$ peak. The black line indicates the linear regression across participants. PAEE, physical activity energy expenditure.

3.4 Discussion

In this study investigating PA in patients with an LVAD *in situ*, we observed that participants with LVADs had a significantly higher level of daily PA, and spent less time being sedentary, than patients with CHF who were well-matched for CHF severity. LVAD participants also reported a better QoL as expressed by the physical component score of the SF-36. These findings support that LVAD implantation is important in the functional rehabilitation of patients with advanced CHF.

Daily PAEE was 70% higher for the LVAD group, compared with the CHF group. This finding is in contrast with that reported by Jakovljevic et al.,[10] who did not observe a significant difference in PAEE, between participants 12 months post LVAD implantation compared with CHF controls. These disparate findings may reflect the less severe exercise intolerance in their CHF group, compared with the current study. Indeed, the $\dot{V}O_2$ peak of Jakovljevic's CHF group was closer to that observed in our LVAD group post implantation. In the current study, the average time spent performing PA at any intensity, defined as an energy expenditure > 1.5 METS, was higher in the LVAD group compared with the CHF group. This was due predominantly to a higher volume of moderate intensity PA (26 min/day versus 12 min/day). The converse of this finding related to PA is that CHF participants spent longer each day being sedentary, which has been associated with a multitude of health risks.[25] Similar to the observation of Jakovljevic et al.,[10] we observed that short-bouts of vigorous activity were more common in LVAD participants than those with CHF. It is worth highlighting that LVAD participants in the current study achieved, on average, just below the daily dose of PA recommended for health benefit by evidence-based guidelines for the general population[26] and patients with cardiovascular disease,[27] whereas the CHF group were well below this. However, compared with observations from a large trial of healthy individuals of similar age that also used the Actiheart device, LVAD participants in the current trial had a much lower level of PAEE (19.7 versus 35 $kJ \cdot kg^{-1} \cdot day^{-1}$). This is in accordance with a previous study, which found that PA in patients with LVADs was only 53% of that measured in age-matched healthy subjects.[9] The suboptimal levels of daily PA in patients with LVAD, and more strikingly in advanced CHF, highlight the importance of strategies to increase PA in these groups, despite their exercise limitations.

There are several factors that may influence PA in patients with LVAD compared to those with CHF. Primarily, the augmented cardiac output resulting from the LVAD is likely to improve the delivery of oxygenated blood to the skeletal muscles during activity. It has also been reported that oxidative capacity of skeletal muscle is increased following LVAD implantation.[28] In combination, these two factors will potentiate an increase $\dot{V}O_2$ peak according to the Fick equation. Indeed, we observed a 52% increase $\dot{V}O_2$ peak from pre- to post-LVAD implantation, consistent with previous studies.[29-31] This will enable a given level of submaximal activity to be conducted at a lower percentage of maximum, reducing symptoms of breathlessness and fatigue and translating to greater tolerance of many daily activities. Furthermore, there was a positive correlation between $\dot{V}O_2$ peak and PA in this study, reflecting that aerobic capacity and PA in patients with advanced CHF (with or without an LVAD) are closely associated, consistent with the findings of Graenneger et al.[9] Another factor that may influence PA level is exercise self-efficacy. Several studies in patients with CHF have reported an association between PA levels and self-efficacy,[32,33] and it has recently been proposed as a mediator for being physically active.[34] In the current study, we found a modest positive correlation between self-efficacy and PA levels that approached statistical significance. Further studies involving a larger cohort of patients are required to elucidate this interesting preliminary finding. Finally, an interesting observation in the current study was the increase in weight and BMI in the LVAD group from the pre-implantation, to the post-implantation assessment. Prior to LVAD implantation, patients are often cachectic and this appeared to be at least partially reversed following a period with an LVAD in situ. However, further studies are required to evaluate the relative changes in muscle versus fat mass that may occur following LVAD implantation, and whether increased muscle mass may also be a factor contributing to improved exercise tolerance.

We also considered the relationship between LVAD implantation and QoL in the current study and observed that the physical function domain of the SF-36 was significantly higher in the LVAD compared with the CHF group, which may reflect the capacity of these patients to participate in physical tasks of daily living with less symptoms. However, there was no difference between groups for the mental health summary score. An improvement in QoL has previously been reported following LVAD implantation in several trials.[3,35,36] In the REMATCH-trial,[35] patients with

LVADs had a higher score in the physical function as well as the emotional role domains compared with CHF controls. Similarly, Jakovljevic et al.[10] documented a better QoL, based on the disease specific Minnesota Living with Heart Failure Questionnaire, in LVAD patients compared with patients with CHF. Our results, combined with those from previous studies provide strong evidence that LVAD implantation significantly improves QoL in advanced CHF patients, and this may be due in part to an enhanced tolerance of PA. Importantly, improved capacity for physical activity allows for a more proactive approach to 'rehabilitating' patients from the debilitating effects of CHF, allowing exercise to be prescribed at higher intensities and for longer durations. This is likely to translate to an improved ability to perform tasks of daily living and increase physiological reserve for surgery in those patients awaiting cardiac transplantation.

There are limitations of the present study that warrant highlighting. Firstly, a within group comparison of PA pre- and post-LVAD implantation would have strengthened the research design. However, this would have reduced the study power because over a third of LVAD implants at our centre are emergency cases. Furthermore, this study only involved patients with HeartWare, HeartMate II and HeartMate 3 LVADs and therefore the findings should not be translated to patients with other LVADs. However, our cohort includes the most diverse group of LVAD participants to be included in a study of PA to date, given the inclusion of multiple devices, the broad age range of participants and duration of LVAD support, the inclusion of females and destination therapy patients. Due to the relatively small sample size, it was not possible to perform sub-group analysis between types of LVADs. However, the sample size was consistent with *a priori* power test for the primary outcome of a difference in PAEE. The study may also have been underpowered to identify associations between PA and other outcomes, such as HDSE Scale score, which approached statistical significance, but didn't quite achieve it.

Finally, we undertook PA assessment as early as 82 days post-implantation and it is possible that PA levels may have increased further with prolonged recovery, meaning that the potential difference in PA level between LVAD patients and CHF patients may be greater than we observed.

In conclusion, we observed that patients with an LVAD *in situ* engage in higher levels of PA compared with well-matched patients with advanced CHF without mechanical circulatory support, which appears to be related to greater aerobic capacity. The improved functional capacity evident in patients with LVADs is likely to translate to an enhanced ability to participate more actively in rehabilitative exercise programs and engage in activities of daily living with less symptoms, important clinical objectives in both patients with advanced CHF being bridged to cardiac transplantation, or on long-term LVAD support.

3.5 References

1. Lenneman AJ, Birks EJ. Treatment strategies for myocardial recovery in heart failure. Curr Treat Options Cardiovasc Med 2014;16:287-96.

2. Kirklin JK, Pagani FD, Kormos RL, et al. Eighth annual INTERMACS report: Special focus on framing the impact of adverse events. J Heart Lung Transplant 2017;36:1080-86.

3. Rogers JG, Aaronson KD, Boyle AJ, et al. Continuous flow left ventricular assist device improves functional capacity and quality of life of advanced heart failure patients. J Am Coll Cardiol 2010;55:1826-34.

4. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009;361:2241-51.

5. McDiarmid A, Gordon B, Wrightson N, et al. Hemodynamic, echocardiographic, and exercise-related effects of the heartware left ventricular assist device in advanced heart failure. Congest Heart Fail 2013;19:11-15.

6. Simon MA, Kormos RL, Gorcsan J, et al. Differential exercise performance on ventricular assist device support. J Heart Lung Transplant 2005;24:1506-12.

7. Allen JG, Weiss ES, Schaffer JM, et al. Quality of life and functional status in patients surviving 12 months after left ventricular assist device implantation. J Heart Lung Transplant 2010;29:278-85.

8. Jung MH, Gustafsson F. Exercise in heart failure patients supported with a left ventricular assist device. J Heart Lung Transplant 2015;34:489-96.

9. Granegger M, Schloglhofer T, Ober H, Zimpfer D, Schima H, Moscato F. Daily life activity in patients with left ventricular assist devices. Int J Artif Organs 2016;39:22-7.

10. Jakovljevic DG, McDiarmid A, Hallsworth K, et al. Effect of left ventricular assist device implantation and heart transplantation on habitual physical activity and quality of life. Am J Cardiol 2014;114:88-93.

11. Hu SX, Keogh AM, Macdonald PS, et al. Interaction between physical activity and continuous-flow left ventricular assist device function in outpatients. J Card Fail 2013;19:169-75.

12. Bayles MP. Diagnostic Procedures for Cardiovacular Disease. ACSM's resource manual for guidelines for exercise testing and prescription. 7th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2012.382.

13. Ingle L. Theoretical rationale and practical recommendations for cardiopulmonary exercise testing in patients with chronic heart failure. Heart Fail Rev 2007;12:12-22.

14. Borg G. Measuring Perceived Exertion and Pain. Borg's Perceived exertion and pain scales. 1th ed. Chicago: Human kinetics; 1998.p. 26.

15. Roul G, Germain P, Bareiss P. Does the 6-minute walk test predict the prognosis in patients with NYHA class II or III chronic heart failure? Am Heart J 1998;136:449-57.

16. Cohen-Solal A, Tabet JY, Logeart D, Bourgoin P, Tokmakova M, Dahan M. A non-invasively determined surrogate of cardiac power ('circulatory power') at peak exercise is a powerful prognostic factor in chronic heart failure. Eur Heart J 2002;23:806-14.

17. Kerrigan DJ, Williams CT, Brawner CA, et al. Heart rate and VO2 concordance in continuous-flow left ventricular assist devices. Med Sci Sports Exerc 2016;48:363-7.

18. Crouter SE, Churilla JR, Bassett DR. Accuracy of the Actiheart for the assessment of energy expenditure in adults. Clin Nutr 2008;62:704-11.

19. Mehdi A, Van der Touw T. Actiheart based estimates of body expenditure are accurate during treadmill walking, arm ergometry and bicycle ergometry. J Sci Med Sport 2012;15, Supplement 1:S224-S25.

20. Brage S, Brage N, Franks PW, Ekelund U, Wareham NJ. Reliability and validity of the combined heart rate and movement sensor Actiheart. Clin Nutr 2005;59:561-70.

21. Brage S, Brage N, Franks PW, et al. Branched equation modeling of simultaneous accelerometry and heart rate monitoring improves estimate of directly measured physical activity energy expenditure. J Appl Physiol 2004;96:343-51.

22. Haworth J, Young C, Thornton E. The effects of an 'exercise and education' programme on exercise self-efficacy and levels of independent activity in adults with acquired neurological pathologies: an exploratory, randomized study. Clin Rehabil 2009;23:371-83.

23. Bandura A. Guide for constructing self-efficacy scales. Self-efficacy beliefs of adolescents. Greenwich: Age Information Publishing; 2006.p. 307.

24. MacIver J, Rao V, Ross HJ. Quality of life for patients supported on a left ventricular assist device. Expert Rev Med Devices 2011;8:325-37.

25. Owen N, Healy GN, Matthews CE, Dunstan DW. Too much sitting: the population health science of sedentary behavior. Exerc Sport Sci Rev 2010;38:105-13.

26. WHO. Global recommendations on physical activity for health. 2010. Accessed 15/09/2018.

27. Briffa TG, Maiorana A, Sheerin NJ, et al. Physical activity for people with cardiovascular disease: recommendations of the National Heart Foundation of Australia. Med J Aust 2006;184:71-5.

28. Khawaja T, Chokshi A, Ji R, et al. Ventricular assist device implantation improves skeletal muscle function, oxidative capacity, and growth hormone/insulin-like growth factor-1 axis signaling in patients with advanced heart failure. J Cachexia Sarcopenia 2014;5:297-305.

29. Maybaum S, Mancini D, Xydas S, et al. Cardiac improvement during mechanical circulatory support: a prospective multicenter study of the LVAD Working Group. Circulation 2007;115:2497-505.

30. Lim HS, Howell N, Ranasinghe A. The effect of left ventricular assist device therapy in patients with heart failure and mixed pulmonary hypertension. Int J Artif Organs 2017;40:67-73.

31. Rose EA, Moskowitz AJ, Packer M, et al. The REMATCH trial: rationale, design, and end points. randomized evaluation of mechanical assistance for the treatment of congestive heart failure. Ann Thorac Surg 1999;67:723-30.

32. Rajati F, Sadeghi M, Feizi A, Sharifirad G, Hasandokht T, Mostafavi F. Self-efficacy strategies to improve exercise in patients with heart failure: a systematic review. ARYA Atheroscler 2014;10:319-33.

33. Klompstra L, Jaarsma T, Stromberg A. Physical activity in patients with heart failure: barriers and motivations with special focus on sex differences. Patient Prefer Adherence 2015;9:1603-10.

34. Klompstra L, Jaarsma T, Stromberg A. Self-efficacy mediates the relationship between motivation and physical activity in patients with heart failure. J Cardiovasc Nurs 2018;33:211-16.

35. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med 2001;345:1435-43.

36. Dahrmann B, Sindermann J, Geldmacher T, Heuft G. [Quality of life and mental health of patients with severe heart failure with or without technical support for the left cardiac ventricle - a cross-sectional study]. Z Psychosom Med Psychother 2017;63:388-404.

Chapter 4 Experimental study 2

Cerebral blood flow during exercise in patients with chronic heart failure: the effect of left ventricular assist device

The following chapter was published as a manuscript in Medicine and Science in Sport and Exercise: Smith KJ, Moreno-Suarez I, Scheer A, et al. Cerebral blood flow during exercise in heart failure: effect of ventricular assist devices. Med Sci Sports Exerc 2019;51:1372-79.

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Declaration of candidate contribution

The following Chapter was published as a shared co-first authorship between the candidate, Jose Ignacio Moreno Suarez, and Dr Kurt Smith as they both worked together and contributed equally to the manuscript. The candidate contributed to conception of the experiment, collection analyses of the data, interpreted the results, and drafted the manuscript.

Mr Jose Ignacio Moreno Suarez | PhD Candidate

Associate Professor Andrew Maiorana | Primary supervisor and senior author

4.1 Introduction

Exercise tolerance is impaired in chronic heart failure (CHF), due to diminished cardiac output, impaired lung function and/or peripheral abnormalities in skeletal muscle and vascular function.[1-4] Exercise training, a class I recommendation in CHF,[5] improves functional capacity,[6,7] but impacts on cardiac function are limited and benefits have traditionally been ascribed to improvements in peripheral factors.[2,8] However, recent studies have proposed a potential role for cerebral blood flow (CBF) as a factor in CHF exercise limitation,[1-4] although it was concluded in a review on the topic that further research is needed regarding of the impacts of exercise on brain perfusion during exercise in CHF.[2]

Left ventricular assist devices (LVADs) are increasingly used in patients with advanced CHF.[9] LVADs improve exercise capacity, an effect which may, in part, be due to enhanced cardiac output.[3] LVAD implantation also facilitates exercise rehabilitation, which in turn targets the peripheral skeletal muscle and vascular abnormalities which can limit functional capacity.[10] A recent experiment by Brassard et al.[3] indicated that increasing LVAD pump speed during exercise enhanced cerebral perfusion, cardiac output and exercise tolerance. However, there are currently no data quantifying and comparing volumetric CBF in patients with CHF or with an LVAD *in situ* during incremental exercise. Accordingly, the main objective of the present study was to assess intra-and extra-cranial arterial blood flow, in both anterior and posterior cerebrovascular circulations, at rest and during exercise in patients with an LVAD, against those with CHF (but no LVAD) and healthy controls, who were matched for age and sex.

4.2 Methods

4.2.1 Participants

Nine participants instrumented with a left ventricular assist device (LVADs; age: 57.8 ± 14.6 yr; weight: 87.38 ± 15.98 kg; height: 1.72 ± 0.08 m, 6♂3♀) and nine age and sex-matched patients with chronic heart failure (CHF age; 57.6 ± 8.3 yr; 83.6 ± 11.49 kg; 1.77 ± 0.06 m, 6♂3♀) were recruited from the Advanced Heart Failure Service at Fiona Stanley Hospital (Perth, Western Australia). Nine healthy control participants

(CTRL; age: 54.8 ± 13.9 yr; weight: 73.80 ± 15.76 kg; height: 1.68 ± 0.1 m, 6♂3♀) were contemporaneously recruited to match the age and sex of the participants with LVADs and CHF. All participants with LVADs were recruited greater than 3 months post-LVAD implantation (76 ± 108 weeks) and had been medically stable for at least 4 weeks prior to participating in the study. The LVAD group had an average ejection fraction of 26.1 ± 7.9% (6275 ± 2740 rpm average pump speed). Four participants with an LVAD had a diagnosis of ischemic aetiology, and five had a diagnosis of idiopathic dilated cardiomyopathy. The LVAD systems included three Heartmate II (Thoratec Corporation), two HVAD (HeartWare) and four Heartmate III devices (Thoratec Corporation). The CHF group had an average ejection fraction of 25.0 ± 9.0%, with three participants having an ischaemic aetiology, five having a diagnosis of idiopathic dilated cardiomyopathy, and one had hypertrophic cardiomyopathy. The drug regimens for LVADs and CHF groups are provided in Table 4.1. The healthy CTRL group were not taking any medication.

The study was approved by Fiona Stanley Hospital (FSH) Human Ethics Research Committee (HREC; REG: 2015-164). Curtin University HREC granted reciprocal approval. All aspects of the study complied with the ethical principles outlined by the Declaration of Helsinki. The participants were informed of all experimental procedures and associated risks. Participants provided written informed consent before the commencement of the study.

Table 4.1 List of medications for the LVAD and the CHF groups

Medical therapy	LVAD (n=9)	CHF (n=9)	*p*-value
ACE-I	9 (100%)	5 (56%)	0.04
Angiotensin II receptor blockers	6 (67%)	4 (44%)	0.32
Beta blockers	8 (89%)	7 (78%)	0.50
Clopidogrel	7 (78%)	6 (67%)	0.50
Warfarin	9 (100%)	5 (56%)	0.04
Diuretics	8 (89%)	7 (78%)	0.50
Digoxin	2 (22%)	4 (44%)	0.32
Aspirin	5 (56%)	5 (56%)	0.68

Sildenafil	3 (33%)	2 (22%)	0.50
Amiodarone	4 (44%)	5 (56%)	0.50

Fisher's exact test conducted on the frequency of use.

4.2.2 Procedures

After inclusion, participants were tested in the Exercise Physiology laboratory of the Advanced Heart Failure and Cardiac Transplant Unit at FSH. Participants visited the laboratory on one occasion, in a fasted state (~ 6 hours), having abstained from alcohol, caffeine and vigorous exercise for 24-hours. Upon arrival, participants were instrumented and underwent a 10 min rest period in a semi-recumbent position. Baseline (BL) recordings of the primary outcome measures were then collected during a further 5-minute period of quiet rest. Resting measures were collected during the final minute of this period. Subsequently, participants performed a cardiopulmonary exercise test (CPET) on a recumbent cycle ergometer (Angio imaging ergometer, Lode, Netherlands), with starting workloads of 15 Watts for LVADs and CHF, and 45 Watts for CTRLs. The exercise intensity increased by 15-watts every 2 minutes until volitional exhaustion. Peak oxygen consumption ($\dot{V}O_2$ peak) was calculated as the highest $\dot{V}O_2$ recorded during the exercise test, averaged over a 30-second period. Cerebrovascular (transcranial Doppler and duplex vascular ultrasound) and cardiorespiratory assessments were continuously collected and compared using the relative workloads (i.e., 20, 40 and 60% of the maximum achievable workload [%Wmax]).

4.2.3 Cerebrovascular assessment

Non-invasive insonation via 2MHz transcranial Doppler ultrasound (TCD; Spencer Technologies, Seattle, WA) was used to assess blood velocity in the middle (MCAv) and posterior (PCAv) cerebral arteries continuously during exercise by transfixing the probes to a specialized head frame (Marc 600, Spencer Technologies, Seattle, WA). The cerebral arteries were identified and optimised according to their signal depth, waveform and velocities, in keeping with previously published guidelines.[11] The MCAv and PCAv were continuously sampled at baseline, and throughout the

incremental CPET at 1000Hz via an analogue-to-digital converter (Powerlab, 16/30 ADInstruments, Colorado Springs, CO, USA), and analysed offline using a specialized analytical software package (LabChart 8, ADInstruments, Colorado Springs, CO, USA).

Blood velocity and diameter of the internal carotid artery (ICA) and vertebral artery (VA) were measured using a 10-15MHz multi-frequency linear array vascular ultrasound (Terason T3200, Teratech, Burlington, MA).[12,13] The ICA and VA recordings were captured at baseline and ICA recordings were continuously captured throughout the incremental exercise test using identical techniques as previously outlined by our research group.[14-16] Briefly, blood velocity and diameter of both arteries was measured using a 10-15MHz multi-frequency linear array vascular ultrasound. B-mode imaging was used to measure arterial diameter, while simultaneously captured pulse-wave mode was used to concurrently measure peak blood flow velocity.[13,17] Diameter and velocity were measured at least 1.5 cm distal to arterial bifurcations to eliminate recordings of turbulent and retrograde flow and non-uniform shear. Care was taken to ensure that the insonation angle (60°) was unchanged throughout each test and there were no alterations of B-mode settings after acquisition of the resting baseline to avoid any artificial changes in arterial wall brightness/thickness. All recordings were made in accordance with our published guidelines,[12,13] with screen capture and storage of video files for offline analysis.[17] This analysis involved concurrent determination of arterial diameter and peak blood velocity at 30Hz, using our customized edge detection and wall tracking software which is automated and designed to mitigate observer bias. We have published extensive reproducibility data using this approach[17] and our *within* day coefficient of variation for the assessment of ICA diameter is 1.5% using this technique.[18] Blood flow and shear rate were calculated as previously described.[14-16,19] It was not technically possible to capture VA responses during exercise due to the challenges of imaging these vessels during movement in the exercising patients.

Twelve-lead electrocardiogram (PC-ECG 1200, Norav Medical Ltd., Yokneam, Israel) and pulse oximetry (Oxypleth 520A, Novametrix Medical Systems Inc., Wallingford, Connecticut, USA) were measured continuously at rest and throughout the CPET. Workloads relative to individual Wmax were compared at 20, 40 and 60%

Wmax. All of the ICA and VA recordings were screen-captured and stored as video files for offline analysis.[17] Arterial blood pressure (MAP) in CTRLS and CHF was assessed using finger-based photoplethysmography (Finometer Pro, Finapres Medical Systems, Amsterdam, the Netherlands) with manual brachial oscillometry for calibration purposes, whereas MAP was measured using Doppler ultrasound (Dopplex MD2, Huntleigh Healthcare Ltd., Cardiff, UK) on the radial artery, which is considered an adequate surrogate measure in patients LVADs who do not typically exhibit an adequate pulse for oscillometric approaches.[20] These assessments of MAP were recorded during the final 30 seconds of each two-minute stage and at peak exercise. Partial pressure of oxygen ($P_{ET}O_2$) and carbon dioxide ($P_{ET}CO_2$) were assessed from a sample tube connected to the mouthpiece using a gas analyser (ADInstruments, Colorado Springs, CO). All cardiorespiratory variables were sampled continuously throughout the CPET protocol. Breath by breath $\dot{V}O_2$ and minute ventilation ($\dot{V}_E$) were measured via indirect calorimetry (Vyntus CPX, Jaeger, CareFusion, Germany).

The CPET workloads relative to individual Wmax were compared at 20, 40, 60% of Wmax for all variables. All of the ICA recordings were screen-captured and stored as video files for offline analysis.[17]

4.2.4 Statistical analyses

Statistical and graphing analysis was performed using GraphPad PRISM 6.01 software (GraphPad Software, LaJolla, CA, USA). All data were normally distributed. All absolute data parameters were compared using two-way repeated-measures ANOVA, whilst changes from baseline scores were compared using a one-way ANOVA. Bonferroni-correction for multiple comparisons were used for all post-hoc analysis of the mean changes from baseline, standard error of the difference and 95% confidence intervals (CIs) are provided as indices of variability. Statistical significance was *a priori* set at $p < 0.05$. All data in tables and figures are reported as mean ± standard deviation (SD) unless otherwise stated.

4.3 Results

4.3.1 Comparison between groups at rest

4.3.1.1 Cardiorespiratory measures

All cardiorespiratory measures can be found in Table 4.2. No differences were observed between BL values of $\dot{V}O_2$, or $P_{ET}CO_2$ in LVAD, CHF and CTRL groups. In contrast, compared to CTRL, MAP was reduced at rest in LVAD (Δ-14 ± 2 mmHg, $p < 0.0001$) and CHF (Δ-24 ± 2 mmHg, $p < 0.0001$). Resting MAP was higher in LVADs that CHF subjects (Δ+10 ± 2 mmHg, $p < 0.001$).

4.3.1.2 Cerebrovascular measures

Cerebrovascular measures obtained for the internal carotid, as well as middle and posterior cerebral arteries are listed in Table 4.2. At BL, ICA haemodynamics (velocity, shear stress and flow), as well as velocities in the MCA and PCA, were greater in LVADs (and CTRLs) compared to CHF participants (Figures 4.1 & 4.2; $p < 0.05$). ICA diameter was reduced in LVAD participants compared with CHF and also the CTRLs ($p < 0.05$). Higher levels of MCAv (Δ+ 5.52 ± 1.59 $cm.s^{-1}$, CI = 1.68 to 9.36, $p = 0.003$) and PCAv (Δ+ 5.82 ± 1.41 $cm.s^{-1}$, CI = 1.85 to 8.69, $p = 0.001$) were observed in LVAD patients than healthy controls. Blood flow in the VA at BL was not significantly different in CTRL, LVAD or CHF participants.

Table 4.2 Cardiorespiratory and cerebrovascular measures during incremental exercise in the LVAD, CHF and CTRL groups.

Variable	Group	BL	20%W_{max}	40% W_{max}	60% W_{max}	Stats
$\dot{V}O_2$ (ml·kg^{-1}·min^{-1})	LVAD$^{\phi}$	3.2 ± 0.3	6.2 ± 1.5*$^{\phi}$	7.8 ± 2.0*$^{\phi}$	9.5 ± 2.9*$^{\phi}$	*Exercise: p < 0.0001;*
	CHF$^{\phi}$	3.6 ± 0.6	8.1 ± 3.0*$^{\phi}$	9.7 ± 3.4*$^{\phi}$	11.4 ± 3.9 *$^{\phi}$	*Group: p = 0.0008;*
	CTRL	3.3 ± 0.5	13.2 ± 3.0*	15.6 ± 3.5*	19.0 ± 4.6*	*Interaction: p < 0.0001*
% $\dot{V}O_2$ peak	LVAD	27.0 ± 7.6	50.9 ± 13.6*$^{\phi}$	62.8 ± 17.1*$^{\phi}$	75.4 ± 18.3*$^{\phi}$	*Exercise: p < 0.0001;*
	CHF	29.2 ± 5.7	64.1 ± 11.3*	76.1 ± 9.1*	89.4 ± 9.2*	*Group: p = 0.01;*
	CTRL$_{\varphi}$	14.8 ± 6.6φ	51.1 ± 14.2*φ	62.0 ± 16.8*φ	72.2 ± 18.5*φ	*Interaction: p < 0.01*
Workload (watts)	LVAD	15 ± 0	28.0± 3.0$^{\phi}$	41.0 ± 5.9*$^{\phi}$	54.0 ± 8.9*$^{\phi}$	*Exercise: p < 0.001;*
	CHF	15 ± 0	27.8 ± 2.6$^{\phi}$	40.5 ± 5.2*$^{\phi}$	53.3 ± 7.8*$^{\phi}$	*Group: p < 0.01;*
	CTRL	45 ± 0	63.0 ± 5.8	90.0 ± 11.7*	105.0 ± 17.5*	*Interaction: p < 0.05*
$P_{ET}CO_2$ (mmHg)	LVAD	30.5 ± 3.2	33.2 ± 4.4*	33.5 ± 4.6*	33.7 ± 5.8*	*Exercise: p < 0.0001;*
	CHF	28.6 ± 2.8	31.1 ± 4.0*	32.6 ± 4.4*	32.9 ± 4.9*	*Group: NS;*
	CTRL	33.3 ± 3.7	38.6 ± 3.5*	39.6 ± 3.3*	39.8 ± 3.0*	*Interaction: NS*
MAP (mmHg)	LVAD	89 ± 12$^{\phi}$φ	97 ± 11*$^{\phi}$φ	97 ± 9*$^{\phi}$φ	101 ± 8*$^{\phi}$φ	*Exercise: p < 0.0001;*
	CHF$^{\phi}$	77 ± 13$^{\phi}$	81 ± 13*$^{\phi}$	84 ± 15*$^{\phi}$	87 ± 12*$^{\phi}$	*Group: p = 0.001;*
	CTRL	100 ± 17	110 ± 18*	117 ± 21*	126 ± 18*	*Interaction: p = 0.002*
ICA velocity (cm.s^{-1})	LVAD	37.1 ± 6.9$^{\phi}$φ	40.6 ± 10.0$_{\varphi}$	39.7 ± 9.5φ	39.4 ± 7.6$^{\phi}$φ	*Exercise: p = 0.0002;*
	CHF	25.7 ± 6.1$^{\phi}$	27.4 ± 9.1$^{\phi}$	27.7 ± 10.2$^{\phi}$	29.3 ± 11.3φ	*Group: p = 0.02;*
	CTRL	33.9 ± 8.3	38.2 ± 8.4	40.0 ± 8.0*	42.2 ± 11.1*	*Interaction: p = 0.016*
ICA diameter (mm)	LVAD	4.86 ± 0.58 $^{\phi}$φ	4.80 ± 0.57$^{\phi}$φ	4.79 ± 0.59$^{\phi}$φ	4.77 ± 0.58$^{\phi}$φ	*Exercise: NS;*
	CHF	5.20 ± 0.69	5.26 ± 0.72	5.26 ± 0.72	5.19 ± 0.76	*Group: NS;*
	CTRL	5.14 ± 0.62	5.28 ± 0.72	5.24 ± 0.67	5.28 ± 0.63	*Interaction: p = 0.04*
ICA flow (ml.min^{-1})	LVAD	212 ± 59.3φ	225 ± 64$^{\phi}$φ	222 ± 79$^{\phi}$φ	206 ± 47$^{\phi}$	*Exercise: p < 0.0001;*
	CHF	162 ± 42$^{\phi}$	177 ± 60$^{\phi}$	184 ± 64$^{\phi}$	188 ± 63$^{\phi}$	*Group: NS;*
	CTRL	220 ± 106	257 ± 106*	271 ± 110*	284 ± 132*	*Interaction: p = 0.004*
MCAv (cm.s^{-1})	LVAD	52.7 ± 14.6$^{\phi}$φ	52.4 ± 14.4$_{\varphi}$	52.6 ± 14.8φ	52.1 ± 14.6$^{\phi}$φ	*Exercise: p = 0.0001;*
	CHF	43.0 ± 15.8$^{\phi}$	45.3 ± 19.2$^{\phi}$	47.5 ± 20.9*$^{\phi}$	47.9 ± 22.7*$^{\phi}$	*Group: NS;*
	CTRL	47.2 ± 14.0	55.5 ± 13.1*	57.3 ± 13.8*	57.2 ± 13.0*	*Interaction: p = 0.0004*
PCAv (cm.s^{-1})	LVADφ	48.8 ± 14.6$^{\phi}$φ	49.7 ± 15.0φ	48.4 ± 13.6φ	46.8 ± 12.3$^{\phi}$φ	*Exercise: p < 0.0001:*
	CHF	34.9 ± 7.6$^{\phi}$	37.8 ± 9.2$^{\phi}$	38.5 ± 9.2$^{\phi}$	37.9 ± 9.2$^{\phi}$	*Group: p = 0.04;*
	CTRL	43.6 ± 9.9	49.5 ± 10.3*	50.9 ± 11.2*	53.4 ± 12.4*	*Interaction: p < 0.0001*

* signifies statistical difference from baseline;$^{\phi}$ signifies statistical difference from CTRL; φ signifies statistical difference from CHF.

4.3.2 Comparison between groups in response to exercise

4.3.2.1 Cardiorespiratory measures

Incremental exercise stimulated progressive increases in $\dot{V}O_2$, MAP and $P_{ET}CO_2$ in all groups. $\dot{V}O_2$ peak values were 12.7 ± 4.4 mL·kg^{-1}·min^{-1} and 13.0 ± 2.7 ml·kg^{-1}·min^{-1} in the CHF and LVAD groups, respectively, both significantly lower compared to CTRL (25.4 ± 8.3 mL·kg^{-1}·min^{-1}). Incremental values for %$\dot{V}O_2$ peak at each absolute exercise workload (Watts) are included in Table 4.2, with main effect differences indicating a lower observer value for CTRL compared to CHF.

A main effect of group was observed for MAP ($p < 0.0001$) and $\dot{V}O_2$ ($p = 0.0008$). Post hoc analysis of the main group effect revealed that MAP was reduced when comparing CHF (Δ-31. 0± 6.9 mmHg, CI = 13 to 49, $p = 0.001$) to CTRL participants. Similarly $\dot{V}O_2$ was lower in CHF (Δ-4.3 ± 1.2 mL·kg^{-1}·min^{-1}, CI = 1.1 to 7.58) and LVAD (Δ-5.4 ± 1.2 mL·kg^{-1}·min^{-1}; CI = 2.2 to 8.6, $p = 0.001$) compared to CTRL. LVAD and CHF participants did not differ in terms of group effects for MAP. Interaction effects were observed for both $\dot{V}O_2$ and MAP and post hoc analyses revealed that $\dot{V}O_2$ and MAP were significantly lower in both LVADs and CHF groups, compared to CTRLs, at 20, 40 and 60 %Wmax. No significant main effects for group, or interactions, were observed for $P_{ET}CO_2$.

4.3.2.2 Cerebrovascular measures

Significant interaction effects for the impact of exercise between groups were apparent for ICA velocity, diameter, flow and shear, as well as MCAv and PCAv (Figure 4.2 & 4.3). Post hoc analysis revealed that exercise increased ICA flow from BL at 20 (Δ+ 36.97 ± 10.8 ml.min^{-1} , CI = 66.6 to 7.32, $p = 0.008$), 40 (Δ 51.26 ± 10.8 ml.min^{-1}, CI = 9 to 21.6, $p = 0.0001$), and 60 (Δ 63.62 ± 10.8 ml.min^{-1}, CI = 93.2 to 34.0, $p < 0.0001$) %Wmax in CTRL participants, whereas no exercise-induced increases in these variables were apparent in the either the CHF or LVAD groups. Nonetheless, the enhanced ICA flow that was apparent in LVAD compared to the CHF group at rest, remained during exercise at 20 (Δ 48.2 ± 10.8 ml.min^{-1} CI = 21.5 to 74.1, $p = 0.0001$) and 40 (Δ 38.1 ± 10.8 ml.min^{-1}, CI = 11.4 to 64.9, $p = 0.002$), but not at 60 %Wmax.

There was no significant main effect of exercise ($p = 0.43$) or group ($p = 0.32$) on ICA diameter. Post hoc analysis of interaction effects revealed significantly lower ICA diameters (Figure 4.2) in LVAD (4.810.57cm, 4.79 ± 0.59cm, 4.77 ± 0.58cm) participants compared to CHF (5.26 ± 0.72 cm, 5.26 ± 0.72 cm, 5.19 ± 0.76 cm) and CTRL (5.28 ± 0.72 cm, 0.524 ± 0.67 cm, 5.28 ± 0.63 cm) participants at 20, 40 and 60 %WMax ($p < 0.0001$), respectively.

Main effects of group ($p = 0.02$) and exercise ($p = 0.0002$) were identified for ICA velocity (Figure 4.2). Post hoc analysis of the main effects revealed ICA velocities were, on average, different when comparing LVADs (Δ+ 11.57 ± 4.205 $cm.s^{-1}$, CI = 0.37 to 22.78, $p = 0.04$) and CHF participants, whereas exercise-induced increases in ICA velocity from BL were only observed in the CTRL group (at 40%WMax Δ 6.03 ± 1.46 $cm.s^{-1}$, CI = 2.02 to 10.05, $p = 0.0009$ and 60%WMax Δ8.25 ± 1.46 $cm.s^{-1}$, CI = 4.23 to 12.26, $p < 0.0001$). Analysis of interaction effects (Table 4.2, Figure 4.2) indicate significantly reduced ICA velocities in CHF compared to CTRLS and LVADs throughout exercise.

Post hoc analysis of the main effect ($p = 0.0001$) for exercise revealed an increase in MCAv from BL in both CHF and CTRL participants, but not in VAD patients. CTRLs increased PCAv from BL (Table 4.2, Figure 4.3), but this effect was not apparent with exercise in the other groups. Significant MCAv and PCAv interactions (Table 4.2, Figure 4.3) were due to higher velocities throughout exercise in LVADs and CTRLS, compared to CHF participants. Comparisons between CTRLs and LVADs revealed significant higher MCAv ($p = 0.006$) and PCAv ($p < 0.0001$) values at 60% WMax in CTRLS.

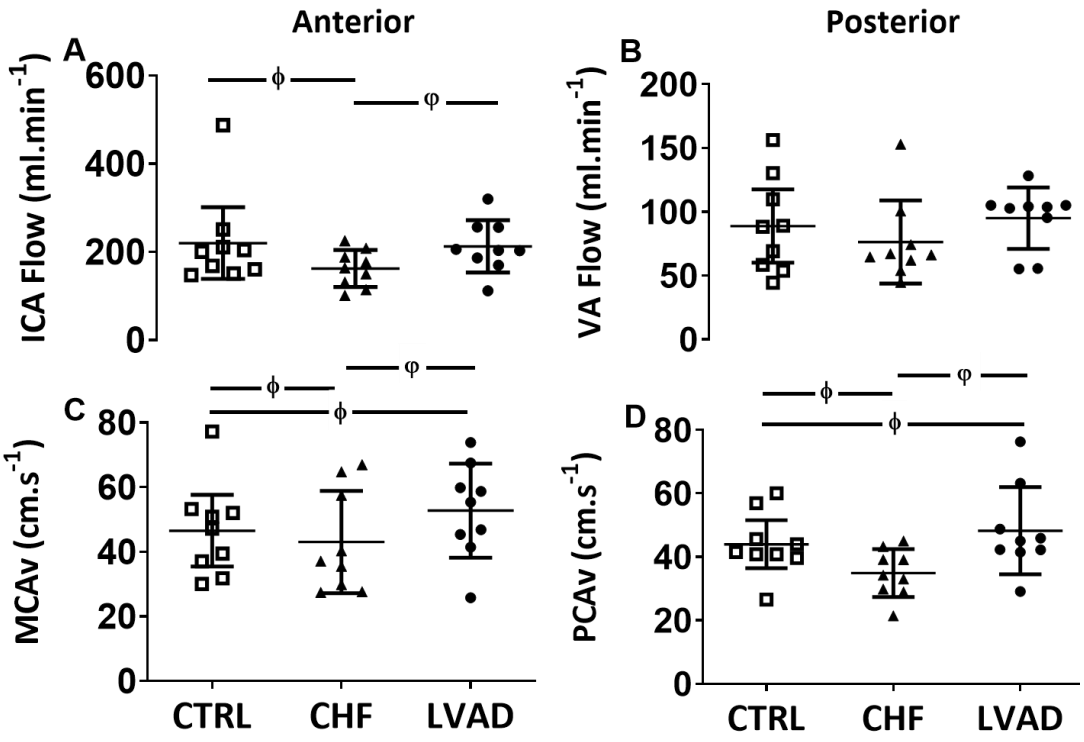

Figure 4.1 Individual (dots) and average (lines) resting flow in the internal carotid (ICA: panel A) and vertebral (VA: panel B) arteries, as well as intracranial velocity in the middle (MCAv: panel C) and posterior (PCAv: panel D) cerebral arteries in participants with left ventricular assist devices (LVAD), chronic heart failure (CHF) and healthy and gender age matched controls (CTRL). ϕ signifies statistical difference from CTRL; φ signifies statistical difference from CHF.

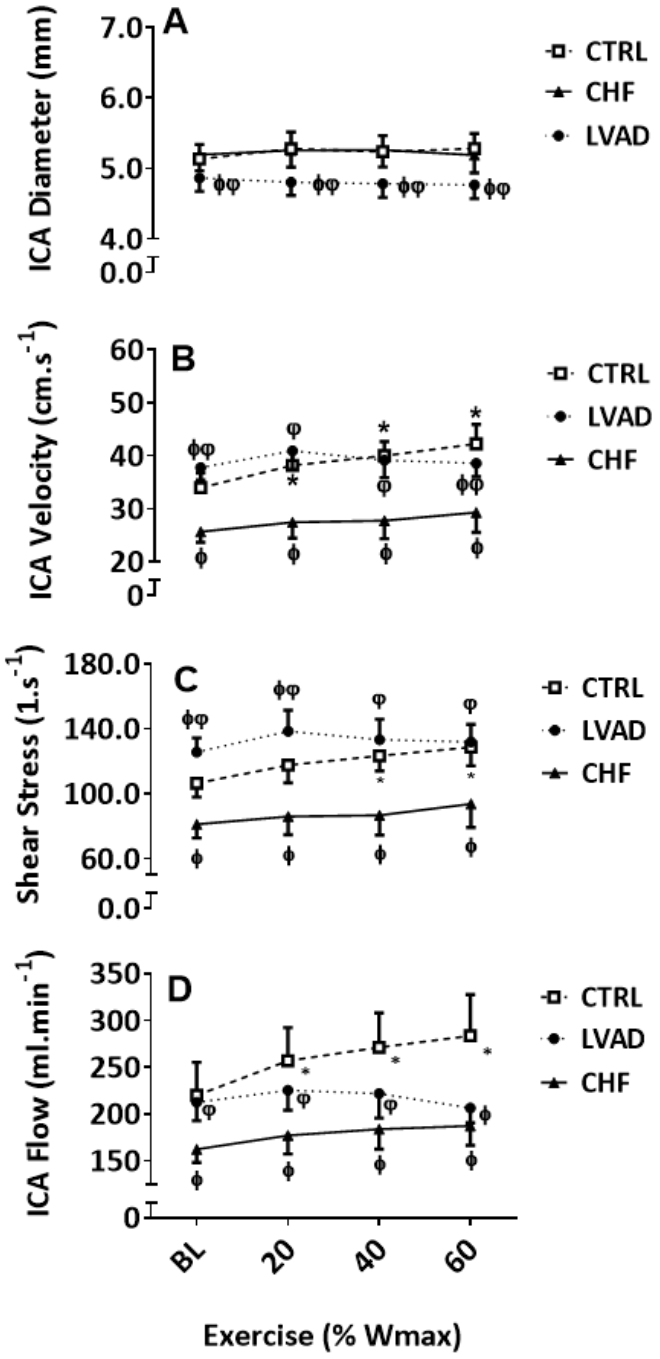

Figure 4.2 Average hemodynamic responses (diameter [A]; velocity [B]; shear [C]; flow [D];) in the internal carotid artery (ICA) during BL and exercise at 20, 40 and 60% of the maximum achievable cycle ergometer workload (%Wmax) in participants with left ventricular assist devices (LVAD), chronic heart failure (CHF) and healthy and gender age matched controls (CTRL). * signifies statistical difference from baseline;ϕ signifies statistical difference from CTRL; and φ signifies statistical difference from CHF.

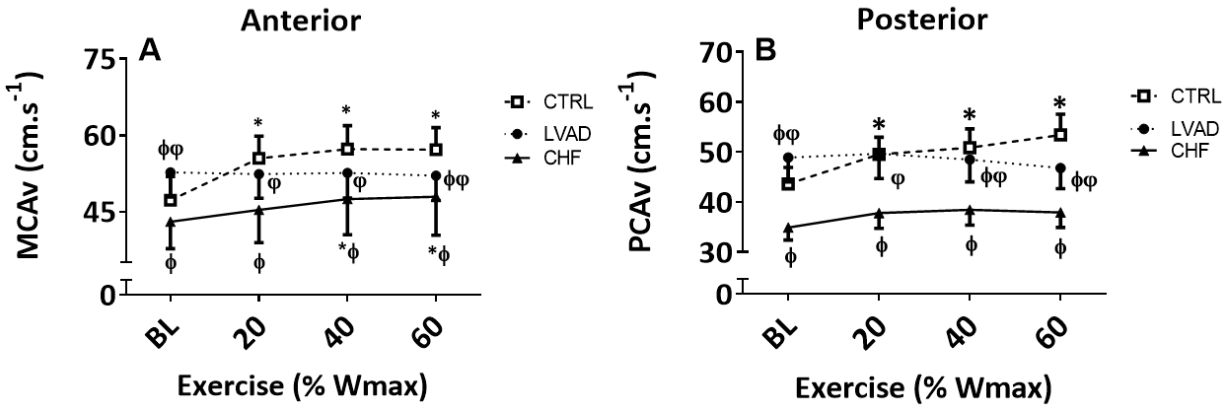

Figure 4.3 Average intracranial cerebral blood velocity at rest and during incremental exercise at 20, 40, and 60% of the maximum achievable workload (%Wmax) in the middle (MCAv; panel A) and posterior (PCAv; panel B) cerebral arteries in participants with left ventricular assist devices (LVAD), chronic heart failure (CHF) and healthy and gender age matched controls (CTRL). * signifies statistical difference from baseline;ϕ signifies statistical difference from CTRL; φ signifies statistical difference from CHF.

4.4 Discussion

It is well established that LVAD implantation, as a treatment for advanced CHF, improves survival and enables rehabilitative approaches to be applied that can enhance functional capacity and quality of life.[9] LVADs are increasingly used as a "destination therapy", alongside their role in bridging to transplant and recovery. This is the first study, to our knowledge, to compare intra- and extra-cranial arterial blood flow at rest and during exercise in LVAD, and age- and sex-matched CHF and healthy control participants. Our principal finding was that participants with LVADs had an enhanced cerebral blood flow at rest compared to participants with CHF and that this resting benefit was sustained during submaximal exercise. Furthermore, at rest, the LVAD group showed a normalised resting intracranial and extracranial blood flows relative to the CTRL group. During exercise, however, intracranial and extracranial arterial flow responses were lower in participants with LVADs compared with healthy CTRLs and did not increase as exercise intensified. As described below, these findings may

have implications for the prescription of effective exercise-based rehabilitation in LVAD patients.

To date, no study has directly assessed the cerebrovascular responses during exercise in patients with LVADs compared with CHF and healthy control groups. In healthy individuals, cerebral blood flow is known to increase during exercise until a plateau at approximately 60-70% of $\dot{V}O_2$ peak.[21] This did not occur in our LVAD group and, in contrast with the CTRL group and to a lesser extent to participants with CHF, responses did not increase as a function of exercise intensity. The disparity between the LVAD flow responses and those of healthy controls increased as exercise intensified. Brassard et al.[3] recently demonstrated that cerebral blood flow velocity (i.e., MCAv) did not significantly increase during incremental exercise in patients with LVADs, but that cerebral perfusion increased modestly when pump speed was progressively increased. Our study complements and adds to this observation in that we report that both anterior and posterior cerebrovascular responses are impaired, relative to well-matched control participants and that LVAD implantation does not adequately compensate for the demands of exercise. Our study also included novel volumetric flow measurements performed in the ICA which confirmed the intracranial velocity data, being lower during exercise in LVAD patients than CTRL. Taken together, our findings, coupled with those of Brassard et al.[3] strongly suggest that the impaired cerebrovascular perfusion evident in CHF subjects during incremental exercise, relative to healthy control subjects, is not fully compensated for by the implantation of LVAD.

The cardiorespiratory mechanisms controlling cerebrovascular perfusion during exercise are complex, inter-dependent and exhibit multiple redundancies.[2,11] Exercise-induced changes occur as a result of the compound influence of metabolic and humoral factors and neuronal activation.[1,2,22] CHF is a model of myriad systemic dysfunction, with abnormalities in each of the links in the Fick equation chain.[2,8] It is possible, for instance, that respiratory inefficiency contributes to the impairment we observed in brain blood flow response to exercise in the present study, but skeletal muscle abnormalities that induce metaboreflex activation likely also contribute, alongside activation of baroreflexes and chemoreflexes. A schema summarising the profound impact of mechanistic abnormalities in CHF on cerebral perfusion was recently

proposed.[2] Interestingly, cardiac transplantation has beneficial impacts of CBF in CHF and increasing LVAD pump speed during exercise also enhances perfusion,[2] supporting the theory that cardiac output is a major regulator of CBF.

In the present study, we elected to match and compare CBF along with cardiorespiratory responses to acute exercise relative to maximal exercise workload, rather than absolute workloads given the marked differences in aerobic capacity between the cohorts with CHF and the healthy control group. However, both the LVAD and CHF groups achieved a similar workload and $\dot{V}O_2$ peak values, suggesting that CBF parameters are equally comparable in absolute workload terms. By contrast, the healthy control group achieved much higher maximal workload and oxygen consumptions values, with significant elevations in MAP, but no differences in $P_{ET}CO_2$ across groups. One could assume that CBF during exercise is largely dependent on arterial blood pressure. However, previous studies have reported a lack of temporal linearity between these parameters during incremental exercise.[23] Thus, it is likely that the CBF response may be the result of the balance between multiple interactions of different factors, such as cardiac output,[24] $P_{ET}CO_2$,[18] shear stress,[15] and cerebral metabolism[25,2,21] Our study was not designed to investigate the specific mechanisms responsible for impaired cerebral perfusion in CHF and LVAD patients. Further investigation into the regulation of brain blood flow in CHF patients including those instrumented with an LVAD, alongside measures of the integrated physiological responses to dynamic exercise, are needed, but, likely, interventions like exercise training,[2,26] that target the multiple dysfunctional pathways would improve cerebral blood flows during exercise. In this context, it is clear that one advantage of LVADs is that they enable CHF patients to participate more actively in exercise-based rehabilitation programs.

The impact that repeated episodes of low cerebral flow may have on brain function, cerebrovascular health and the risk of atherothrombotic events should be considered. Studies investigating cerebrovascular function in aging have indicated that enhanced brain blood flow is associated with greater fitness across the life span, alongside improved cognition and quality of life.[27,28] The long-term consequences of exposing patients to repeated conditions where cerebral perfusion is compromised in the face of increased cerebral metabolic demands induced by exercise are currently unknown, but

given that the matching of cerebral perfusion to metabolic demand (termed neurovascular coupling)[29] is a critical process regulating the supply oxygen and nutrients to the brain, any impairment in this response may be associated with poor cerebrovascular outcomes in the longer term.[30] Moreover, since elevations in cerebral perfusion and related shear patterns are key mechanisms to improve cerebrovascular health,[31] attenuated cerebral blood flow responses may hinder the potential cognitive benefits of exercise-based rehabilitation.

A technical limitation of TCD ultrasound is that one ipsilateral assessed is typically performed. To account for potential variation in contralateral blood flow distribution, we employed our standardized imaging practices[12,18] to screen for any differences in contralateral flow in the extracranial arteries. No observable differences in contralateral flow were observed in any of our LVAD, CHF or CTRL subjects; therefore, resting intracranial (MCA and PCA) and extracranial (ICA and VA) cerebral arteries were assessed as valid surrogates for global brain vascular function. There is no evidence, to our knowledge, suggesting a disparate contralateral flow pattern in response to exercise in LVADs and healthy individuals. We used "volitional exhaustion" as a criterion for test cessation in our subjects and this may have resulted in some of the controls achieving a criterion for maximal effort, whilst, as it is typical, many of the CHF subjects will not have attained this level of exertion. Indeed, it was recently observed that almost 50% of CHF individuals fail to achieve an RER >1.10 during CPET.[32] We, therefore, opted to present data at matched Watts and also at %Wmax, allowing comparisons at both absolute and relative levels which are relevant to the performance of tasks of daily living. Another factor to consider is that participants did not perform a familiarisation session (to reduce the assessment burden on participants). However, it is unlikely that this biased the results because none of the participants across groups had previously performed this test on a semi-recumbent cycle with this kind of instrumentation. Furthermore, it should be acknowledged that a higher proportion of participants in the LVAD group than the CHF group were taking angiotensin-converting-enzyme inhibitors (100% vs 56%, respectively). Although its impact on cerebrovasculature function is not currently known, this drug has vascular effects in other vascular beds, which could have affected the function of intracranial and extracranial arteries at rest and during exercise. A further limitation of this study was that intracranial diameters were not assessed. However, a novel aspect of our study

was the assessment of ICA diameters as a surrogate for calibre changes that may contribute to cerebrovascular modulation. A further limitation is that our sample size did not allow for sub-group analysis of the impacts of sex, drugs or LVAD type on outcomes; this should be a focus in larger future studies. Finally, although we measured both intra- and extra-cranial blood flow and velocity, we did not assess cerebral oxygenation. We are therefore not in a position to characterise Fick components related to oxygen delivery versus extraction.[1-4] Such additional measures should be considered in future studies.

In conclusion, we have found in the present study that volumetric CBF is attenuated during exercise in patients with LVAD compared to healthy controls and that, in common with CHF patients, there is limited compensatory increase in cerebrovascular perfusion to cope with the physiological demands of exercise.

4.5 References

1. Malenfant S, Brassard P, Paquette M, et al. Compromised cerebrovascular regulation and cerebral oxygenation in pulmonary arterial hypertension. JAHA 2017;6:e006126.

2. Brassard P, Gustafsson F. Exercise intolerance in heart failure: did we forget the brain? Can J Cardiol 2016;32:475-84.

3. Brassard P, Jensen AS, Nordsborg N, et al. Central and peripheral blood flow during exercise with a continuous-flow left ventricular assist device: constant versus increasing pump speed: a pilot study. Circ Heart Fail 2011;4:554–60.

4. Jung MH, Gustafsson F. Exercise in heart failure patients supported with a left ventricular assist device. J Heart Lung Transplant 2015;34:489-96.

5. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147-e239.

6. Maiorana A, O'Driscoll G, Cheetham C, et al. Combined aerobic and resistance exercise training improves functional capacity and strength in CHF. J Appl Physiol 2000;88:1565-70.

7. Maiorana A, O'Driscoll G, Dembo L, et al. Effect of aerobic and resistance exercise training on vascular function in heart failure. Am J Physiol Heart Circ Physiol 2000;279:H1999-2005.

8. Green DJ, Panizzolo FA, Lloyd DG, Rubenson J, Maiorana AJ. Soleus muscle as a surrogate for health status in human heart failure. Exerc Sport Sci Rev 2016;44:45-50.

9. Kirklin JK, Pagani FD, Kormos RL, et al. Eighth annual INTERMACS report: special focus on framing the impact of adverse events. J Heart Lung Transplant 2017;36:1080–86.

10. Haddad TM, Saurav A, Smer A, et al. Cardiac rehabilitation in patients with left ventricular assist device: a systematic review and meta-analysis. J Cardiopulm Rehabil Prev 2017;37:390–96.

11. Willie CK, Colino FL, Tzeng YC, et al. Utility of transcranial Doppler ultrasound for the integrative assessment of cerebrovasclar function. J Neurosci Meth 2011;196:221-37.

12. Thomas KN, Lewis NCS, Hill BG, Ainslie PN. Technical recommendations for the use of carotid duplex ultrasound for the assessment of extracranial blood flow. Am J Physiol 2015;309:R707–20.

13. Thijssen DH, Black MA, Pyke KE, et al. Assessment of flow-mediated dilation in humans: a methodological and physiological guideline. Am J Physiol Heart Circ Physiol 2011;300:H2-12.

14. Smith KJ, Hoiland RL, Grove R, et al. Matched increases in cerebral artery shear stress, irrespective of stimulus, induce similar changes in extra-cranial arterial diameter in humans. J Cereb Blood Flow Metab 2019;39:849-58.

15. Carter HH, Atkinson CL, Heinonen IHA, et al. Evidence for shear stress-mediated dilation of the internal carotid artery in humans. Hypertension 2016;68:1217-24.

16. Hoiland RL, Smith KJ, Carter HH, et al. Shear-mediated dilation of the internal carotid artery occurs independent of hypercapnia. Am J Physiol Heart Circ Physiol 2017;313:H24-H31.

17. Woodman RJ, Playford DA, Watts GF, et al. Improved analysis of brachial artery ultrasound using a novel edge-detection software system. J Appl Physiol 2001;91:929-37.

18. Smith KJ, Wildfong KW, Hoiland RL, et al. Role of CO2 in the cerebral hyperemic response to incremental normoxic and hyperoxic exercise. J Appl Physiol 2016;120:843-54.

19. Black MA, Cable NT, Thijssen DHJ, Green DJ. Importance of measuring the time-course of flow-mediated dilation (FMD) in humans. Hypertension 2008;51:203-10.

20. Bennett MK, Roberts CA, Dordunoo D, Shah A. Ideal methodology to assess systemic blood pressure in patients with continuous-flow left ventricular assist devices. J Heart Lung Transplant 2010;29:593–94.

21. Smith KJ, Ainslie PN. Regulation of cerebral blood flow and metabolism during exercise. Exp Physiol 2017;102:1356-71.

22. Kim Y-S, Seifert T, Brassard P, et al. Impaired cerebral blood flow and oxygenation during exercise in type 2 diabetic patients. Physiol Rep 2015;3:e12430.

23. Lucas SJE, Cotter JD, Brassard P, Bailey DM. High-intensity interval exercise and cerebrovascular health: curiosity, cause, and consequence. J Cereb Blood Flow Metab 2015;35:902-11.

24. Smirl JD, Haykowsky MJ, Nelson MD, Altamirano-Diaz LA, Ainslie PN. Resting and exercise cerebral blood flow in long-term heart transplant recipients. J Heart Lung Tnansplant 2012;31:906-08.

25. Smith KJ, MacLeod D, Willie CK, et al. Influence of high altitude on cerebral blood flow and fuel utilization during exercise and recovery. J Physiol 2014;592:5507-27.

26. Murrell CJ, Cotter JD, Thomas KN, Lucas SJE, Williams MJA, Ainslie PN. Cerebral blood flow and cerebrovascular reactivity at rest and during sub-maximal exercise: Effect of age and 12-week exercise training. Age 2013;35:905-20.

27. Ainslie PN, Cotter JD, George KP, et al. Elevation in cerebral blood flow velocity with aerobic fitness throughout healthy human ageing. J Physiol 2008;586:4005-10.

28. Tarumi T, Zhang R. Cerebral blood flow in normal aging adults: cardiovascular determinants, clinical implications, and aerobic fitness. J Neurochem 2018;144:595-608.

29. Phillips AA, Chan FHN, Zheng MMZ, Krassioukov AV, Ainslie PN. Neurovascular coupling in humans: Physiology, methodological advances and clinical implications. J Cereb Blood Flow Metab 2016;36:647-64.

30. Aries MJH, Elting JW, De Keyser J, Kremer BPH, Vroomen PCAJ. Cerebral autoregulation in stroke: a review of transcranial Doppler studies. Stroke 2010;41:2697–704.

31. Guiney H, Lucas SJ, Cotter JD, Machado L. Evidence cerebral blood-flow regulation mediates exercise-cognition links in healthy young adults. Neuropsychology 2015;29:1-9.

32. Chase PJ, Kenjale A, Cahalin LP, et al. Effects of respiratory exchange ratio on the prognostic value of peak oxygen consumption and ventilatory efficiency in patients with systolic heart failure. JACC: Heart Fail 2013;1:427-32.

Chapter 5 Experimental study 3

Cerebral blood flow responses to exercise are enhanced following an exercise rehabilitation program in patients with left ventricular assist devices

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Declaration of candidate contribution

The following Chapter was published as a shared co-first authorship between the candidate, Jose Ignacio Moreno Suarez, and Dr Kurt Smith as they both worked together and contributed equally to the manuscript. The candidate contributed to conception of the experiment, delivered the exercise training program, contributed to data collection and analyses, interpreted the results, and drafted the manuscript.

Mr Jose Ignacio Moreno Suarez | PhD Candidate

Associate Professor Andrew Maiorana | Primary supervisor and senior author

5.1 Introduction

Left ventricular assist device implantation (LVAD) is an increasingly common approach for the treatment of advanced chronic heart failure (CHF).[1] Augmented cardiac output and peripheral blood flow are factors commonly proposed to underpin enhanced exercise capacity following LVAD implantation.[2] However, relatively little is known about the impact of LVAD implantation on cerebral blood flow (CBF) during exercise in this group. Despite the observation that LVADs normalise CBF at rest,[3-5] in the previous chapter we found no observable increases during incremental exercise.[5] This impairment may be ameliorated if pump speed is progressively increased in conjunction with exercise intensity.[6] The relative lack of cerebral hyperemia during exercise may relate to a lack of reflex increase in cardiac output,[6] as well as the absence of an increase in intra-cranial vasodilation due to impaired shear stress and the lack of pulsatility.[7] Cerebrovascular dysfunction during aerobic exercise in CHF that persists despite LVAD implantation[6-8], may have potential long-term implications for brain function and health.

Exercise rehabilitation programs are now recommended as usual care to improve functional capacity and quality of life in patients with LVADs.[1] We have demonstrated that arterial function can be enhanced, including in patients with CHF, as a result of repetitive and episodic increases in intra-arterial shear stress during exercise.[9-11] However, a paucity of studies have investigated the impact of exercise training (ET) in patients with LVADs,[12-14] and none to our knowledge have evaluated training effects on cerebrovascular responses during exercise. Therefore, the present study aimed to evaluate the effects of a 12-week supervised and structured exercise rehabilitation program on CBF responses at rest and during exercise, in patients implanted with an LVAD *in situ*. We hypothesised that ET would enhance cerebrovascular function during exercise.

5.2 Methods

5.2.1 Participants

Fifteen participants were recruited after being implanted with an LVAD for clinical reasons. Twelve participants completed the intervention, and eleven subjects had sufficient ICA windows for pre and post-assessments (5♀, age: 53.6 ± 11.8 years; weight: 84.2 ± 15.7 kg; height: 1.73 ± 0.08 m). Participants were recruited from the Advanced Heart Failure and Cardiac Transplant Service at Fiona Stanley Hospital (FSH; Perth, Western Australia) and were on average 68 ± 99 weeks post-LVAD implantation (range: 12 - 311 weeks) at the time of enrolment. All participants had been hemodynamically stable for more than 4 weeks prior to participating in the study. Routine transthoracic echocardiography was performed at intervals in these patients to characterize ejection fraction (EF%).

The study protocol was approved by the Royal Perth Hospital Human Research Ethics Committee (HREC) and Fiona Stanley Hospital Governance Unit (REG15-164). Reciprocal ethics approval was granted by Curtin University (HR13/2016). The study was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12616001596493*)*. All aspects of the study complied with the ethical principles outlined by the Declaration of Helsinki. The participants were informed of all experimental procedures and associated risks. They provided written informed consent before the commencement of the study.

5.2.2 Cerebrovascular assessment

Participants underwent a series of baseline assessments which were repeated after the 12-week ET program. The cerebrovascular assessment procedure and methodology was identical as described in the previous chapter in section 4.2.3.

5.2.3 Exercise training intervention

The ET program consisted of three one-hour sessions weekly for 12 weeks. Sessions were supervised by experienced exercise physiologists and physiotherapists in a dedicated cardiac rehabilitation facility at FSH.

Each exercise session commenced and concluded with a warm-up/cool-down involving 5 minutes of low intensity continuous aerobic exercise, followed by 5 minutes of muscular stretching. Participants undertook aerobic exercise on a treadmill for 28 minutes at an intensity ranging from 50 to 90% of $\dot{V}O_2$ reserve; this was refined based on the rating of perceived exertion from 11 ("fairly light") to 15 ("hard") on the Borg Category Scale.[15] ET involved both continuous and interval modes of exercise and was progressed across the 12-week training period according to individual adaptation. The ET program was reviewed every fortnight during the course of the intervention to adapt for cardiopulmonary changes by progressively increasing the intensity, as tolerated. Following the aerobic exercise component, participants undertook a set of resistance exercises involving three lower-body (leg press, hamstring curl, and leg extension) and three upper body exercises (incline bench press, lat pull-down and biceps curl) at 50-60% of the baseline one-repetition maximum test.

We chose our exercise intervention based on our previous extensive experience of combined aerobic and resistance training in patients with end-stage CHF[10,11,16] and other comorbidities. The rationale is to include an aerobic stimulus for cardiopulmonary conditioning, alongside a resistance stimulus to enhance skeletal muscle adaptation. We have previously demonstrated improvements in aerobic capacity, skeletal muscle strength and vascular function using this approach, which is routinely applied clinically in our advanced heart failure and cardiac transplant service.[10,11,16] Whilst we used treadmill exercise in the training program to maximize the training stimulus, we used recumbent cycling for outcome testing since it allowed us to optimize the imaging we performed.

5.2.4 Statistical Analysis

Statistical analysis was performed using SPSS 25 software (IBM, Chicago, IL, USA) and GraphPad PRISM 6.01 software (GraphPad Software, LaJolla, CA, USA). Changes from baseline during exercise were assessed using two-way repeated-measures ANOVA. Post-hoc corrections for multiple comparisons were also performed for main effect and interaction effects between pre-training (PreTR) and post-training (PostTR) measures. To measure the strength of association between variables, either Pearson's or Spearman's rank correlation coefficient was used, depending on normality assumptions, as appropriate. All statistical testing was two-

sided with a level of significance set at $p < 0.05$. All data are presented as mean ± standard deviation (SD) unless otherwise stated.

5.3 Results

Participants had a mean EF of 24.8 ± 7.6 % at baseline. Several different continuous-flow LVAD systems were implanted in participants (two Heartmate II, Thoratec Corporation; two HVAD, HeartWare, and seven Heartmate 3, Thoratec Corporation), and no changes in pump speed (6275 ± 2741 rpm) were made between PreTR and PostTR. The medication regimen of participants are provided in Table 5.1. Compliance with the ET sessions was 95% (sessions attended). Post-training evaluations were performed between three to five days after training ceased.

Table 5.1 Frequency of medication use for participants with LVADs

Medical therapy	**Pre-training (n=11)**
ACE inhibitors	10 (91%)
Angiotensin II receptor blockers	7 (64%)
β-blockers	8 (72%)
Clopidogrel	7 (64%)
Warfarin	11 (100%)
Diuretics	7 (64%)
Digoxin	3 (27%)
Aspirin	5 (45%)
Sildenafil	4 (36%)
Amiodarone	4 (36%)

ACE, Angiotensin-converting-enzyme.

5.3.1 Effect of training on $\dot{V}O_2$ peak and workload maximum

Based on data derived from the recumbent bicycle ergometer cardiopulmonary exercise test (CPET), peak oxygen consumption ($\dot{V}O_2$ peak) increased from 11.7 ± 3.1 to 14.6 ± 3.7 $mL \cdot kg^{-1} \cdot min^{-1}$ ($p < 0.005$). Mean respiratory exchange ratio at PreTR assessment was 1.2 ± 0.1 and 1.3 ± 0.1 $\dot{V}CO_2/\dot{V}O_2$ PostTR. Workload maximum increased from 64 ± 19 to 85 ± 19 Watts ($p < 0.001$).

5.3.2 Effect of training on cerebral haemodynamics at rest

Resting ICA blood flow, and MCAv were unchanged PostTR, whereas PCAv PostTR ($p < 0.05$) was lower than the PreTR value (Table 5.2, Figure 5.1). Similarly, velocity and shear rate were not significantly altered following training. In contrast, ICA diameter (4.9 ± 0.5 vs 5.2 ± 0.8 mm; $p < 0.05$) increased following training. Resting $P_{ET}CO_2$ (29.8 ± 2.5 vs. 30.9 ± 2.3 mmHg; $p = 0.26$) and MAP were both unaltered by training (85.8 ± 9.8 vs. 92.5 ± 9.0 mmHg; $p = 0.43$).

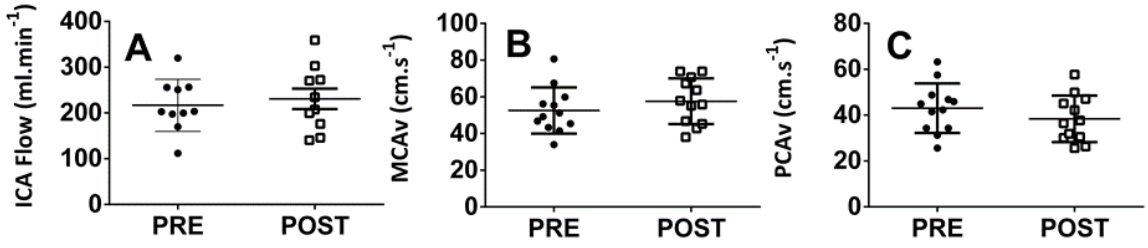

Figure 5.1 Data presented as mean ± standard deviation, along with individual values. Pre and post-training internal carotid artery flow (ICA) and middle (MCAv) and posterior (PCAv) cerebral artery velocity at rest, in panels A, B and C respectively.

5.3.3 Effect of training on cerebral haemodynamics during exercise

Table 5.2 presents cerebral hemodynamic responses measured during exercise, both PreTR and PostTR. A main effect for exercise intensity and an interaction between exercise training and intensity ($p < 0.001$) were observed for PCAv. Post hoc analysis revealed that only PreTR PCAv at 100% Wmax was reduced from baseline (2.4 ± 0.8

cm.s^{-1}) (Figure 5.2: B; $p < 0.01$), with greater reductions in PCAv from baseline at 80 (5.4 ± 1.8 %) and 100 (5.2 ± 1.8 %) %WMax PreTR than PostTR (Figure 5.2: B and D; $p < 0.001$). No post hoc differences were observed for MCAv (Fig 5.2: A and C).

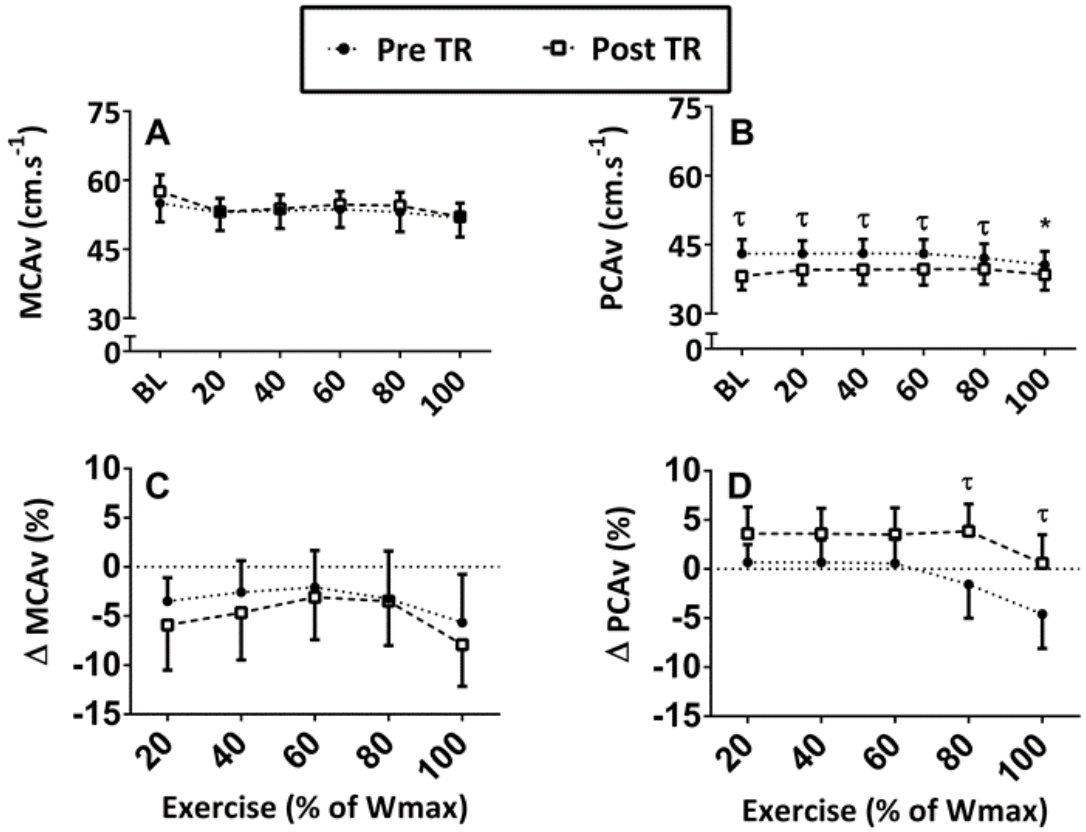

Figure 5.2 Data presented as mean ± standard deviation. Absolute middle (MCAv) and posterior (PCAv) cerebral artery velocities (A, and B) at rest (BL) and during exercise at 20, 40, 60, 80 and 100% of the maximum achieved workload (% of Wmax). Relative percent change from baseline are shown in C, and D. * signifies main effect difference from baseline, $p < 0.05$. τ signifies interaction and post-hoc revealed difference between difference (PreTR) and post-training (PostTR), $p < 0.001$.

A main effect for exercise intensity was observed for ICA diameter (Figure 5.3: A; $p < 0.05$). No main effects of group or exercise intensity were observed for ICA velocity or flow. However, there were significant interaction effects for ICA velocity and flow (Figure 5.3 and 5.4; $p < 0.001$). Post hoc analysis revealed that PreTR, but not PostTR, ICA flows were reduced from baseline (-24.6 ± 8.1 ml.min^{-1}) at 60% WMax ($p = 0.02$). Post hoc assessment of the interactions between relative changes (i.e., Δ%) from baseline revealed divergent pre and post-training ICA velocity and flow responses to incremental exercise. Mean differences between PreTR and PosTR changes from

baseline in ICA velocity at 40 and 60% WMax were 8.6 ± 2.7% and 10.6 ± 2.7% (Figure 5.4: B; p = 0.02), respectively. Similarly, mean differences between PreTR and PostTR ICA flow at 40 and 60% WMax were 8.6 ± 2.9 % and 13.7 ± 2.9 % (Figure 5.4: D; p = 0.004), respectively. No main effect or interactions were observed for ICA shear rate (Figure 5.4).

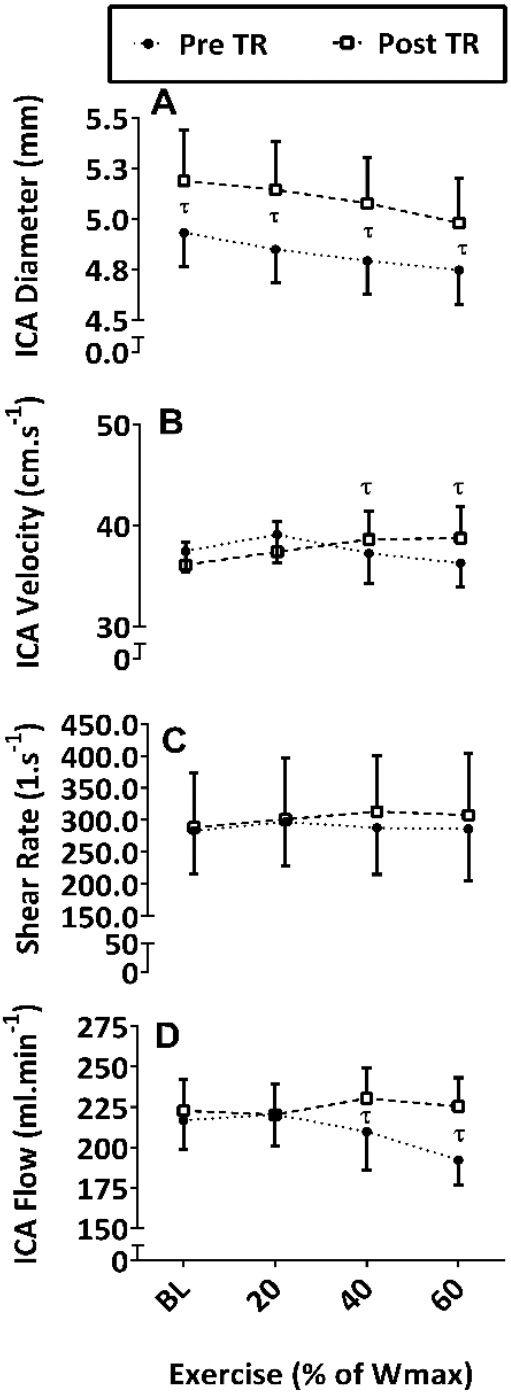

Figure 5.3 Data presented as mean ± standard deviation. Internal carotid artery diameter (A), velocity (B), shear stress (C) and flow at rest (BL) and during 20, 40, and 60% of the maximum achieved workload (% of Wmax). τ signifies interaction and post-hoc revealed differences between pre-training (PreTR) and post-training (PostTR), $p < 0.001$.

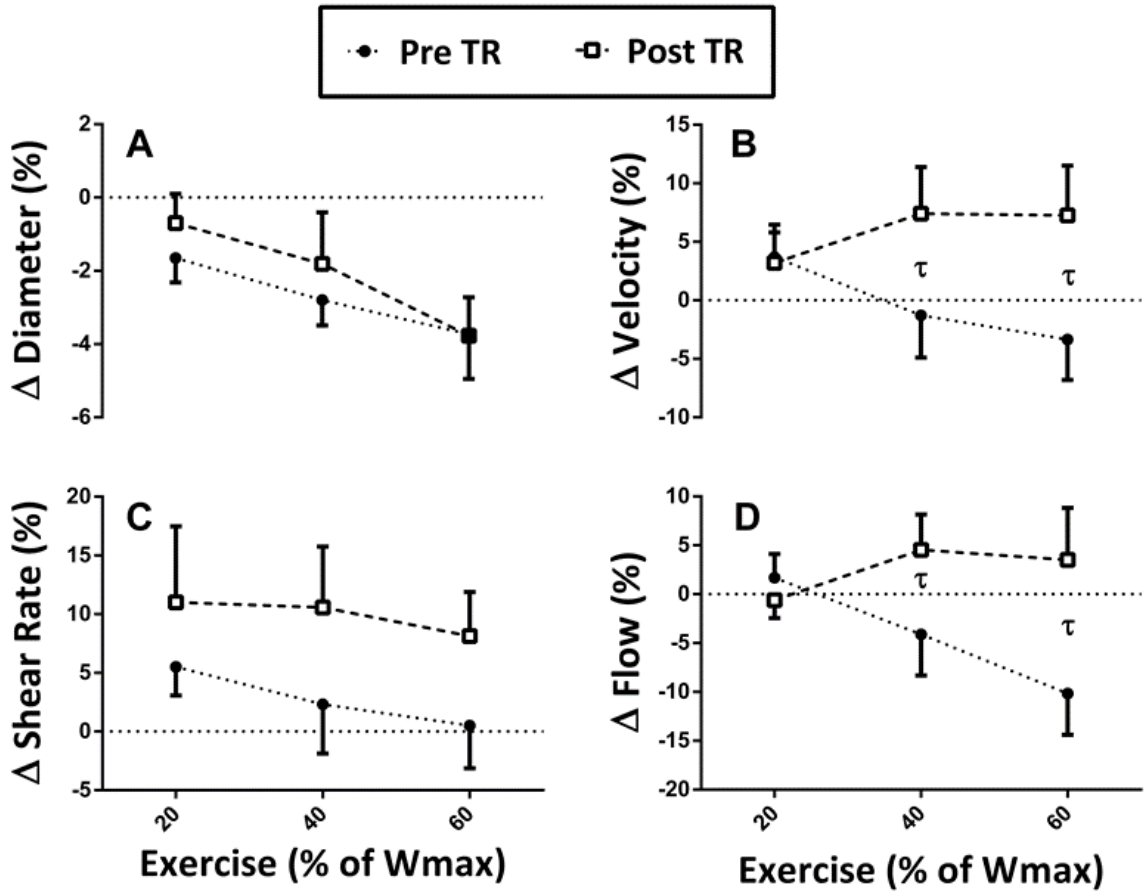

Figure 5.4 Data presented as mean ± standard deviation. Relative change from resting internal carotid artery diameter (A), velocity (B), shear stress (C), and flow (D) during 20, 40, and 60% of the maximum achieved workload (% of Wmax). τ signifies interaction and post-hoc revealed difference between pre-training (PreTR) and post-training (PostTR), $p < 0.001$.

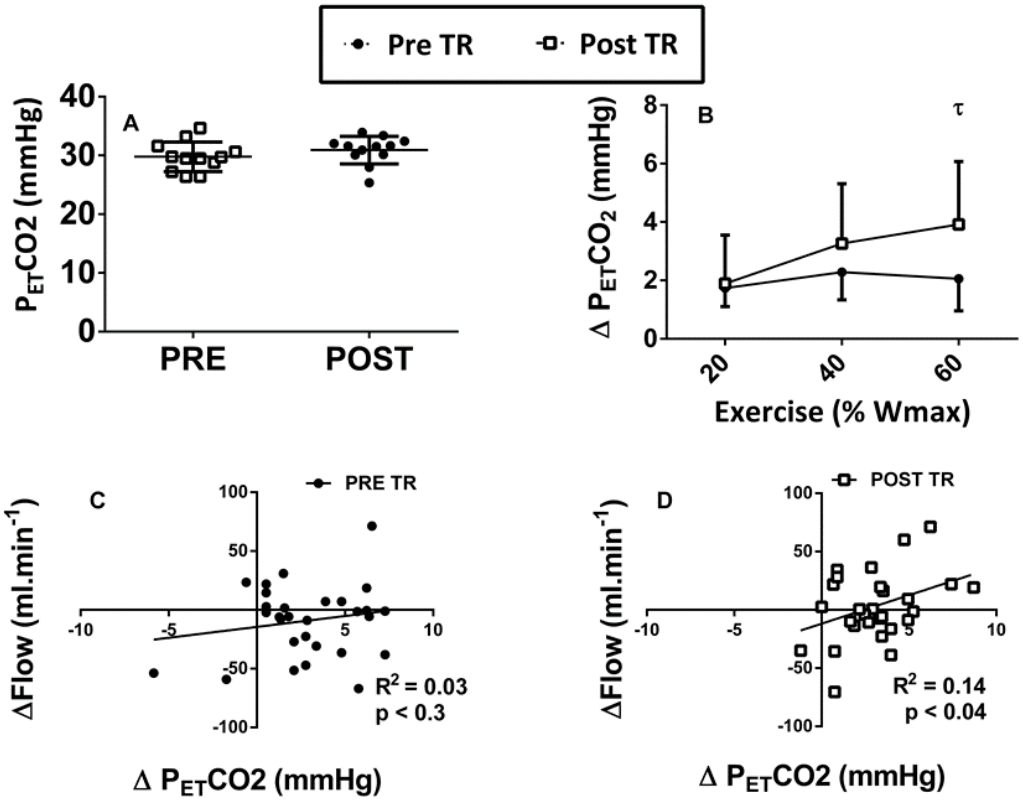

Figure 5.5 Data presented as mean ± standard deviation. Resting (A) partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) and the relative percent change (B) from rest at 20, 40, and 60% of the maximum achieved workload (% of Wmax). Pre (C) and post (D) training relationship between the change in internal carotid artery flow and $P_{ET}CO_2$ during exercise. τ signifies interaction and post-hoc revealed differences between pre-training (PreTR) and post-training (PostTR), $p < 0.001$.

5.3.4 Effect of training on cardiorespiratory measures during exercise

Elevated $P_{ET}CO_2$ was identified at 40, 60, 80 and 100% WMax for both PreTR and PostTR (Table 5.2; $p < 0.001$). A main effect was observed between PreTR and PostTR, revealing a greater post-training $P_{ET}CO_2$ during 40, 60, 80 and 100% Wmax (Figure 5.5: B mean difference = 2.6 ± 0.4 mmHg, $p = 0.03$). No correlation between the change in ICA flow and $P_{ET}CO_2$ was observed PreTR, but a significant correlation was observed PostTR (r = 0.37; $p < 0.05$).

Similar MAP values were observed at each intensity, except during 100% Wmax for pre-training (102 ± 8.7 mmHg) and post-training (108 ± 8.4 mmHg) groups (Figure

5.6: B; $p < 0.01$). Post-hoc analysis following interaction, revealed for the MAP increases from baseline (Figure 5.6: $p = 0.0006$), indicated pre-training changes were lower than post-training at 80 (mean difference between pre and post-training Δ from baseline = -5.8 ± 1.7 mmHg) and 100% Wmax (mean difference between pre and post-training Δ from baseline = -8.2 ± 1.7 mmHg). Post hoc interaction analysis revealed a higher ICA vascular conductance (CVCi) at 60 %Wmax PostTR (Figure 5.6: C; $p = 0.0003$) compared to PreTR values. Exercise progressively increased heart rate similarly in both PreTR and postTR (Table 5.2; $p < 0.05$). No difference between conditions was observed.

5.3.5 Correlations between variables

At rest, $\dot{V}O_2$ peak correlated with ICA velocity (r = 0.596; $p < 0.05$), and ICA flow (r = 0.695; $p < 0.01$). Regarding pre-training data collected during exercise, specifically at 60%Wmax, $\dot{V}O_2$ peak was correlated with PCA (r = 0.551; $p < 0.05$), ICA velocity (r = 0.747; $p < 0.01$), and ICA flow (r = 0.673; $p < 0.05$). There were no correlations between the change in cerebral blood flow parameters and the change of $\dot{V}O_2$ peak.

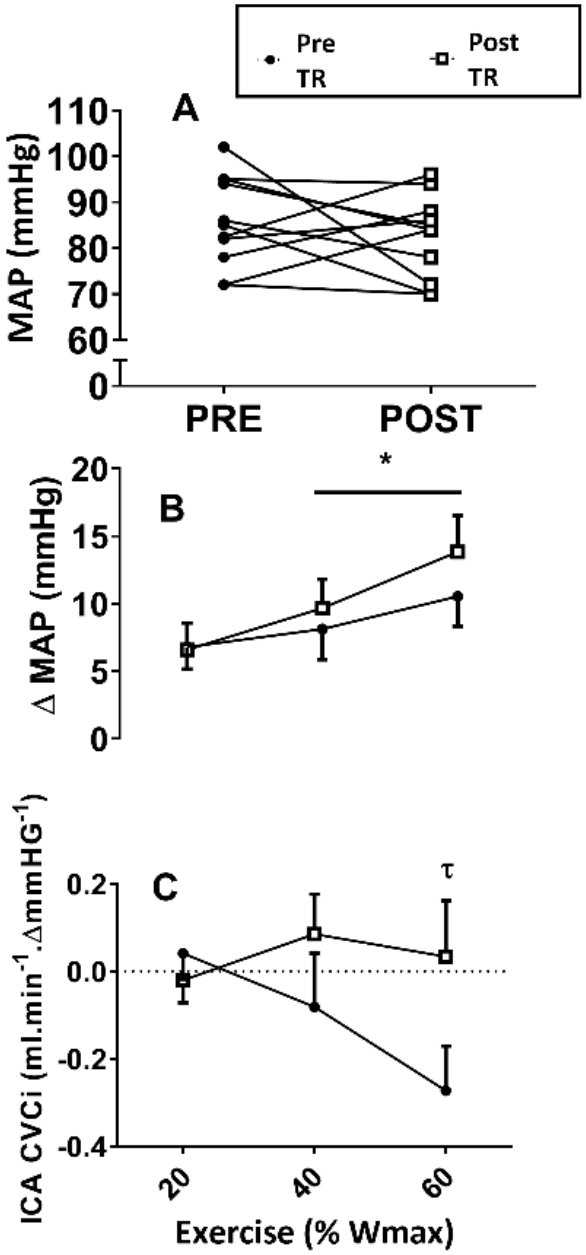

Figure 5.6 Mean arterial pressure (MAP) at rest (panel A) and the absolute change in MAP (panel B: 20–100 of the maximum achieved workload [% of Wmax]) and internal carotid conductance (ICA CVCi: panel C: 20 – 60% Wmax), in participants implanted with left ventricular assist devices (n = 12 - ♀5: ♂7). * signifies main effect difference from BL, $p < 0.05$. τ signifies interaction and post-hoc revealed differences between pre-training (PreTR) and post-training (PostTR), $p < 0.0$

Table 5.2 Cardiorespiratory and cerebrovascular parameters at rest and during exercise (%workload maximum), pre- and post-exercise training

Variable		BL	20	40	60	80	100	Significance
MCAv ($cm.s^{-1}$)	Pre	55.0 ± 14.1	53.0 ± 13.7	53.4 ± 13.4	53.7 ± 13.8	53.1 ± 14.8	51.8 ± 14.3	
	Post	57.6 ± 12.5	53.1 ± 10.3	53.8 ± 10.5	54.7 ± 10.1	54.4 ± 10.2	52.0 ± 10.3	
PCAv ($cm.s^{-1}$)	Pre	43.0 ± 10.8	43.0 ± 9.9	43.1 ± 10.5	43.0 ± 10.7	42.1 ± 10.8	40.6 ± 10.0*****	ME: * $p < 0.05$;
	Post	38.1 ± 10.4 **τ**	39.5 ± 11.2 **τ**	39.6 ± 11.5 **τ**	39.7 ± 12.0 **τ**	39.7 ± 11.6 **τ**	38.5 ± 11.6	INT: τ $p < 0.001$
ICA flow ($ml.min^{-1}$)	Pre	216.8 ± 56.8	220.5 ± 62.2	209.8 ± 75.9	192.2 ± 48.5	-	-	INT: τ $p<0.001$
	Post	222.6 ± 62.5	220.4 ± 59.9	230.4 ± 60.0 **τ**	225.4 ± 56.0 **τ**	-	-	
ICA diameter (mm)	Pre	4.9 ± 0.5	4.8 ± 0.5	4.8 ± 0.5	4.7 ± 0.5	-	-	ME:* $p < 0.05$
	Post	5.2 ± 0.8 **τ**	5.1 ± 0.8 **τ**	5.1 ± 0.7 **τ**	5.0 ± 0.7 **τ**	-	-	
ICA velocity ($cm.s^{-1}$)	Pre	37.4 ± 6.4	39.1 ± 9.0	37.2 ± 9.5	36.3 ± 7.5	-	-	INT: τ $p<0.001$
	Post	36.1 ± 7.3	37.4 ± 9.6	38.6 ± 8.7 **τ**	38.7 ± 9.8 **τ**	-	-	
$P_{ET}CO_2$ (mmHg)	Pre	29.8 ± 2.5	31.5 ± 3.1*****	32.1 ± 3.0*****	31.8 ± 2.9*	31.5 ± 3.3*	30.9 ± 3.4*	ME: * $p < 0.05$;
	Post	30.9 ± 2.3	32.8 ± 2.0***τ**	34.2 ± 2.3***τ**	34.8 ± 2.3***τ**	34.4 ± 2.4***τ**	33.4 ± 3.4***τ**	INT: τ $p < 0.001$
MAP (mmHg)	Pre	85.8 ± 9.8	93.2 ± 10.5	94.6 ± 8.8	97.3 ± 8.7	99.5 ± 7.9	102.6 ± 8.7	ME: * $p < 0.05$;
	Post	82.5 ± 9.0	89.6 ± 8.7	93.0 ± 10.3	97.5 ± 9.6	102.5 ± 8.3	108.3 ± 8.4 **τ**	INT: τ $p < 0.001$
Heart Rate (1/min)	Pre	83 ± 8	95 ± 13*	100 ± 17*	105 ± 21*	110 ± 20*	117 ± 23*	ME:* $p < 0.05$
	Post	78 ± 9	91 ± 6*	96 ± 7*	101 ± 9*	109 ± 12*	119 ± 14*	

Data expressed as mean ± SD. BL, baseline (resting); ICA, internal carotid artery; MAP, mean arterial pressure; MCAv, middle cerebral artery velocity; PCAv, posterior cerebral artery velocity; $P_{ET}CO_2$, end-tidal partial pressure of carbon dioxide; Pre, pre-training; Post, post-training. ME, main effect; INT, interaction effect. * Signifies statistical difference from BL ($p < 0.05$); **τ** signifies statistical difference from Pre-training ($p < 0.001$).

5.4 Discussion

This is the first study, to our knowledge, to measure cerebrovascular function during incremental exercise in patients with LVADs before and after an ET intervention. Our principal finding is that a 12-week ET program significantly enhanced CBF responses to incremental exercise, despite a reduction in absolute intracranial PCAv.

The improved durability of third-generation LVADs and the continuing scarcity of donor organs has led to an increase in the number of LVAD implantations worldwide as destination therapy.[17] Although functional capacity improves from pre-implantation status, recipients of LVADs still experience impaired aerobic capacity and cerebrovascular function during exercise.[5-7] ET is an evidence-based adjunct treatment for patients with CHF.[18-20] While ET is currently being delivered in cardiac-rehabilitation settings to improve functional capacity and health,[1] there is a paucity of evidence regarding its specific effects in patients with LVADs.[12,14,21] We found that a comprehensive ET program, involving aerobic and resistance exercise, is associated with improvements in cerebrovascular function.

In the previous chapter, we found that LVAD implantation normalises CBF at rest, but fails to compensate during exercise, compared with age-matched healthy controls and patients with CHF.[5] In healthy individuals, the exercise CBF response follows a biphasic pattern of initial vasodilation during submaximal exercise, followed by a plateau.[22-24] During submaximal exercise (from 20% to 60% $\dot{V}O_2$ peak), there is typically a 10-20% vasodilatory increase in CBF, which is positively correlated with increases in $P_{ET}CO_2$, MAP and intra-arterial shear rate.[25] We did not observe such increases during exercise in LVAD individuals in our recent study,[5] or in our pre-training LVAD group in this study. A novel study by Brassard et al.[6] found that, in order to increase CBF during exercise in untrained patients with LVADs with continuous-flow pumps, increases in pump speed were required. Other studies investigating the effect of pump speed manipulation during exercise have resulted in trivial[26,27] or no improvement[28,29] in aerobic capacity. These findings suggest that peripheral factors (e.g., cardiorespiratory and musculoskeletal) are likely to play an important role in the ongoing exercise intolerance experienced by patients with LVADs.[1] Following the training program, our cohort of participants with LVADs

improved aerobic capacity, peak workload and cardiorespiratory (i.e., MAP and $P_{ET}CO_2$) responses during incremental exercise. Non-cardiac (musculoskeletal and respiratory) improvements following ET both have the capacity to enhance aerobic capacity and peak achievable workload.[1,7] We did not design or power the present study to identify the relative contribution of specific cardiorespiratory and/or musculoskeletal variables to the changes in cerebral blood flows we observed. Nevertheless, our findings suggest that training-induced improvements occur in parallel with systemic cardiorespiratory responses associated with healthy cerebral hemodynamics during exercise. Therefore the improved aerobic capacity, peak workload and cardiorespiratory responses in the study may be linked to the improved cerebrovascular function in patients with LVADs, in keeping with the suggestion of Brassard et al.,[7] who postulated links between exercise intolerance and cerebral perfusion in CHF.

The enhanced capacity of the brain to respond to physiological and regulatory stimuli is important to maintaining brain health across the lifespan.[30,31] Although a few cross-sectional studies indicate an overall heightened cerebrovascular function in exercise-trained individuals, a more recent study demonstrated that dynamic cerebrovascular autoregulation is modestly attenuated in athletes following six-weeks of high intensity interval training (HIIT), despite no change in resting CBF.[32] It is unknown what impact interval and continuous training intervention had on cerebral autoregulation in our clinical population, but Lewis et al.[33] observed no significant improvement in cerebral autoregulation following an 8-week exercise intervention that included three weeks of HIIT in chronic obstructive pulmonary disease patients, despite a significant increase in $\dot{V}O_2$ peak, which was similar to that observed in the current study. The benefits of HIIT in other clinical populations are not fully established, particularly with respect to changes in brain perfusion. Future research investigating the impact of different forms of ET on cerebrovascular function in clinical populations, including those with heart failure, is warranted.

Cerebrovascular endothelial function is quantified via hypercapnic shear-mediated vasodilation in the internal and common carotid arteries.[34,35] Shear-mediated vasodilation in the extracranial arteries also occurs during exercise in healthy individuals,[25] but not in patients with LVADs.[5] Our findings, including those related

to resting carotid diameters, suggest that ET in patients with LVADs may improve cerebrovascular vasodilation in extracranial arteries. The observed mismatch between relative ICA flow and MCA responses during exercise suggests that intracranial dilation may be present in patients with LVADs in the current study. Because the 5-10% change in ICA flow was not observed in MCA velocity, MCA artery dilation must occur (~2-3%) to achieve conservation of blood flow. Unfortunately, because of technological limitations associated with measuring diameter and velocity in intracranial vessels (i.e., MCA), it is unknown if intracranial blood flow, shear stress and endothelial function can be enhanced by ET in patients with LVADs. Future studies are needed to directly assess cerebrovascular endothelial in patients with LVADs during exercise and resting conditions.

Few studies have assessed the posterior cerebral circulation in patients with LVADs. Our findings indicate that, during exercise, PCAv decreased significantly below baseline levels prior to training, but this did not occur after training. The lack of volumetric blood flow data through the vertebral artery during exercise (technically difficult to obtain) makes it difficult to discern the impact that a lower posterior cerebrovascular perfusion may have on LVAD cerebrovascular health. However, it would appear that ET improves PCAv responses to exercise, potentially via an elevation in cardiorespiratory responses (e.g., a greater increase in MAP and $P_{ET}CO_2$ responses at maximal exercise). Warnert et al.[36] suggested, by the "selfish brain" hypothesis, that maintaining adequate posterior cerebral perfusion is a critical regulatory factor. Although speculative, our data suggest that training may act to maintain adequate perfusion to autonomic centres of the brain. Unfortunately, our data are unable to fully address this speculation, and future studies investigating exercise which control for the impacts of CO_2 and MAP and utilize volumetric posterior CBF measures in patients with LVADs will be required.

Recently, Stohr et al.[37,38] and Cromwell et al.[39,40] discussed the importance of pulsatile flow in maintaining normal cerebral perfusion in patients with LVADs. Both authors stated that resting cerebral perfusion was relatively normalised by LVAD implantation. While Cromwell et al.[39,40] suggested that evidence does not indicate adverse impacts on cerebral processes in non-pulsatile systems, Stohr et al.[37,38] argued that micro-bleeds and endothelial dysfunction may be higher in individuals implanted

with non-pulsatile, compared to pulsatile systems. Our experimental findings indicate that cerebral perfusion can be enhanced in patients implanted with LVADs during exercise and that training generally enhances cerebrovascular perfusion variables. We cannot speculate about the impact of pulsatile versus non-pulsatile LVADs on endothelial function or other outcomes such as cognition or infarction, but the relationships between perfusion and these variables deserve a larger dedicated trial. Since one outcome of LVAD implantation is that enables many patients to return to the gym and undertake more robust and targeted exercise therapy, our findings are encouraging for the positive effects observed in cerebrovascular function. It is also worth remarking that the test modality (semi-recumbent cycle) was different to that undertaking during training (treadmill), our findings therefore reflect a more generalised response to ET that appears to be transferable to other modes of exercise.

There are several limitations to the current study. The most important relates to the lack of a control group, which restricts the interpretation of our results to distinguish between the effects of ET versus spontaneous effects occurring over time. However, participants were recruited to the study, on average, 68 weeks post-LVAD implantation, while receiving optimal medical therapy, pump speed and medication was not changed throughout the intervention. It seems unlikely that our findings were due to spontaneous recovery in such a group or to the short-term impacts of device implantation. Furthermore, in a previous study of ET in patients with LVADs commencing after a similar period of recovery to the current study (>12 weeks), control participants did not show spontaneous changes in aerobic capacity, pulmonary function or quality of life,[14] suggesting that, like our cohort, they were physiologically stable. Similarly to the previous study (Chapter 4), we elected to match CBF responses during incremental aerobic exercise relative to maximal workload achieved in the CPET, rather than absolute workloads. We opted for this approach as CBF has been previously studied and reported relative to maximal capacity, allowing thus comparisons of CBF parameters across individuals with different cardiorespiratory capacity. Furthermore, there is no data to compare at the highest intensities of exercise in the pre-training group due to the lower peak exercise capacity. Another limitation relates to the use of transcranial Doppler ultrasound to assess intracranial cerebral blood flow has some technical limitations. As mentioned above, it is unable to measure intracranial arterial diameters, and thus provides only an index of blood flow via

velocity profiling. Typically, MCA*v* and ICA flow measures follow similar responses, and measurement of ICA calibre is an appropriate surrogate for changes in MCA calibre. However, our findings indicate divergent responses, with ICA flow increasing, due largely to an enhanced velocity, in contrast to no observable changes in MCA velocity. Downstream vasodilation would reduce resistance, or inversely increase conductance, which might explain the lack of velocity change in the MCA. Nonetheless, the lack of direct intracranial diameter assessment in the study remains a limitation and hinders quantification of the contribution of intracranial diameter change during exercise. We have previously mentioned the potential confound of the contralateral differences that may exist in cerebral artery responses,[5] however we applied standardized ultrasound imaging techniques to screen for differences in all intracranial[41] and extracranial[42] vessels. No differences were observed; thus, we interpreted our ICA, MCA and PCA measures to be valid surrogates or global cerebrovascular hemodynamic responses to exercise. Disparate contralateral flow patterns during exercise in patients with LVADs have not been previously observed, and no evidence suggests that contralateral flow patterns would differ in vessels that have been screened to rule out any divergent patterns at rest. Finally, we observed no correlations between the change in cerebral blood flow parameters and the change of $\dot{V}O_2$ peak, which may relate to the relatively modest sample size in this study.

In conclusion, this pilot intervention study found that CBF responses to exercise were increased following a 12-week ET program in patients with LVADs. Our findings, therefore, support the role of short-term ET to improve cerebrovascular function in LVAD patients. Future studies investigating long-term training programs and cerebral and peripheral vascular adaptation are needed.

5.5 References

1. Adamopoulos S, Corra U, Laoutaris ID, et al. Exercise training in patients with ventricular assist devices: a review of the evidence and practical advice. A position paper from the Committee on Exercise Physiology and Training and the Committee of Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2019;21:3-13.
2. Jung MH, Gustafsson F. Exercise in heart failure patients supported with a left ventricular assist device. J Heart Lung Transplant 2015;34:489-96.
3. Cornwell WK, 3rd, Tarumi T, Aengevaeren VL, et al. Effect of pulsatile and nonpulsatile flow on cerebral perfusion in patients with left ventricular assist devices. J Heart Lung Transplant 2014;33:1295-303.
4. Ono M, Joshi B, Brady K, et al. Cerebral blood flow autoregulation is preserved after continuous-flow left ventricular assist device implantation. J Cardiothorac Vasc Anesth 2012;26:1022-8.
5. Smith KJ, Suarez IM, Scheer A, et al. Cerebral Blood Flow during Exercise in Heart Failure: Effect of Ventricular Assist Devices. Med Sci Sports Exerc 2019;51:1372-79.
6. Brassard P, Jensen AS, Nordsborg N, et al. Central and peripheral blood flow during exercise with a continuous-flow left ventricular assist device: constant versus increasing pump speed: a pilot study. Circ Heart Fail 2011;4:554-60.
7. Brassard P, Gustafsson F. Exercise Intolerance in Heart Failure: Did We Forget the Brain? Can J Cardiol 2016;32:475-84.
8. Black MA, Cable NT, Thijssen DH, Green DJ. Importance of measuring the time course of flow-mediated dilatation in humans. Hypertension 2008;51:203-10.
9. Green DJ, Hopman MT, Padilla J, Laughlin MH, Thijssen DH. Vascular Adaptation to Exercise in Humans: Role of Hemodynamic Stimuli. Physiol Rev 2017;97:495-528.

10. Maiorana A, O'Driscoll G, Dembo L, et al. Effect of aerobic and resistance exercise training on vascular function in heart failure. Am J Physiol Heart Circ Physiol 2000;279:H1999-2005.

11. Maiorana A, O'Driscoll G, Cheetham C, et al. The effect of combined aerobic and resistance exercise training on vascular function in type 2 diabetes. Journal of the American College of Cardiology 2001;38:860-66.

12. Hayes K, Leet AS, Bradley SJ, Holland AE. Effects of exercise training on exercise capacity and quality of life in patients with a left ventricular assist device: a preliminary randomized controlled trial. J Heart Lung Transplant 2012;31:729-34.

13. Kerrigan DJ, Williams CT, Ehrman JK, et al. Cardiac Rehabilitation Improves Functional Capacity and Patient-Reported Health Status in Patients With Continuous-Flow Left Ventricular Assist Devices. JACC: Heart Failure 2014;2:653-59.

14. Laoutaris ID, Dritsas A, Adamopoulos S, et al. Benefits of physical training on exercise capacity, inspiratory muscle function, and quality of life in patients with ventricular assist devices long-term postimplantation. European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology 2011;18:33-40.

15. Noble BJ, Borg GA, Jacobs I, Ceci R, Kaiser P. A category-ratio perceived exertion scale: relationship to blood and muscle lactates and heart rate. Med Sci Sports Exerc 1983;15:523-8.

16. Maiorana A, O'Driscoll G, Cheetham C, et al. Combined aerobic and resistance exercise training improves functional capacity and strength in CHF. Journal of Applied Physiology 2000;88:1565-70.

17. Acharya D, Loyaga-Rendon R, Morgan CJ, et al. INTERMACS Analysis of Stroke During Support With Continuous-Flow Left Ventricular Assist Devices: Risk Factors and Outcomes. JACC Heart Fail 2017;5:703-11.

18. Taylor RS, Sagar VA, Davies EJ, et al. Exercise-based rehabilitation for heart failure. Cochrane Database of Systematic Reviews 2014.

19. Swank Ann M, Horton J, Fleg Jerome L, et al. Modest Increase in Peak VO2 Is Related to Better Clinical Outcomes in Chronic Heart Failure Patients. Circ Heart Fail 2012;5:579-85.

20. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur J Heart Fail 2016;18:891-975.

21. Kerrigan DJ, Williams CT, Ehrman JK, et al. Cardiac rehabilitation improves functional capacity and patient-reported health status in patients with continuous-flow left ventricular assist devices: the Rehab-VAD randomized controlled trial. JACC Heart Fail 2014;2:653-9.

22. Moraine JJ, Lamotte M, Berre J, Leduc A, Naeije R. Relationship of mmiddle cerebral artery blood flow velocity to intensity during dynamic exercise in normal subjects. Eur J Appl Physiol 1993;67:35-38.

23. Smith KJ, Wildfong KW, Hoiland RL, et al. Role of CO2 in the cerebral hyperemic response to incremental normoxic and hyperoxic exercise. J Appl Physiol (1985) 2016;120:843-54.

24. Brugniaux JV, Marley CJ, Hodson DA, New KJ, Bailey DM. Acute Exercise Stress Reveals Cerebrovascular Benefits Associated with Moderate Gains in Cardiorespiratory Fitness. J Cereb Blood Flow Metab 2014;34:1873-76.

25. Smith KJ, Hoiland RL, Grove R, et al. Matched increases in cerebral artery shear stress, irrespective of stimulus, induce similar changes in extra-cranial arterial diameter in humans. J Cereb Blood Flow Metab 2019;39:849-58.

26. Jung MH, Hansen PB, Sander K, et al. Effect of increasing pump speed during exercise on peak oxygen uptake in heart failure patients supported with a continuous-flow left ventricular assist device. A double-blind randomized study. Eur J Heart Fail 2014;16:403-8.

27. Mezzani A, Pistono M, Corrà U, et al. Systemic perfusion at peak incremental exercise in left ventricular assist device recipients: Partitioning pump and native left ventricle relative contribution. IJC Heart & Vessels 2014;4:40-45.

28. Fresiello L, Buys R, Timmermans P, et al. Exercise capacity in ventricular assist device patients: clinical relevance of pump speed and power. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2016;50:752-57.

29. Noor MR, Bowles C, Banner NR. Relationship between pump speed and exercise capacity during HeartMate II left ventricular assist device support: influence of residual left ventricular function. Eur J Heart Fail 2012;14:613-20.

30. Ainslie PN, Cotter JD, George KP, et al. Elevation in cerebral blood flow velocity with aerobic fitness throughout healthy human ageing. J Physiol 2008;586:4005-10.

31. Bennett MK, Roberts CA, Dordunoo D, Shah A, Russell SD. Ideal methodology to assess systemic blood pressure in patients with continuous-flow left ventricular assist devices. J Heart Lung Transplant 2010;29:593-94.

32. Drapeau A, Labrecque L, Imhoff S, et al. Six weeks of high-intensity interval training to exhaustion attenuates dynamic cerebral autoregulation without influencing resting cerebral blood velocity in young fit men. Physiol Rep 2019;7:e14185.

33. Lewis N, Gelinas JCM, Ainslie PN, et al. Cerebrovascular function in patients with chronic obstructive pulmonary disease: the impact of exercise training. Am J Physiol Heart Circ Physiol 2019;316:H380-H91.

34. Hoiland RL, Smith KJ, Carter HH, et al. Shear-mediated dilation of the internal carotid artery occurs independent of hypercapnia. Am J Physiol Heart Circ Physiol 2017;313:H24-H31.

35. Carter HH, Atkinson CL, Heinonen IHA, et al. Evidence for Shear Stress–Mediated Dilation of the Internal Carotid Artery in Humans. Hypertension 2016;68:1217-24.

36. Warnert EAH, Hart EC, Hall JE, Murphy K, Wise RG. The major cerebral arteries proximal to the Circle of Willis contribute to cerebrovascular resistance in humans. J Cereb Blood Flow Metab 2016;36:1384-95.

37. Stöhr EJ, McDonnell BJ, Colombo PC, Willey JZ. CrossTalk proposal: Blood flow pulsatility in left ventricular assist device patients is essential to maintain normal brain physiology. J Physiol 2019;597:353-56.

38. Stohr EJ, McDonnell BJ, Colombo PC, Willey JZ. Rebuttal from Eric J. Stohr, Barry J. McDonnell, Paolo C. Colombo and Joshua Z. Willey. J Physiol 2019;597:361-62.

39. Cornwell WK, 3rd, Tarumi T, Lawley J, Ambardekar AV. CrossTalk opposing view: Blood flow pulsatility in left ventricular assist device patients is not essential to maintain normal brain physiology. J Physiol 2019;597:357-59.

40. Cornwell WK, 3rd, Tarumi T, Lawley J, Ambardekar AV. Rebuttal from William K. Cornwell III, Takashi Tarumi, Justin Lawley and Amrut V. Ambardekar. J Physiol 2019;597:363-64.

41. Willie CK, Colino FL, Bailey DM, et al. Utility of transcranial Doppler ultrasound for the integrative assessment of cerebrovascular function. J Neurosci Methods 2011;196:221-37.

42. Thomas KN, Lewis NC, Hill BG, Ainslie PN. Technical recommendations for the use of carotid duplex ultrasound for the assessment of extracranial blood flow. Am J Physiol Regul Integr Comp Physiol 2015;309:R707-20.

Chapter 6 Experimental study 4

The effects of different intensities of exercise training in patients with left ventricular assist devices

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The following chapter has been submitted for publication as original research work to the Journal of Heart and Lung Transplantation.

Declaration of candidate contribution

For the following co-authored manuscript, the candidate contributed to the conception of the experiment, acquisition and analyses of the data, interpreted the results, and drafted the manuscript.

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6.1 Introduction

Left ventricular assist devices (LVADs) are becoming an increasingly common treatment for patients with advanced chronic heart failure (CHF), resulting in improved survival,[1-3] quality of life (QoL) and exercise tolerance.[4,5] However, despite the augmented cardiac output resulting from an LVAD, aerobic capacity an important prognostic indicator in CHF,[6] remains significantly impaired compared with normative values.[7] While exercise rehabilitation is an evidence-based adjunct to medical management in the treatment of patients with CHF, there remains a dearth of research into the effects of supervised exercise training (ET) in patients with LVADs, with only three randomised controlled trials (RCTs) to date.[8-10] These studies applied short duration periods of training (6-10 weeks) and moderate intensity training (50 to 60% of cardiorespiratory reserve) but failed to demonstrate an increase in aerobic capacity with ET, compared with a home walking program prescribed in the control groups.[8-10]

A method of ET that has gained popularity in recent years in cardiac rehabilitation is high intensity interval training (HIIT).[11-14] HIIT involves alternating bouts of high and moderate-intensity exercise and has consistently been found to be well-tolerated[15] and more effective at improving aerobic capacity than moderate-intensity continuous aerobic exercise (MICT).[14] In the seminal work of Wisloff et al.,[16] 12 weeks of HIIT in patients with CHF increased $\dot{V}O_2$ peak significantly more than MICT. Furthermore, a recent meta-analysis found that HIIT was more effective than MICT at improving vascular endothelial function,[12] an important indicator of vascular health, which is commonly impaired in patients with CHF.[17] However, it remains unknown as to whether HIIT training is feasible, safe and effective for patients with an LVAD *in situ*. Therefore, the primary objective of the present trial was to evaluate the safety and efficacy of a 12-week HIIT program compared with MICT on $\dot{V}O_2$ peak. Secondary outcomes included functional capacity as measured by six-minute walk test distance (6MWTD), cardiac function and structure, vascular endothelial function, body composition, leg strength, QoL and biomedical blood markers.

6.2 Methods

6.2.1 Study design

This was a prospective, parallel-group RCT with 1:1 participant ratio involving three participating sites in Australia: Fiona Stanley Hospital (FSH, Perth), St Vincent's Hospital (SVH, Sydney) and The Alfred Hospital (TAH, Melbourne). The trial was approved by the Ethics and Research Governance Units of FSH (REG15-164) as well as by TAH and SVH (HREC/297/16). Curtin University Human Research Ethics Committee (HR13/2016) granted reciprocal ethical approval. The study was prospectively registered with Australia and New Zealand Clinical Trials Registry (ACTRN12616001596493) and conducted and reported according to SPIRIT and CONSORT guidelines. Moreover, it was notified under the Clinical Trial Notification Scheme (CT2016CTN040471) and received by The Therapeutic Goods Administration (TGA). All participants provided written and oral informed consent prior to enrolment in the study. The trial was conducted between November 2016 and July 2019.

6.2.2 Participants

Patients who had undergone continuous-flow LVAD implantation were screened for participation. Eligibility criteria included having an LVAD for a minimum period of six weeks, haemodynamic stability and aged older than 18 years. Exclusion criteria were having contraindications to exercise testing or training (e.g. unstable angina, uncontrolled arrhythmias, severe symptomatic aortic valve stenosis, acute systemic infection), myocardial/skeletal muscle ischemia, or severe musculoskeletal disorders, respiratory disease or any other non-cardiac condition that would preclude participation in an exercise program.

6.2.3 Study procedure

Assessments were conducted at baseline and after the completion of the 12-week ET program. Baseline and follow-up assessments were performed at the same time of day to exclude diurnal variation and were tested with participants taking their prescribed medications. Participants were block randomised to either HIIT or MICT according to the recruitment site using an automated clinical trials allocation system operated by a

third party. To ensure allocation concealment, researchers conducted randomisation once baseline assessments were completed. Participants were instructed not to alter their routine level of physical activity, conducted outside the trial, during the study.

6.2.3.1 Aerobic capacity assessment

A cardiopulmonary exercise test (CPET) was performed using a Modified Naughton Protocol to volitional exhaustion on a treadmill, commencing at Stage 2 with two-minutely increments in grade and/or speed.[18] Breath-by-breath expired gas analysis was measured by indirect calorimetry using a calibrated metabolic analysis system (Vyntus Jaeger CPX, Carefusion, Hoechberg, Germany). Peak oxygen consumption ($\dot{V}O_2$ peak) was calculated as the highest $\dot{V}O_2$ recorded during the exercise test averaged over a 30-second period. Twelve-lead electrocardiogram (PC-ECG 1200, Norav Medical Ltd., Yokneam, Israel) and pulse oximetry (Oxypleth 520A, Novametrix Medical Systems Inc., Wallingford, Connecticut, USA) were measured continuously at rest and throughout exercise. Mean arterial pressure (MAP) (Dopplex MD2, Huntleigh Healthcare Ltd., Cardiff, UK) and rating of perceived exertion (Borg Category Scale)[19] were recorded during the final 30 seconds of each two-minute stage and at peak exercise.[20,21]

6.2.3.2 Submaximal exercise capacity assessment

A 6MWT was performed using a standardised protocol according to the American Thoracic Society guidelines.[22] The 6MWT was conducted at least two days apart from the CPET, in a temperature-controlled, flat, quiet and straight corridor, with marked lines to indicate a 30-metre course. Two tests were conducted at baseline to account for familiarisation, with at least 30-minutes rest between each test and the best result utilised for analysis.

6.2.3.3 Stress echocardiographic assessment

Echocardiographic assessment was performed at rest, and immediately following completion of the CPET to determine peak exercise cardiac function. Immediately after the CPET termination, participants returned to a left lateral decubitus position. A standardised protocol was employed across sites to ensure comparability of results.[23] Experienced echocardiographers performed traditional diagnostic echocardiographic

assessments using a Doppler ultrasound system (Epiq 5, Phillips Medical Systems, Eindhoven, The Netherlands), with 2D and novel post-hoc myocardial tissue imaging (speckle and strain) to assess regional diastolic and systolic function. Left ventricular (LV) reserve was determined using traditional LV dimensions (linear and volume). In addition, longitudinal and circumferential strain was assessed to evaluate residual contractility. Right heart function was measured in the lateral tricuspid annular region in the apical four-chamber view. Raw data were recorded as DICOM files and sent to the coordinating site (FSH) to allow post-hoc analysis by the same analyser.

6.2.3.4 Vascular endothelial function assessment

Endothelium-dependent arterial function was assessed using flow-mediated dilation (FMD) of the brachial artery. In accordance with guidelines,[24] participants were assessed in a quiet, temperature-controlled room after fasting for ≥6 hours and after abstaining from moderate to vigorous exercise, alcohol, and caffeine for ≥24 hours. Prior to imaging, participants rested in a supine position for 20 minutes. Mean arterial blood pressure was assessed at 18 minutes and 20 minutes of rest and measurements were undertaken once blood pressure was stable. A portable high-resolution duplex ultrasound system (Terason T3200, Teratech, Burlington, MA) was used to record B-mode images of the brachial artery in the longitudinal plane proximal to the antecubital fossa. A high- resolution linear array ultrasound transducer was used for measurements (15L4; Terason) and the angle of insonation was <60°. Vessel diameter and blood flow velocity were recorded for a 1-minute baseline. Subsequently, a blood pressure cuff (Flexi Port, Welch Allyn, New York, USA) positioned on the participant's forearm distal to the olecranon process, was inflated to 220mmHg for 5 minutes to provide an ischaemic stimulus. Recording resumed 30 seconds prior to cuff deflation and continued for 3 minutes post-ischaemic stimulus. Images were then analysed with custom-designed edge detection software. This method has been previously described in detail and found to reduce examiner variability compared to manual methods.[25,26]

6.2.3.5 Anthropometric assessment

A whole-body fan-beam dual-energy X-ray absorptiometry (DXA) scan (Hologic Discovery A SN87390 DPX-IQ, Massachusetts, USA) was employed to determine total skeletal muscle mass, fat mass, and bone mineral density.

6.2.3.6 Muscular leg strength assessment

Maximal isotonic voluntary strength was assessed by using the one-repetition maximum (1-RM) method on a seated dual leg press pin-loaded resistance training equipment (Cybex International Inc., Medway, MA, USA). Participants were instructed to lift the weight with the correct technique and avoiding the Valsalva Manoeuvre. One-repetition maximum was defined as the weight that the subject could lift only once, with three minutes of rest between sets and load increments of 5 kg.

6.2.3.7 Quality of life and self-efficacy assessments

The 12-item Short Form Health Survey (SF-12) was administered to all participants to measure health-related QoL. This self-reported questionnaire measures a variety of health domains and gives two aggregate summary measures: the physical component score (PCS) and the mental component score (MCS). These scores rank in a scale from 0-100, where the higher the score, the less disability.[27] Additionally, exercise self-efficacy was measured by using the 16-item Heart Disease Self-Efficacy (HDSE) scale, slightly modified from a previously validated physical activity scale[28,29] to make it more appropriate for patients with CHF. This scale was used to rate the perceived ability of the participants to begin, continue and complete activities under a range of specific circumstances. The scale measures the strength of efficacy beliefs against a 100-point scale, ranging in 10-unit intervals from '0' (cannot do), through '50' (moderately certain can do), to 100 (absolutely certain can do).

6.2.3.8 Blood analyses

Blood samples were drawn by standard venepuncture between 8 to 10 am after an overnight fast. Full blood picture, serum creatinine (CR), C-reactive protein (CRP), total cholesterol (Chol), serum triglycerides (TG), low-density lipoprotein cholesterol (LDL), high-density lipoprotein (HDL) and B-type natriuretic peptide (BNP) were analysed by standard laboratory methods according to the clinical pathology laboratory procedures at the site.

6.2.4 Exercise training protocol

Exercise training occurred for approximately one hour, three times per week for 12 weeks, in a hospital gymnasium supervised by experienced exercise physiologists and

physiotherapists. Each session commenced/concluded with a warm-up/cool-down, involving five minutes of low-intensity aerobic exercise (<40% of $\dot{V}O_2$ reserve), followed by five minutes of muscular stretching. A detailed log of attendance and exercise performed by each participant was kept and an independent safety monitoring board was established. Safety was assessed by the rate of serious adverse events (SAEs), defined as all-cause death, worsening heart failure requiring hospitalisation or intensified medication treatment, atrial and ventricular arrhythmias, unstable angina, inappropriate implantable cardioverter-defibrillator shocks, and other events leading to hospital admission. Any SAEs were required to be reported to the trial cardiologist and HREC, in accordance with the Therapeutic Goods Administration guidelines for Good Clinical Practice in Australia.[30]

6.2.4.1 High-intensity interval training

The HIIT protocol consisted of aerobic exercise performed on a treadmill and comprised of four sets of four-minute efforts at 80-90% of $\dot{V}O_2$ reserve, interspersed with 3-minutes active recovery at 50-60% of $\dot{V}O_2$ reserve (Figure 6.1: Panel A), consistent with training protocols employed in previous studies.[12,31]

6.2.4.2 Moderate-intensity continuous training

The MICT protocol consisted of continuous aerobic exercise, also performed on a treadmill at 50-60% $\dot{V}O_2$ reserve for 28 minutes, such that the total duration of ET was matched across both groups (Figure 6.1: Panel B). This is similar to the ET intervention employed in previous RCTs in patients with LVADs,[8,9] and typical of usual care exercise rehabilitation in clinical practice.[32,33]

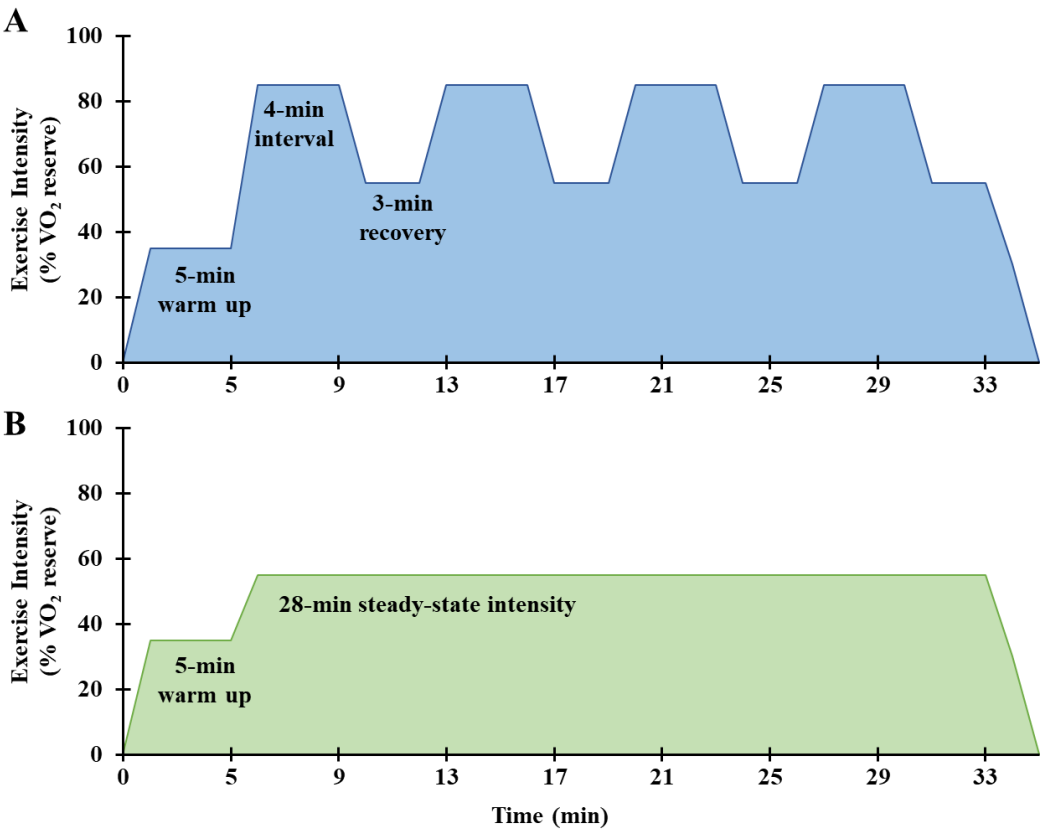

Figure 6.1 Comparison of training interventions. Panel A, HIIT protocol: 4x4 min at 80-90% $\dot{V}O_2$ reserve interspersed with 3-min active recovery at 50-60% $\dot{V}O_2$ reserve. Panel B, MICT protocol: 28-min at 50-60% $\dot{V}O_2$ reserve walking up an incline on the treadmill.

6.2.4.3 Exercise training prescription

Aerobic exercise intensity was primarily guided by the speed and grade of the treadmill based on the baseline CPET that elicited the desired percentage of $\dot{V}O_2$ reserve. Heart rate (HR) reserve, which correlates well with $\dot{V}O_2$ reserve in patients with LVADs,[34] and rating of perceived exertion using Borg's Category Scale, measured during the fourth minute of the final high intensity interval (HIIT group) and the final minute of aerobic exercise (MICT group) were used to refine the training intensities.[35] The exercise program was reviewed every two weeks to adapt to cardiopulmonary changes by progressively increasing the intensity as tolerated. This was progressed based on the rating of perceived exertion by using Borg's Category Scale and HR monitoring, so that participants remain in their target training intensity zone.

Both groups undertook identical resistance training protocols, following the aerobic training component of the exercise session. The resistance training exercises involved one set (8 to 12 repetitions) of three lower body exercises (leg press, hamstring curl, leg extension) and three upper body exercises (incline press, lat. pulldown and biceps curl) at 50-60% 1-RM.

6.2.5 Statistical analysis

A power test based on data from a previous study comparing HIIT vs. MICT in CHF[16], indicated a sample size of 24 was required to test the primary hypothesis based on a mean difference between groups in the change in the primary outcome ($\dot{V}O_2$ peak) of 2.5 $mL \cdot kg^{-1} \cdot min^{-1}$ and a standard deviation (SD) of 2.5 $mL \cdot kg^{-1} \cdot min^{-1}$ assuming 80% power and $p < 0.05$ level of significance. Statistical analysis was conducted using STATA software (version 15.1, StataCorp, College Station, TX, USA). Baseline characteristics and ET intensity of the two groups were compared using Student's independent *t*-test or the Mann-Whitney *U*-test, depending on whether data were parametric or not. For nominal data, chi-square test was used. The principle of intention-to-treat was applied using linear mixed models (LMM) in which all available data were included, with random subject effects to estimate within- and between-group differences in primary and secondary outcomes over time adjusting for recruitment site. The model fit was checked by residual plots.[36] Contrast were employed to assess the difference of change between groups based on the model. Results are summarised as marginal means with 95% confidence intervals (CIs), unless otherwise stated. All analyses were two-tailed and $p < 0.05$ was considered statistically significant.

6.3 Results

6.3.1 Baseline characteristics

Twenty-three patients consented to participate in the trial (20 from FSH, two from SVH and one participant from TAH). Complete data were obtained from 16 participants (Figure 6.2). Baseline characteristics were not significantly different between groups (Table 6.1). Prior to study commencement, HIIT group participants had the LVAD *in situ* for a median of 90 days (range: 49 to 1223), while participants

in the MICT group had the LVAD *in situ* for a median of 103 days (range: 54 – 2139); (p = 0.623). Participants in the HIIT and MICT groups who completed the trial attended 93 ± 4% and 94 ± 5% of their scheduled exercise sessions, respectively.

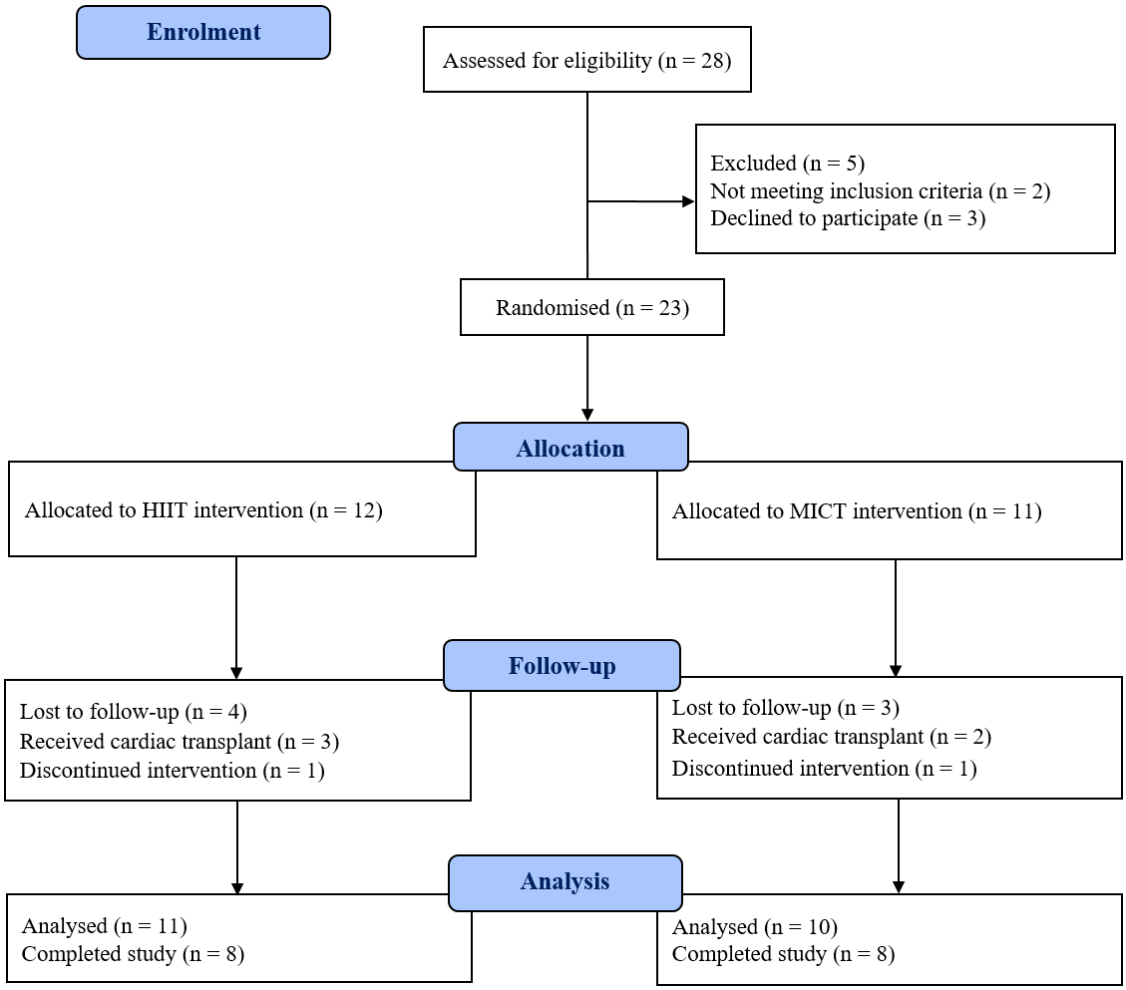

Figure 6.2 Consolidated Standards of Reporting Trials (CONSORT)[37] flow diagram of participants through the trial.

Table 6.1 Participant's characteristics at baseline

Characteristic	**HIIT group (n = 11)**	**MICT group (n =10)**	*p*-value
Age (years)	57.7 ± 13.1	55.6 ± 14.2	0.736
Female sex (%)	3 (28%)	5 (50%)	0.313
Weight (kg)	83.6 ± 14.9	82.6 ± 13.0	0.908
Height (cm)	175.3 ± 9.5	169.3 ± 4.1	0.473
BMI (kg/m^2)	27.3 ± 4.2	29.0 ± 4.4	0.376
BSA (cm^2)	2413 ± 261	2459 ± 174	0.847
Ischemic cardiomyopathy	6 (55%)	5 (50%)	0.823
HR rest (1/min)	86.7 ± 8.7	84.3 ± 9.3	0.683
MAP rest (mmHg)	86.4 ± 9.6	85.1 ± 9.5	0.847
MPA (mmHg)	34.8 ± 14.6	39.9 ± 14.6	0.300
EF (%) pre-LVAD	23.6 ± 11.3	21.2 ± 5.2	0.424
CO (L/min) pre-LVAD	3.6 ± 1.2	4.4 ± 1.3	0.251
CI ($L/min/m^2$) pre-LVAD	1.9 ± 0.6	2.2 ± 0.7	0.206
PAWP (mmHg) pre-LVAD	26.6 ± 8.5	27.4 ± 6.2	0.932
Haemoglobin (g/L)	129 ± 4	126 ± 4	0.662
Haematocrit (L/L)	0.40 ± 0.0	0.39 ± 0.0	0.725
INTERMACS profile			0.530
2	2 (18%)	2 (10%)	
3	5 (27%)	3 (30%)	
4	2 (36%)	1 (30%)	
5	0 (9%)	2 (20%)	
6	1 (9%)	2 (10%)	

Indication for LVAD (%)			0.517
Bridge-to-transplant	7 (55%)	7 (70%)	
Bridge-to-candidacy	0 (0%)	1 (10%)	
Bridge-to-recovery	1 (9%)	0 (0%)	
Destination therapy	3 (36%)	2 (20%)	
LVAD type			0.856
HeartMate II	2 (18%)	1 (30%)	
HeartMate 3	5 (36%)	6 (50%)	
HeartWare	4 (45%)	3 (30%)	
CRT/CRTD	3 (28%)	2 (20%)	0.713
Medical therapy			
ACE-I or ARB	9 (82%)	8 (80%)	0.909
β-blockers	5 (45%)	6 (60%)	0.502
Aldosterone antagonist	2 (18%)	2 (20%)	0.909
Anticoagulants	10 (90%)	10 (100%)	0.316
Loop diuretics	8 (72%)	9 (90%)	0.310
Antiarrhythmic	3 (28%)	2 (20%)	0.677

Values are expressed as mean ± standard deviation, or as number and percentage where appropriate. BMI, body mass index; INTERMACS, interagency registry for mechanically assisted circulatory support; HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; EF, ejection fraction; CO, cardiac output; CI, cardiac index; PAWP, pulmonary artery wedge pressure; CRT/CRTD, cardiac resynchronization therapy defibrillator ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker. *p*-value for comparison between groups.

6.3.2 Exercise training intensity

The average estimated workload on the treadmill during the aerobic ET protocol was significantly higher in the HIIT group (3.6 ± 0.9 METs) compared with the MICT group (3.0 ± 0.4 METs; $p < 0.001$, Figure 6.3). This corresponded to a mean relative ET intensity of 72 ± 15 %$\dot{V}O_2$ reserve for the HIIT, versus 54 ± 5 %$\dot{V}O_2$ reserve for the MICT group ($p < 0.001$). The median rating of perceived exertion reported was significantly higher in the HIIT group (16 (IQR: 14-17)) in comparison with the MICT group (13 (IQR: 12-14); $p < 0.001$).

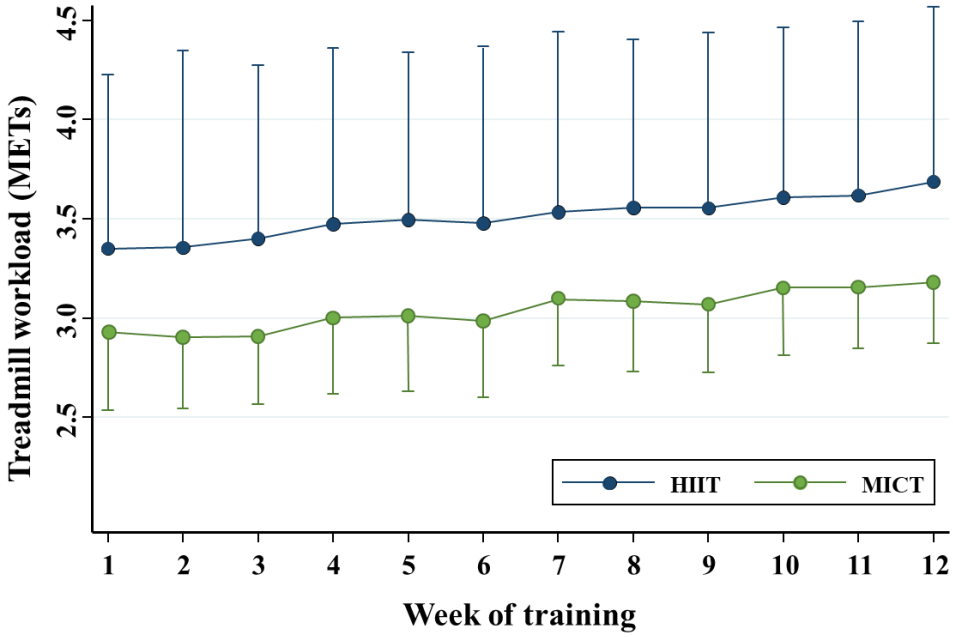

Figure 6.3 Average workload (mean ± SD) on treadmill during aerobic exercise training protocol over the 12 weeks of training.

6.3.3 Safety of exercise

No SAEs occurred in either of the training interventions. Of the total 336 individual exercise sessions in the MICT group, one participant experienced an episode of supraventricular tachycardia during a training session and stopped exercising prematurely. There were no adverse events of any kind in the 345 individual exercise sessions in the HIIT group. Similarly, no adverse events occurred during the CPET in either group.

6.3.4 Aerobic capacity

There was no significant difference in $\dot{V}O_2$ peak between groups at baseline. HIIT improved $\dot{V}O_2$ peak ($p < 0.001$), while the change in $\dot{V}O_2$ peak in the MICT group was not significant (Figure 6.4). There was a significant difference in the change in $\dot{V}O_2$ peak between groups of 1.9 $mL \cdot kg^{-1} \cdot min^{-1}$ (95% CI, 0.3 to 4.2; $p < 0.05$) (Table 6.2). The minute ventilation/carbon dioxide production ($\dot{V}E/\dot{V}CO_2$) slope decreased in the HIIT group ($p < 0.01$), while no change was observed in the MICT group. Test duration was significantly increased in both groups after training. There were no differences in peak HR, MAP or RER between groups, either before or after training.

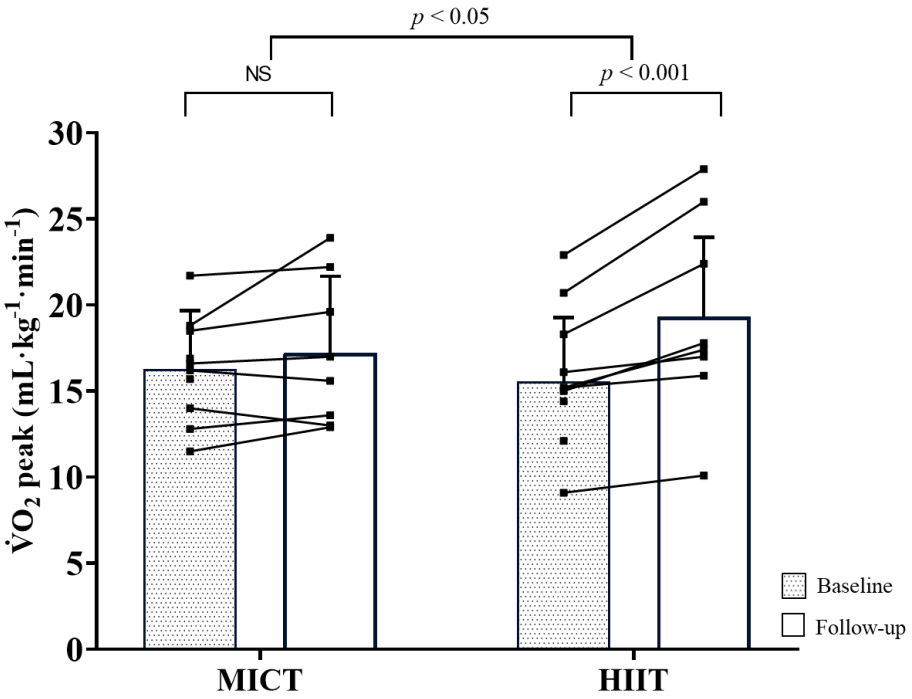

Figure 6.4 Change in peak oxygen uptake before and after training in the MICT versus the HIIT group.

Table 6.2 Cardiopulmonary exercise testing data.

	HIIT group		MICT group		
Parameter	Baseline	Follow up	Baseline	Follow up	*p*-value
$\dot{V}O_2$ peak ($mL \cdot kg^{-1} \cdot min^{-1}$)	15.6 (13.2 to 17.8)	18.4 (16.0 to 20.8)**	16.2 (13.8 to 18.7)	17.2 (14.6 to 19.7)	0.029
$\dot{V}O_2$ peak ($L \cdot min^{-1}$)	1.31 (1.07 to 1.55)	1.60 (1.35 to 1.86)**	1.38 (1.13 to 1.64)	1.48 (1.21 to 1.75)	0.067
% of predicted $\dot{V}O_2$ peak	48.2 (41.6 to 54.8)	56.8 (50.0 to 65.7)**	50.2 (43.2 to 57.1)	53.0 (45.7 to 60.3)	0.045
MAP peak (mmHg)	112 (104 to 119)	117 (109 to 126)	105 (97 to 112)	108 (99 to 117)	0.772
HR peak (1/min)	131 (119 to 142)	139 (126 to 152)	129 (116 to 141)	133 (120 to 146)	0.486
$\dot{V}E/\dot{V}CO_2$ slope	34.3 (32.0 to 36.6)	31.2 (28.7 to 33.7)*	32.9 (30.6 to 35.2)	31.5 (28.7 to 34.3)	0.352
Test duration (s)	621 (502 to 741)	764 (641 to 887)*	582 (457 to 708)	690 (560 to 819)*	0.374
Peak RER	1.12 (0.98 to 1.27)	1.11 (0.96 to 1.25)	1.13 (0.98 to 1.28)	1.18 (1.03 to 1.35)	0.129

Data are presented as estimated marginal mean with 95% CIs. *p*-value for between-group comparisons calculated as adjusted contrast by LMM. * signifies statistically significant within-group difference for $p < 0.05$ and ** for $p \leq 0.001$ by using LMM. $\dot{V}O_2$, oxygen consumption; MAP, mean arterial pressure; HR, heart rate; $\dot{V}E/\dot{V}CO_2$, minute ventilation/carbon dioxide production; RER, respiratory exchange ratio.

6.3.5 Six minute walk test results

There was no difference between groups in 6MWTD at baseline. Both MICT and HIIT increased 6MWTD from baseline to follow-up ($p < 0.001$) but there was no difference between groups (27 m, 95%CI, -18 to 73; $p = 0.241$); Figure 6.5.

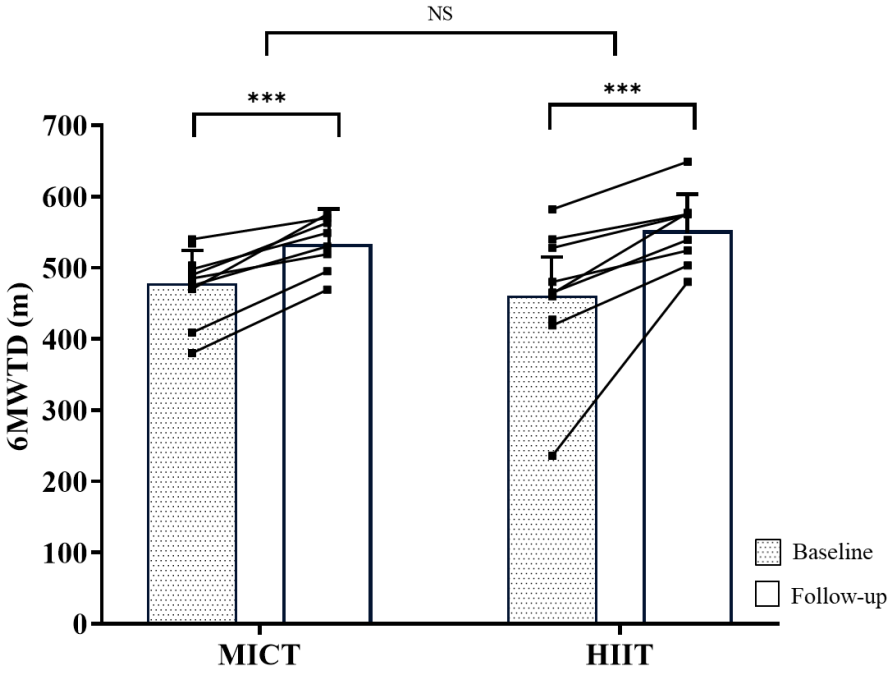

Figure 6.5 Change in 6-minute walk test distance before and after training in the MICT versus the HIIT group.

6.3.6 Muscular leg strength

Leg strength was similar in both groups before the exercise intervention. Both the HIIT [from 107 (95%CI, 93-121) to 125 (95%CI, 110-139 kg] and the MICT group [94 kg (95%CI, 80 to 107) to 113 kg (95%CI, 100 to 126)] improved significantly after the completion of the ET program, but there was no difference between groups ($p = 0.778$).

6.3.7 Vascular endothelial function

Similar values for baseline and peak diameters, FMD%, time to peak and shear rate area under the curve were observed in both groups at baseline (pre-training). MICT significantly increased FMD% ($p < 0.05$) but there was no change in the HIIT group (Table 6.3) and no significant difference between groups (-0.78%, 95%CI, -2.4 to 0.9).

Table 6.3 Vascular endothelial function data by flow-mediated dilation on the brachial artery

	HIIT group		MICT group		
Variable	**Baseline**	**Follow up**	**Baseline**	**Follow up**	*p*-value
Baseline diameter (mm)	3.9 (3.4 to 4.3)	3.9 (3.3 to 4.4)	3.6 (3.2 to 4.0)	3.6 (3.2 to 3.9)	0.823
Peak diameter (mm)	4.2 (3.7 to 4.7)	4.2 (3.6 to 4.7)	3.5 (3.0 to 4.1)	3.9 (3.4 to 4.5)	0.313
FMD (%)	7.4 (5.6 to 9.2)	8.0 (6.1 to 9.9)	6.9 (5.1 to 8.8)	8.5 (6.6 to 10.4)*	0.182
Time to peak (s)	102 (85 to 119)	72 (51 to 92)*	92 (75 to 110)	65 (45 to 87)*	0.833
SR_{AUC} (a.u.)	34992 (25358 to 44627)	27033 (16564 to 37502)	37946 (28311 to 47579)	35574 (25106 to 46043)	0.292

Data are presented as estimated marginal means with 95% CIs. *p*-value for between-group comparisons calculated as adjusted contrast by LMM. FMD, flow-mediated dilation; $SR_{AUC,}$ shear rate area under the curve. * signifies $p < 0.05$ for within-group comparison by LMM.

6.3.8 Cardiac function and structure

The HIIT and MICT groups were well matched for echocardiographic parameters at baseline and there were no significant differences, either at rest or peak exercise, within or between groups (Table 6.4).

Table 6.4 Effects of HIIT versus MICT on cardiac function parameters at rest and peak exercise

		HIIT group		MICT group		
Parameter	**Stress**	**Baseline**	**Follow-up**	**Baseline**	**Follow up**	***p*-value**
LVEDD (cm)	Rest	5.7 (5.0 to 6.6)	5.8 (5.1 to 6.3)	6.4 (5.6 to 7.2)	6.3 (5.6 to 7.0)	0.674
	PE	5.8 (5.1 to 6.6)	5.7 (4.7 to 6.5)	6.2 (5.4 to 7.0)	6.3 (5.4 to 7.2)	0.413
LVESD (cm)	Rest	5.1 (4.0 to 6.1)	5.0 (4.1 to 5.9)	5.7 (4.6 to 6.8)	5.4 (4.3 to 6.4)	0.788
	PE	5.0 (4.0 to 5.9)	4.8 (3.7 to 6.0)	5.2 (4.2 to 6.2)	5.7 (7.0)	0.148
AR VC (cm)	Rest	0.19 (0.08 to 0.30)	0.46 (0.16 to 0.76)	0.13 (0.05 to 0.22)	0.08 (-0.18 to 0.35)	0.100
AR ASE	Rest	1.17 (0.52 to 1.81)	1.50 (0.72 to 2.28)	1.14 (0.55 to 1.74)	1.17 (0.42 to 1.87)	0.405
	PE	0.67 (-0.25 to 1.59)	1.17 (0.01 to 2.34)	0.25 (-0.55 to 1.05)	1.0 (0.09 to 1.91)	0.494
MR ASE	Rest	1.00 (-0.23 to 2.22)	1.17 (0.06 to 2.27)	2.07 (1.03 to 3.11)	1.43 (0.41 to 2.45)	0.730
	PE	1.33 (0.41 to 2.26)	1.30 (0.11 to 2.49)	1.50 (0.58 to 2.43)	1.80 (0.61 to 2.99)	0.696
MR VC (cm)	Rest	0.10 (-1.21 to 1.41)	0.09 (-1.11 to 0.29)	1.19 (-0.27 to 2.66)	0.10 (0.29 to 0.28)	0.453
RVOT VTI	Rest	12.1 (9.6 to 14.6)	10.6 (8.5 to 12.7)	9.7 (7.3 to 12.2)	10.2 (8.0 to 12.4)	0.855
	PE	11.6 (8.8 to 14.5)	12.2 (9.6 to 14.7)	13.6 (10.8 to 16.5)	12.4 (9.6 to 15.2)	0.589
TR ASE	Rest	1.1 (0.6 to 1.6)	1.4 (0.4 to 2.4)	1.6 (1.1 to 2.1)	1.1 (0.2 to 2.0)	0.452
	PE	1.8 (0.8 to 2.7)	0.8 (-0.1 to 1.8)	1.4 (0.7 to 2.1)	1.5 (0.5 to 2.5)	0.276
TRv max (m/sec)	Rest	2.4 (2.0 to 2.9)	2.2 (1.5 to 3.0)	2.4 (2.3 to 2.7)	2.6 (2.0 to 3.2)	0.966
	PE	2.9 (2.6 to 3.1)	2.9 (2.3 to 3.6)	2.9 (2.7 to 3.1)	2.9 (2.4 to 3.4)	0.884
LA size (ml/ m^2)	Rest	38.4 (23.2 to 53.6)	47.1 (24.2 to 70.0)	47.7 (34.1 to 61.3)	53.5 (34.1 to 72.8)	0.493
	PE	54.9 (38.2 to 71.6)	52.0 (32.2 to 71.8)	64.6 (50.1 to 79.0)	46.2 (30.1 to 62.4)	0.913
RA size (ml/ m^2)	Rest	29.8 (12.3 to 47.2)	31.5 (17.2 to 45.7)	39.8 (25.6 to 54.1)	37.5 (25.9 to 49.1)	0.812

	PE	32.3 (10.6 to 54.0)	32.7 (21.0 to 44.5)	47.5 (25.8 to 69.2)	38.8 (29.2 to 48.4)	0.459
RV EDA (cm^2)	Rest	24.8 (9.9 to 39.7)	26.4 (17.7 to 35.2)	23.5 (10.6 to 36.5)	22.9 (12.2 to 33.6)	0.378
	PE	22.2 (8.3 to 36.2)	21.6 (9.7 to 33.5)	23.6 (11.5 to 35.7)	21.0 (12.6 to 29.4)	0.742
RV ESA (cm^2)	Rest	17.4 (5.4 to 29.4)	18.3 (12.3 to 24.4)	17.1 (6.7 to 27.4)	16.8 (9.4 to 24.1)	0.588
	PE	15.3 (5.3 to 25.3)	13.9 (2.8 to 24.9)	14.8 (7.2 to 24.5)	14.0 (6.2 to 21.8)	0.405
RV EDD (cm)	Rest	5.0 (4.1 to 5.8)	4.4 (3.9 to 4.9)	4.3 (3.6 to 4.9)	4.3 (3.8 to 4.8)	0.535
	PE	4.2 (2.7 to 5.7)	3.6 (3.2 to 4.1)	4.3 (3.0 to 5.6)	4.3 (4.0 to 4.7)	0.099
RVs´ (cm/s)	Rest	6.2 (4.5 to 7.9)	5.6 (3.2 to 7.9)	6.3 (4.6 to 8.0)	5.9 (3.5 to 8.2)	0.164
	PE	10.0 (7.0 to 13.0)	7.6 (8.0 to 13.7)	10.8 (4.3 to 10.9)	6.8 (4.0 to 9.7)	0.201
RV FAC (%)	Rest	30.6 (19.8 to 41.4)	30.6 (30.3 to 31.0)	28.8 (19.4 to 38.1)	26.9 (26.5 to 27.2)	0.073
	PE	27.6 (10.6 to 44.6)	37.9 (24.7 to 51.0)	34.2 (19.4 to 48.9)	34.5 (25.3 to 43.9)	0.628
IVC (cm)	Rest	1.8 (1.3 to 2.3)	2.3 (1.5 to 3.0)	1.7 (1.3 to 2.1)	1.8 (1.3 to 2.2)	0.297

Data are presented as adjusted marginal mean (95% confidence intervals). *p*-value for between-group comparisons calculated as adjusted contrast by LMM. PE, post exercise; LVEDD, left ventricular end-diastolic diameter, LVESD, left ventricular end-diastolic diameter; AV, aortic valve; AR VC, aortic regurgitation vena contracta (width of the regurgitating jet); AR, aortic regurgitation; ASE, American Society of Echocardiography; MR, mitral regurgitation, MR VC, mitral regurgitation vena contracta; RVOT VTI, right ventricular outflow track velocity time integral; TR, tricuspid regurgitation; TR Vmax, tricuspid regurgitation velocity maximal; LA, left atrium; RA, right atrium; RV, right ventricular; EDA, end-diastolic area, ESA, end-systolic area; EDD, end diastolic dimension; S', right systolic myocardial velocity; FAC, fractional area change, IVC, inferior vena cava.

6.3.9 Anthropometry

Participants in both groups demonstrated similar whole-body composition outcomes at baseline. Following the ET intervention, no statistically significant changes in body composition were detected between groups (Table 6.5).

Table 6.5 Body composition derived from dual exergy X-ray absorptiometry.

	HIIT group		**MICT group**		
Parameter	**Baseline**	**Follow up**	**Baseline**	**Follow up**	*p*-value
Total fat mass (kg)	24.8 (20.8 to 28.9)	26.1 (22.0 to 30.1)	25.5 (21.1 to 30.0)	26.7 (22.2 to 31.2)	0.976
Fat mass index (kg/m^2)	8.0 (6.6 to 9.3)	8.4 (7.0 to 9.4)	8.8 (7.3 to 10.3)	9.2 (7.7 to 10.7)	0.956
Total lean mass (kg)	56.1 (51.2 to 61.1)	56.6 (52.0 to 61.6)	52.7 (47.2 to 58.1)	54.8 (49.3 to 60.4)	0.210
Lean index (kg/m^2)	18.0 (16.8 to 19.3)	18.2 (16.9 to 19.4)	18.0 (16.6 to 19.4)	18.8 (17.3 to 20.2)	0.147
BMC (g)	5059 (4303 to 5815)	5260 (4483 to 6038)	5430 (4594 to 6265)	55428 (4581 to 6276)	0.359
BMD (g/cm^2)	2.01 (1.81 to 2.24)	2.03 (1.81 to 2.24)	2 20 (1.98 to 2.43)	2.22 (1.99 to 2.45)	0.996
Total body fat (% body mass)	29.2 (26.4 to 32.1)	29.9 (27.0 to 32.8)	30.1 (26.9 to 33.3)	30.4 (27.2 to 33.6)	0.599
Leg BMD (g/cm^2)	1.48 (0.99 to 1.97)	1.72 (1.21 to 2.23)	2.12 (1.58 to 2.66)	2.17 (1.61 to 2.72)	0.356

Leg fat mass (g)	8.2 (6.3 to 10.2)	8.3 (6.3 to 10.3)	9.1 (6.3 to 10.3)	9.6 (7.4 to 11.8)	0.194
Leg lean mass (g)	16.8 (14.8 to 18.8)	16.9 (14.8 to 19.0)	15.8 (13.6 to 18.0)	16.7 (14.4 to 18.9)	0.380
Leg fat mass (%)	31.9 (27.2 to 36.7)	31.1 (26.4 to 35.9)	32.9 (27.6 to 38.1)	31.2 (26.4 to 35.9)	0.480

Data are presented as adjusted marginal mean 95% CIs. *p*-value for between-group comparisons calculated as adjusted contrast by LMM. BMC, bone mineral content; BMD, bone mineral density.

6.3.10 Quality of life and self-efficacy

HIIT and MICT both improved the physical functioning and role physical domains, PSC and HDSE (Table 6.6) but there were no significant differences between groups.

Table 6.6 Quality of life and heart disease self-efficacy data

	HIIT group		**MICT group**		
Domain	**Baseline**	**Follow up**	**Baseline**	**Follow up**	*p*-value
Physical Functioning	36.6 (32.1 to 41.1)	43.7 (38.9 to 48.5)*	36.6 (32.1 to 41.1)	43.1 (38.0 to 48.1*	0.816
Role Physical	36.7 (32.7 to 40.8)	43.6 (39.3 to 48.0)**	36.7 (32.7 to 40.8)	46.8 (42.3 to 51.4)**	0.825
Bodily pain	46.0 (41.3 to 50.8)	48.9 (43.7 to 54.2)	41.5 (36.8 to 46.2	47.1 (41.6 to 52.7)	0.527
General Health	33.6 (26.8 to 40.5)	38.3 (30.8 to 45.7)	33.6 (26.8 to 40.5)	38.3 (30.8 to 45.7)	0.713

Vitality	51.1 (44.2 to 57.9)	56.7 (49.3 to 64.1)	53.0 (46.2 to 59.6)	58.0 (50.2 to 65.7)	0.892
Social Functioning	40.9 (35.5 to 46.3)	47.1 (41.1 to 53.0)	40.9 (35.5 to 46.3)	45.5 (39.1 to 51.8)	0.751
Role Emotional	55.7 (50.0 to 61.6)	53.8 (47.7 to 59.8)	49.0 (43.2 to 54.8)	49. 3 (42.3 to 55.8)	0.400
Mental Health	61.9 (56.3 to 67.5)	64.0 (58.3 to 69.8)	56.2 (50.5 to 61.8)	59.7 (53.9 to 65.6)	0.422
Summary scores					
PCS	30.7 (26.3 to 35.0)	38.1 (33.6 to 42.6)**	33.4 (29.1 to 37.8)	40.0 (35.4 to 44.6)**	0.685
MCS	61.5 (55.5 to 67.4)	61.7 (55.6 to 67.8)	56.1 (50.2 to 62.0)	56.9 (50.7 to 63.2)	0.853
HDSE score	67.4 (60.0 to 74.9)	75.8 (68.3 to 83.3)*	69.3 (61.3 to 77.2)	80.4 (72.4 to 88.3)*	0.597

Data are presented as adjusted marginal mean 95% CIs. *p*-value for between-group comparison calculated as adjusted contrast by LMM. * signifies $p < 0.05$ and ** $p \leq 0.001$ for significant difference compared with baseline values. PCS, physical component score; MCS, mental component score; HDSE, heart disease self-efficacy.

6.3.11 Biomarkers

HIIT decreased CPR, and TG, while CR increased significantly. There were no changes following MICT. There were no between-group differences following the exercise intervention (Table 6.7).

Table 6.7 Haematological and biochemical data

	HIIT group		MICT group		
Variable	**Baseline**	**Follow up**	**Baseline**	**Follow up**	*p*-value
BNP (ng/L)	404 (252 to 555)	279 (104 to 453)	361 (194 to 530)	236 (48 to 423)	0.992
Hb (g/L)	129 (122 to 136)	135 (128 to 144)	126 (118 to 133)	133 (124 to 143)	0.808
CRP (mg/L)	9.1 (1.3 to 16.9)	6.8 (-1.3 to 14.9)**	9.1 (1.3 to 16.9)	9.3 (1.0 to 17.6)	0.474
CR (μmol/L)	101 (87 to 114)	112 (98 to 126)*	101 (88 to 115)	107 (92 to 122)	0.256
Chol (mmol/L)	4.7 (4.1 to 5.3)	4.3 (3.7 to 5.0)	3.9 (3.2 to 5.0)	3.9 (3.1 to 4.6)	0.386
HDL (mmol/L)	1.1 (0.9 to 1.3)	1.1 (0.9 to1.2)	1.1 (1.0 to 1.3)	1.1 (0.9 to 1.3)	0.784
LDL (mmol/L)	2.8 (2.3 to 3.3)	2.6 (2.1 to 3.1)	2.2 (1.7 to 2.7)	2.2 (1.6 to 2.8)	0.700
TG (mmol/L)	1.8 (1.3 to 2.2)	1.4 (1.0 to 1.9)*	1.6 (1.1 to 2.0)	1.6 (1.1 to 2.1)	0.121

Data presented as estimated marginal means with 95% CIs. *p*-value for between-group comparison calculated as adjusted contrast by LMM. * signifies $p < 0.05$ and ** $p \leq 0.001$ for significant within-group difference. BNP, B-type natriuretic peptide; Hb, haemoglobin; CPR, c-reactive protein-serum; CR, serum creatinine; Chol, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides.

6.4 Discussion

To our knowledge, this is the first RCT comparing the effects of HIIT versus MICT in patients with a continuous-flow LVAD *in situ*. We observed that HIIT was feasible, well tolerated and superior to MICT for improving aerobic capacity. This finding contrasts with previous studies of low to moderate intensity ET in patients with LVADs, which have failed to demonstrate an improvement in aerobic capacity beyond that observed in a control group and supports the use of higher intensity ET in stable patients with LVADs, to optimise cardiorespiratory fitness.

There have been very few RCTs of structured ET in patients with LVADs and none to date that has found a greater effect of structured ET on aerobic capacity, compared with a control group.[8-10] Laoutaris et al.[10] prescribed 10-weeks of combined home-walking, cycling and inspiratory muscle training in patients supported with first-generation pulsatile LVADs. While $\dot{V}O_2$ peak improved, the change in aerobic capacity was not significantly greater than a control group who undertook a home-walking program. Similarly, of the two studies involving participants with continuous-flow LVADs,[8,9] neither observed a significant difference between the ET and the control group. These trials also applied low-to-moderate intensity ET, at an intensity similar to the MICT group in the current study.

LVAD trials (ELEVATE, MOMENTUM 3) have consistently shown marked 6MWTD gains at 6-month post-implantation (>2.5 times pre-LVAD distance).[38.39] However, increases in $\dot{V}O_2$ peak have been less dramatic, typically remaining at approximately 50% of predicted values.[40,41] It has been proposed that while the fixed pump speed characteristic of current LVADs may provide adequate haemodynamic support during submaximal exercise, it may be insufficient to meet the metabolic demands of higher workloads,[42-44] limiting an increase in $\dot{V}O_2$ peak. The 'ceiling effect' on circulatory output[45] may also restrict the effect of exercise training on aerobic capacity, and improvements likely reflecting peripheral adaptations such as increased oxidative capacity of skeletal muscles. Given the modest increase in $\dot{V}O_2$ peak observed following LVAD implantation, and also moderate intensity training, ET that specifically targets skeletal muscle oxidative capacity may be the 'best bet' to increase this clinically important physiological parameter.

In recent years, HIIT has been extensively studied for the rehabilitation of cardiovascular disease.[13,46-49] However, the effects in patients with CHF remain equivocal. Wisloff et al.[16] reported a 46% increase in $\dot{V}O_2$ peak. In contrast, a recent multicentre trial of HIIT, also in patients with CHF (SMARTEX HF),[50] reported an increase of just 8% in $\dot{V}O_2$ peak, despite prescribing a similar HIIT protocol. The magnitude of improvement in $\dot{V}O_2$ peak of 17% with HIIT in the current study lies between these extremes. Several factors may explain the variability in results. The Wisloff study[16] was a single centre trial, with exercise that was closely supervised, whereas the SMARTEX HF[50] study was a multi-centre trial and adherence to both the HIIT and MICT training protocols was suboptimal; 51% of HIIT participants exercised below the prescribed heart rate, while 80% of the MICT participants exercised above their target. The current trial was also closely monitored, with no less than a 1:3 supervisor to participant ratio during exercise sessions, suggesting that close supervision may be necessary to help patients adhere to the relatively high ratings of perceived exertion we observed during HIIT versus MICT, which can be challenging to maintain for some people.[51] Participants in the current study had all undergone a standard rehabilitation regimen of supervised, progressive exercise at up to a moderate intensity for at least 8 weeks post-implantation, which may have reduced the training response to some extent, leading to a more modest effect of HIIT compared with that reported by Wisloff et al. Moreover, the differing effects on aerobic capacity may have been influenced by the aetiology of CHF (all post-myocardial infarction in Wisloff study), age (approximately 15 years older in Wisloff study) and clinical characteristics of participants (CHF versus LVAD). Nevertheless, the change in $\dot{V}O_2$ peak in the HIIT group in the current study is likely to be clinically meaningful. Although no data exist specifically for patients with LVADs, in patients with CHF a 1.0 $mL \cdot kg^{-1} \cdot min^{-1}$ increase in $\dot{V}O_2$ peak is associated with an 8% reduction in mortality.[6] Importantly, we incorporated a broad eligibility criterion, including patients supported with three different continuous-flow LVAD systems currently used in clinical settings, as well as a broad indication for LVAD implantation (bridge to transplant, eligibility, recovery and destination therapy) and included patients recently implanted (<10 weeks) and those on long-term support to ensure that our results are generalisable across a broad spectrum of patients with LVADs.

An important consideration relating to HIIT is safety. A recent systematic review analysing safety data in patients with coronary heart disease and CHF found only one SAE related to HIIT (cardiac arrest with successful resuscitation) out of 17,083 training sessions.[46] These results suggest that HIIT may be a safe alternative to MICT, in haemodynamically stable patients exercising in a medically controlled environment. Although our sample is small, we also observed that HIIT was well tolerated in patients with LVADs with no SAEs occurring during the 12-week training period. While HIIT was not associated with any SAE, we acknowledge that the current study did not have the power to conclusively assess the safety of HIIT and that further research is required in this setting before the safety of HIIT in patients with LVADs can be stated conclusively.

There were no significant changes in cardiac function or structure in either group in the current study. Our observations are in accordance with the majority of previous trials involving a similar 12-week HIIT protocol in patients with CHF,[49,52-54] as well as a recent meta-analysis.[55] The exception being the by Wisloff et al.[16] which reported reverse LV remodelling with HIIT. The SMARTEX HF study[50] found a modest effect of HIIT on LVEDD (-2.8 mm), but this was not significantly different to the MICT group (-1.6 mm). Most studies showing reverse cardiac remodelling with aerobic ET in CHF patients have involved at least 6 months of training,[48,55] so the relatively short intervention period of the present study may have limited the potential for improvement in cardiac function in our cohort of LVAD patients. The absence of a change in cardiac structure and function is supported by no change in plasma BNP levels, a marker of cardiac hypertrophy and myocardial stretching, in either group.

It has been proposed that the low-pulsatility environment, associated with continuous-flow LVAD systems might be detrimental to vascular endothelial function.[56,57] ET has consistently been found to improve endothelial function in chronic conditions,[58,59] including CHF,[60] but its impact in patients with LVADs has not previously been tested. In the present study, we found that endothelial function significantly improved following MICT but not HIIT, with no differences between groups. This finding is in agreement with a recent meta-analysis in CHF,[61] but in contrast with Wisloff et al.[16] who found a greater improvement in endothelial function following HIIT versus the MICT in patients with CHF. A previous investigation in healthy individuals,[62] found

that moderated intensity aerobic exercise may augment endothelial function to a greater extent than higher intensity training, because exercise above the anaerobic threshold may increase reactive oxygen species, which scavenge circulating antioxidants and ultimately attenuate nitric oxide production.

Considering our findings of a lack of effect of HIIT on cardiac or vascular function, in the context of the Fick principle, we could deduct that the observed increase in $\dot{V}O_2$ peak is likely due to peripheral adaptations pertaining to aerobic capacity of skeletal muscle. It is well established that skeletal muscle oxidative capacity is impaired in patients with CHF,[63] but this only partially improves following LVAD implantation.[64] Aerobic ET has consistently been found to improve skeletal muscle ultrastructure, oxidative capacity and function in patients with CHF,[65-67] including through increased mitochondrial volume and enzyme density,[68] and a shift to a greater proportion of oxidative muscular fibres,[69] adaptations which have correlated with changes in $\dot{V}O_2$ peak.[65,70] Although we didn't measure skeletal function in the current study, we speculate that HIIT may have enhanced the intrinsic ability of the skeletal muscle to extract and utilise oxygen to a greater extent than MICT, resulting in the observed increase in $\dot{V}O_2$ peak. This hypothesis remains to be confirmed by future studies.

Reduced skeletal muscle mass also contributes to exercise intolerance in CHF,[71-73] and is a strong prognostic indicator.[74] Given the cachexia experienced by patients receiving LVADs[64,75], restoration of skeletal muscle strength and mass is an important clinical outcome in these patients. Combined HIIT and resistance training has been found to provide a greater increase in muscle strength than HIIT alone in patients with CHF.[76] Therefore, we included an identical resistance training component for both groups, consistent with best-practice exercise prescription.[77] While there was no change in either whole-body or leg muscle mass following either training intervention, leg strength significantly improved in both groups to a similar extent, suggesting that HIIT did not provide additive to strength compared with MICT. In the absence of muscle hypertrophy, the observed improvement in strength likely reflects neural[78] adaptations. This finding is consistent with previous studies in patients with CHF, which have reported an increase in muscle strength after 12 weeks of resistance exercise, despite no change in skeletal muscle mass.[76,79]

Following LVAD implantation, patients experience clinically relevant improvements in QoL, mainly attributed to enhanced physical function.[80,81] However, QoL remains impaired compared with healthy, age-matched individuals and patients following cardiac transplantation[82] but may be further improved by ET.[83] In the present study, we found an improvement in several QoL domains related to physical health with ET, but no difference between MICT and HIIT. In contrast, no changes in the mental health component were observed. Our results concur with those of a recent meta-analysis in CHF,[13] which reported that structured and supervised training improves QoL, independent of the intensity of exercise. Of the RCTs to date evaluating ET in LVADs,[8-10] only the study by Kerrigan et al.[9] has shown a significant difference between the ET and the control group in QoL, as assessed by the Kansas City Cardiomyopathy Questionnaire. We also assessed whether training improved exercise self-efficacy, a key determinant of self-care in CHF,[84] as well as long-term compliance with exercise recommendations.[85] Similar to QoL, self-efficacy was improved in both groups, but no difference existed between groups.

The current study has some limitations that warrant highlighting. Firstly, several participants who enrolled in the trial were lost to follow-up, predominantly due to cardiac transplantation before they completed the intervention. The characteristics of these participants were similar to those who completed the study, so it is unlikely that this would have created bias. While this reduced the sample size and compromised the power to detect changes in some of the secondary outcomes, in the final analysis, we had a similar numbers of participants to previous ET trials in patients with an LVAD,[8-10] and we were able to address our primary hypothesis comparing the effect of HIIT versus MICT on $\dot{V}O_2$ peak. While our findings should be confirmed in larger trials, the current research provides a valuable 'proof of concept' for the prescription of HIIT in clinically stable patients with an LVAD *in situ*. This study only involved patients implanted with HeartWare, HeartMate II and HeartMate 3 LVADs and therefore the findings should not be extrapolated to patients with other types of LVADs. Total energy expenditure was not matched between training protocols in the current study because we elected to apply a pragmatic study design that matched training protocols for total exercise duration, acknowledging that time is a well-documented factor limiting attendance at cardiac-rehabilitation sessions.[86,87] Finally, it is important to note that HIIT was performed in a closely supervised environment in a hospital-based

gymnasium and these findings may not necessarily translate to an unsupervised or non-clinical setting.

To conclude, in this preliminary trial of HIIT in patients with LVADs, we found that 12 weeks of HIIT was well-tolerated and resulted in a greater increase in aerobic capacity than MICT, which has typically been applied in the rehabilitation of these patients. In the absence of significant changes in cardiac structure and function, it is likely that the improvement in aerobic capacity occurs as a result of skeletal muscle adaptations, however future studies that directly assess muscle metabolomics are required to confirm this hypothesis. These findings should encourage rehabilitation providers to prescribe exercise at higher intensities for clinically stable patients with LVADs, once an initial period of low to moderate exercise has been successfully completed.

6.5 References

1. Kirklin JK, Pagani FD, Kormos RL, et al. Eighth annual INTERMACS report: Special focus on framing the impact of adverse events. J Heart Lung Transplant 2017;36:1080-86.

2. Lenneman AJ, Birks EJ. Treatment strategies for myocardial recovery in heart failure. Curr Treat Options Cardiovasc Med 2014;16:287.

3. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009;361:2241-51.

4. Rogers JG, Aaronson KD, Boyle AJ, et al. Continuous flow left ventricular assist device improves functional capacity and quality of life of advanced heart failure patients. J Am Coll Cardiol 2010;55:1826-34.

5. Maybaum S, Mancini D, Xydas S, et al. Cardiac improvement during mechanical circulatory support: a prospective multicenter study of the LVAD Working Group. Circulation 2007;115:2497-505.

6. Swank AM, Horton J, Fleg JL, et al. Modest increase in peak VO2 is related to better clinical outcomes in chronic heart failure patients: results from heart failure and a controlled trial to investigate outcomes of exercise training. Circ Heart Fail 2012;5:579-85.

7. Simon MA, Kormos RL, Gorcsan J, et al. Differential exercise performance on ventricular assist device support. J Heart Lung Transplant 2005;24:1506-12.

8. Hayes K, Leet AS, Bradley SJ, Holland AE. Effects of exercise training on exercise capacity and quality of life in patients with a left ventricular assist device: a preliminary randomized controlled trial. J Heart Lung Transplant 2012;31:729-34.

9. Kerrigan DJ, Williams CT, Ehrman JK, et al. Cardiac rehabilitation improves functional capacity and patient-reported health status in patients with

continuous-flow left ventricular assist devices: the Rehab-VAD randomized controlled trial. JACC Heart Fail 2014;2:653-9.

10. Laoutaris ID, Dritsas A, Adamopoulos S, et al. Benefits of physical training on exercise capacity, inspiratory muscle function, and quality of life in patients with ventricular assist devices long-term postimplantation. European Journal of Cardiovascular Prevention & Rehabilitation 2011;18:33-40.

11. Hannan AL, Hing W, Simas V, et al. High-intensity interval training versus moderate-intensity continuous training within cardiac rehabilitation: a systematic review and meta-analysis. Open Access J Sports Med 2018;9:1-17.

12. Ramos JS, Dalleck LC, Tjonna AE, Beetham KS, Coombes JS. The impact of high-intensity interval training versus moderate-intensity continuous training on vascular function: a systematic review and meta-analysis. Sports Med 2015;45:679-92.

13. Gomes Neto M, Duraes AR, Conceicao LSR, Saquetto MB, Ellingsen O, Carvalho VO. High intensity interval training versus moderate intensity continuous training on exercise capacity and quality of life in patients with heart failure with reduced ejection fraction: A systematic review and meta-analysis. Int J Cardiol 2018;261:134-41.

14. Haykowsky MJ, Timmons MP, Kruger C, McNeely M, Taylor DA, Clark AM. Meta-analysis of aerobic interval training on exercise capacity and systolic function in patients with heart failure and reduced ejection fractions. Am J Cardiol 2013;111:1466-9.

15. Rognmo O, Moholdt T, Bakken H, et al. Cardiovascular risk of high- versus moderate-intensity aerobic exercise in coronary heart disease patients. Circulation 2012;126:1436-40.

16. Wisloff U, Stoylen A, Loennechen JP, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. Circulation 2007;115:3086-94.

17. Fischer D, Rossa S, Landmesser U, et al. Endothelial dysfunction in patients with chronic heart failure is independently associated with increased incidence of hospitalization, cardiac transplantation, or death. Eur Heart J 2005;26:65-9.

18. Ingle L. Theoretical rationale and practical recommendations for cardiopulmonary exercise testing in patients with chronic heart failure. Heart Fail Rev 2007;12:12-22.

19. Borg G. Measuring Perceived Exertion and Pain. Borg's Perceived exertion and pain scales. 1th ed. Chicago: Human kinetics; 1998.p. 26.

20. Roul G, Germain P, Bareiss P. Does the 6-minute walk test predict the prognosis in patients with NYHA class II or III chronic heart failure? Am Heart J 1998;136:449-57.

21. Cohen-Solal A, Tabet JY, Logeart D, Bourgoin P, Tokmakova M, Dahan M. A non-invasively determined surrogate of cardiac power ('circulatory power') at peak exercise is a powerful prognostic factor in chronic heart failure. Eur Heart J 2002;23:806-14.

22. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-7.

23. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography 2016;29:277-314.

24. Corretti M, Anderson T, Benjamin E, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery a report of the international brachial artery reactivity task force. J Am Coll Cardiol 2002;39:257-65.

25. Black M, Cable T, Thijssen D, Green D. Importance of measuring the time course of flow-mediated dilatation in humans. Hypertension 2008;51:203-10.

26. Woodman R, Playford D, Watts G, et al. Improved analysis of brachial artery ultrasound using a novel edge-detection software system. J Appl Physiol 2001;91:929-37.

27. MacIver J, Rao V, Ross HJ. Quality of life for patients supported on a left ventricular assist device. Expert Rev Med Devices 2011;8:325-37.

28. Haworth J, Young C, Thornton E. The effects of an 'exercise and education' programme on exercise self-efficacy and levels of independent activity in adults with acquired neurological pathologies: an exploratory, randomized study. Clin Rehabil 2009;23:371-83.

29. Bandura A. Guide for constructing self-efficacy scales. Self-efficacy beliefs of adolescents. Greenwich: Age Information Publishing; 2006.p. 307.

30. Council NHMR. Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods. In: Health Do, ed. Camberra: National Health and Medical Research Council; 2016.

31. Kemi OJ, Wisloff U. High-intensity aerobic exercise training improves the heart in health and disease. J Cardiopulm Rehabil Prev 2010;30:2-11.

32. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European Heart Journal 2016;37:2129-200.

33. Crespo-Leiro MG, Metra M, Lund LH, et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2018;20:1505-35.

34. Kerrigan DJ, Williams CT, Brawner CA, et al. Heart rate and VO2 concordance in continuous-flow left ventricular assist devices. Med Sci Sports Exerc 2016;48:363-7.

35. Aamot IL, Forbord SH, Karlsen T, Stoylen A. Does rating of perceived exertion result in target exercise intensity during interval training in cardiac rehabilitation? A study of the Borg scale versus a heart rate monitor. J Sci Med Sport 2014;17:541-5.

36. Mehmetoglu M, Jakobsen TG. *Applied statistics using Stata: a guide for the social sciences.* Sage; 2016.

37. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Annals of internal medicine 2010;152:726-32.

38. Gustafsson F, Shaw S, Lavee J, et al. Six-month outcomes after treatment of advanced heart failure with a full magnetically levitated continuous flow left ventricular assist device: report from the ELEVATE registry. European Heart Journal 2018;39:3454-60.

39. Mehra MR, Naka Y, Uriel N, et al. A Fully Magnetically Levitated Circulatory Pump for Advanced Heart Failure. N Engl J Med 2017;376:440-50.

40. Benton CR, Sayer G, Nair AP, et al. Left ventricular assist devices improve functional class without normalizing peak oxygen consumption. Asaio j 2015;61:237-43.

41. Simon MA, Kormos RL, Gorcsan J, III, et al. Differential Exercise Performance on Ventricular Assist Device Support. The Journal of Heart and Lung Transplantation 2005;24:1506-12.

42. Jung MH, Gustafsson F. Exercise in heart failure patients supported with a left ventricular assist device. J Heart Lung Transplant 2015;34:489-96.

43. Jung MH, Hansen PB, Sander K, et al. Effect of increasing pump speed during exercise on peak oxygen uptake in heart failure patients supported with a continuous-flow left ventricular assist device. A double-blind randomized study. Eur J Heart Fail 2014;16:403-8.

44. Gross C, Marko C, Mikl J, et al. LVAD Pump Flow Does Not Adequately Increase With Exercise. Artificial organs 2019;43:222-28.

45. Hayward CS, Fresiello L, Meyns B. Exercise physiology in chronic mechanical circulatory support patients: vascular function and beyond. Current Opinion in Cardiology 2016;31:292-98.

46. Wewege MA, Ahn D, Yu J, Liou K, Keech A. High-Intensity Interval Training for Patients With Cardiovascular Disease-Is It Safe? A Systematic Review. J Am Heart Assoc 2018;7:e009305.

47. Kuehn Bridget M. Evidence for HIIT Benefits in Cardiac Rehabilitation Grow. Circulation 2019;140:514-15.

48. Haykowsky MJ, Liang Y, Pechter D, Jones LW, McAlister FA, Clark AM. A meta-analysis of the effect of exercise training on left ventricular remodeling in heart failure patients: the benefit depends on the type of training performed. J Am Coll Cardiol 2007;49:2329-36.

49. Iellamo F, Caminiti G, Sposato B, et al. Effect of High-Intensity interval training versus moderate continuous training on 24-h blood pressure profile and insulin resistance in patients with chronic heart failure. Internal and emergency medicine 2014;9:547-52.

50. Ellingsen O, Halle M, Conraads V, et al. High-Intensity Interval Training in Patients With Heart Failure With Reduced Ejection Fraction. Circulation 2017;135:839-49.

51. Arena R, Myers J, Forman DE, Lavie CJ, Guazzi M. Should high-intensity-aerobic interval training become the clinical standard in heart failure? Heart Fail Rev 2013;18:95-105.

52. Iellamo F, Manzi V, Caminiti G, et al. Matched dose interval and continuous exercise training induce similar cardiorespiratory and metabolic adaptations in patients with heart failure. Int J Cardiol 2013;167:2561-5.

53. Benda NM, Seeger JP, Stevens GG, et al. Effects of High-Intensity Interval Training versus Continuous Training on Physical Fitness, Cardiovascular Function and Quality of Life in Heart Failure Patients. PLoS One 2015;10:e0141256.

54. Smart NA, Steele M. A comparison of 16 weeks of continuous vs intermittent exercise training in chronic heart failure patients. Congest Heart Fail 2012;18:205-11.

55. Tucker WJ, Beaudry RI, Liang Y, et al. Meta-analysis of Exercise Training on Left Ventricular Ejection Fraction in Heart Failure with Reduced Ejection Fraction: A 10-year Update. Progress in Cardiovascular Diseases 2019;62:163-71.

56. Hasin T, Matsuzawa Y, Guddeti RR, et al. Attenuation in Peripheral Endothelial Function After Continuous Flow Left Ventricular Assist Device Therapy Is Associated With Cardiovascular Adverse Events. Circulation Journal 2015;79:770-77.

57. Witman MA, Garten RS, Gifford JR, et al. Further Peripheral Vascular Dysfunction in Heart Failure Patients With a Continuous-Flow Left Ventricular Assist Device: The Role of Pulsatility. JACC Heart Fail 2015;3:703-11.

58. Maiorana A, O'Driscoll G, Cheetham C, et al. The effect of combined aerobic and resistance exercise training on vascular function in type 2 diabetes. J Am Coll Cardiol 2001;38:860-6.

59. Walsh JH, Bilsborough W, Maiorana A, et al. Exercise training improves conduit vessel function in patients with coronary artery disease. J Appl Physiol (1985) 2003;95:20-5.

60. Maiorana A, O'Driscoll G, Dembo L, et al. Effect of aerobic and resistance exercise training on vascular function in heart failure. Am J Physiol Heart Circ Physiol 2000;279:H1999-2005.

61. Pearson MJ, Smart NA. Aerobic Training Intensity for Improved Endothelial Function in Heart Failure Patients: A Systematic Review and Meta-Analysis. Cardiol Res Pract 2017;2017:2450202.

62. Goto C, Higashi Y, Kimura M, et al. Effect of Different Intensities of Exercise on Endothelium-Dependent Vasodilation in Humans. Circulation 2003;108:530-35.

63. Drexler H, Riede U, Munzel T, Konig H, Funke E, Just H. Alterations of skeletal muscle in chronic heart failure. Circulation 1992;85:1751-9.

64. Khawaja T, Chokshi A, Ji R, et al. Ventricular assist device implantation improves skeletal muscle function, oxidative capacity, and growth hormone/insulin-like growth factor-1 axis signaling in patients with advanced heart failure. Journal of cachexia, sarcopenia and muscle 2014;5:297-305.

65. Esposito F, Reese V, Shabetai R, Wagner PD, Richardson RS. Isolated quadriceps training increases maximal exercise capacity in chronic heart failure: the role of skeletal muscle convective and diffusive oxygen transport. J Am Coll Cardiol 2011;58:1353-62.

66. Tyni-Lenné R, Gordon A, Jensen-Urstad M, Dencker K, Jansson E, Sylvén C. Aerobic training involving a minor muscle mass shows greater efficiency than training involving a major muscle mass in chronic heart failure patients. Journal of cardiac failure 1999;5:300-07.

67. Tucker WJ, Lijauco CC, Hearon CM, et al. Mechanisms of the Improvement in Peak VO2 With Exercise Training in Heart Failure With Reduced or Preserved Ejection Fraction. Heart, Lung and Circulation 2018;27:9-21.

68. Gielen S, Adams V, Möbius-Winkler S, et al. Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. Journal of the American College of Cardiology 2003;42:861-68.

69. Hambrecht R, Fiehn E, Yu J, et al. Effects of endurance training on mitochondrial ultrastructure and fiber type distribution in skeletal muscle of patients with stable chronic heart failure. J Am Coll Cardiol 1997;29:1067-73.

70. Hambrecht R, Niebauer J, Fiehn E, et al. Physical training in patients with stable chronic heart failure: effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. J Am Coll Cardiol 1995;25:1239-49.

71. Vescovo G, Volterrani M, Zennaro R, et al. Apoptosis in the skeletal muscle of patients with heart failure: investigation of clinical and biochemical changes. Heart 2000;84:431-7.

72. Cicoira M, Zanolla L, Franceschini L, et al. Skeletal muscle mass independently predicts peak oxygen consumption and ventilatory response during exercise in noncachectic patients with chronic heart failure. J Am Coll Cardiol 2001;37:2080-5.

73. Panizzolo FA, Maiorana AJ, Naylor LH, et al. Is the soleus a sentinel muscle for impaired aerobic capacity in heart failure? Medicine & Science in Sports & Exercise 2015;47:498-508.

74. Anker SD, Ponikowski P, Varney S, et al. Wasting as independent risk factor for mortality in chronic heart failure. Lancet 1997;349:1050-3.

75. Loyaga-Rendon RY, Plaisance EP, Arena R, Shah K. Exercise physiology, testing, and training in patients supported by a left ventricular assist device. J Heart Lung Transplant 2015;34:1005-16.

76. Bouchla A, Karatzanos E, Dimopoulos S, et al. The addition of strength training to aerobic interval training: effects on muscle strength and body composition in CHF patients. J Cardiopulm Rehabil Prev 2011;31:47-51.

77. Piepoli MF, Conraads V, Corra U, et al. Exercise training in heart failure: from theory to practice. A consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation. Eur J Heart Fail 2011;13:347-57.

78. Hakkinen K, Kallinen M, Izquierdo M, et al. Changes in agonist-antagonist EMG, muscle CSA, and force during strength training in middle-aged and older people. J Appl Physiol (1985) 1998;84:1341-9.

79. Jankowska EA, Wegrzynowska K, Superlak M, et al. The 12-week progressive quadriceps resistance training improves muscle strength, exercise capacity and quality of life in patients with stable chronic heart failure. Int J Cardiol 2008;130:36-43.

80. Rogers JG, Aaronson KD, Boyle AJ, et al. Continuous Flow Left Ventricular Assist Device Improves Functional Capacity and Quality of Life of Advanced Heart Failure Patients. Journal of the American College of Cardiology 2010;55:1826-34.

81. Moreno-Suarez I, Liew S, Dembo LG, Larbalestier R, Maiorana A. Physical Activity Is Higher in Patients with LVADs Compared to Chronic Heart Failure. Med Sci Sports Exerc 2019.

82. Grady KL, Meyer PM, Dressler D, et al. Longitudinal change in quality of life and impact on survival after left ventricular assist device implantation. The Annals of thoracic surgery 2004;77:1321-7.

83. Taylor RS, Sagar VA, Davies EJ, et al. Exercise-based rehabilitation for heart failure. Cochrane Database of Systematic Reviews 2014.

84. Ha FJ, Hare DL, Cameron JD, Toukhsati SR. Heart Failure and Exercise: A Narrative Review of the Role of Self-Efficacy. Heart, Lung and Circulation 2018;27:22-27.

85. Klompstra L, Jaarsma T, Stromberg A. Self-efficacy Mediates the Relationship Between Motivation and Physical Activity in Patients With Heart Failure. J Cardiovasc Nurs 2018;33:211-16.

86. Skinner JS, Cooper A, Feder GS. Secondary prevention for patients after a myocardial infarction: summary of NICE guidance. BMJ 2007;334:1112-13.

87. Stutts WC. Physical activity determinants in adults. Perceived benefits, barriers, and self efficacy. AAOHN journal : official journal of the American Association of Occupational Health Nurses 2002;50:499-507.

Chapter 7 General discussion

7.1 Introduction

This thesis examined the impact of third generation, continuous-flow left ventricular assist device (CF-LVAD) implantation on daily physical activity (PA) levels, and the acute and chronic responses to exercise. To achieve these objectives, four experimental studies were conducted. The first study (Chapter 3) evaluated how LVAD implantation affects aerobic capacity and daily PA levels compared with well-matched patients with chronic heart failure (CHF) without mechanical circulatory support. Chapter 4 assessed the cerebrovascular responses at rest and during exercise in patients with LVADs in comparison with matched patients with CHF and healthy controls. In Chapter 5, the effects of 12-weeks of supervised exercise training (ET) on cerebrovascular function during exercise were evaluated in patients with LVADs. Lastly, a randomised controlled trial (RCT) was conducted to evaluate the effects of different ET intensities on aerobic capacity, cardiovascular and functional outcomes in patients with LVADs (Chapter 6).

In the present Chapter, a summary of the overall findings from the project is provided, along with implications for clinical practice. Following the main summary, the limitations of the thesis are discussed. Finally, the general conclusions of the research project are presented along with future research considerations.

7.2 Summary of key findings

In the present thesis, there are several key findings to highlight. In Chapter 3, we observed that patients implanted with an LVAD undertake higher levels of daily PA compared with well-matched patients with advanced CHF, without mechanical circulatory support. This is likely attributed to an augmented peak oxygen uptake post-LVAD implantation. Chapter 4 revealed that patients with advanced CHF, either on LVAD support or not, exhibit cerebrovascular dysfunction during rest and exercise relative to age-matched healthy individuals. However, patients supported with an

LVAD had enhanced resting volumetric cerebral blood flow (CBF) compared with patients with CHF, but no LVAD. This difference was also evident during incremental aerobic exercise. In Chapter 5, we found that the cerebrovascular function of the internal carotid artery (ICA) during exercise was improved following12-weeks of supervised ET. This was associated with an improved partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$), suggesting that improved exercise ventilation may be a possible mediator for the change in cerebrovascular function post ET. In Chapter 6, we observed that high-intensity interval training (HIIT) was feasible, safe and superior to the conventional approach to ET in patients with LVADs, involving moderate-intensity continuous training (MICT). Taken together, our findings indicate that LVAD implantation provides clinically relevant benefits for the rehabilitation of patients with advanced CHF, and in combination with comprehensive, structured and supervised ET, functional and haemodynamic outcomes can be further improved, with higher intensity exercise appearing to be more effective than moderate intensity.

7.3 What does this thesis add to the existing body of scientific literature?

Currently, the literature investigating PA in patients with LVADs remains scarce, as only three previous studies have been conducted. An early study[1] reported that patients with LVADs continue living a sedentary lifestyle, engaging only in low-intensity PA. More recent studies have observed that while LVAD patients augmented their daily PA during the initial recovery period post-implantation (<3 months), it plateaued after this point.[2,3] Jakovljevic et al.[3] found that patients with LVADs engaged in similar habitual PA levels compared with patients with advanced CHF not undergoing LVAD support. This finding suggested that LVAD support does not improve PA levels, however, the CHF control group in this study had a peak oxygen consumption ($\dot{V}O_2$) above the cuff-off value for cardiac transplant, suggesting they were not well-matched at baseline for disease severity and had an aerobic capacity more akin to that observed following LVAD implantation. Moreover, only male participants were included in the study, and participants were only implanted with a HeartWare device. As such, the generalisability of these findings are limited and should be interpreted with caution.

In order to make our sample generalisable to a broader cohort of patients implanted with LVADs, we included female patients, indications for implantation across the spectrum of clinical management (i.e., as a bridge-to-transplant, destination-therapy, bridge-to-recovery and bridge-to-eligibility), as well as three different third-generation CF-LVAD models (HeartWare, HeartMate II and 3) in our sample. In contrast to Jakovljevic et al.,[3] we found that patients with LVADs achieved significantly higher daily PA levels compared with patients with advanced CHF, who were well-matched for CHF severity, age and sex. This was predominantly due to the LVAD group engaging in a higher volume of moderate-intensity exercise compared with the CHF group.

In line with previous studies,[4,5] participants in the LVAD group had a $\dot{V}O_2$ peak 52% higher than the CHF group. It is likely that this higher aerobic fitness translates to an improved capacity to perform activities at a lower relative percentage of maximum, making it less demanding and reducing thus symptoms of breathlessness and fatigue. Indeed, we found a positive correlation between $\dot{V}O_2$ peak and PA levels, in agreement with Granegger et al.[2] These findings supports the notion that aerobic capacity is an important determinant of PA in patients with advanced CHF. Furthermore, we also found that LVAD implantation was associated with an increased quality of life (QoL) related to physical health, consistently with previous reports.[4,6,7] Another important determinant of PA in CHF that has been proposed is self-efficacy.[8] In our study, we found a positive association that approached statistical significance. Further studies involving a larger sample size are needed to clarify this relationship.

In the general population, low PA levels have been shown to be an independent predictor of all-cause mortality and cardiovascular events.[9] Similarly, recent evidence in patients with CHF suggests that PA levels strongly predict prognosis.[10,11] Likewise, engaging daily in PA decreases disease progression and loss of independence, while improving functional capacity and QoL.[12-14] However, despite the general awareness of the PA guidelines,[15] a considerable proportion of patients still fail to meet these recommendations. While exercise intolerance is an important limitation for these patients that must be acknowledged, sedentary behaviour should be avoided.[16] It is suggested that, in addition to routinely attending ET programs as an integral part of cardiac-rehabilitation, daily PA outside the gymnasium should be considered as an

adjunctive therapy, and prescribed accordingly. Because PA is also involved during activities of daily living, such as routine domestic chores, taking stairs instead of an elevator, going for regular walks, etc., incidental activities such as these should be further promoted to encourage patients with CHF, with or without an LVAD, to achieve PA requirements. Research has shown that in order to be effective, advice should be individualised to the patient's preferences and capacities, structured, specific, measurable and achievable.[8,17] We propose that medical, nursing and allied health providers in CHF management teams and rehabilitation programs can play an important role in promoting PA.

Chapter 4 focused on the cerebral haemodynamic response to acute exercise. Previous research has shown that CBF is reduced in patients with mild through to advanced CHF[18-20] and is proportional to disease severity.[18,19] These patients also exhibit impaired cerebral autoregulation.[21] Although no study to date has directly compared cerebral autoregulation pre- versus post-LVAD implantation, two studies[22,23] found that patients with LVADs show virtually identical indices of cerebral autoregulation to age-matched healthy controls. This suggests that LVAD implantation may normalise cerebral autoregulatory function. However, it is unclear the extent to which cerebral perfusion is impacted in patients with LVADs. Brassard et al.[24] reported that resting cerebral perfusion in LVADs was only 80% of that in normal subjects, however, no control group was included. Conversely, a more recent study conducted by and Cornwell et al.[25] found that resting CBF in patients with LVADs was comparable to age-matched healthy individuals, suggesting that LVAD implantation may normalise CBF, at least under resting conditions.

These studies only measured cerebral perfusion at rest, and there is currently a paucity of information regarding the effects of CHF on the cerebral haemodynamics during exercise. Fu et al.[26] initially showed that patients with CHF exhibit an abnormal cerebral oxygenation response to aerobic exercise. In patients supported with LVADs, Brassard et al.[24] observed that middle cerebral artery velocity (MCAv) LVADs remained unchanged during exercise, while the normal response is to increase up to 60-70% of $\dot{V}O_2$ peak, followed by a plateau.[27] However, when LVAD pump speed was manipulated to increase gradually during exercise, participants experienced a significant elevation in MCAv. Although this response did not achieve normal levels,

it was significantly improved. These findings suggest that cardiac output (CO) is an important determinant of cerebral perfusion during exercise in patients with LVADs. In our study, we followed the recommendations suggested by Brassard and Gustafsson[28] for conducting an integrative assessment of the cerebrovascular function, including the monitoring of intra- and extra-cranial arteries from both the anterior (i.e., MCA / ICA) and posterior circulation (i.e., posterior cerebral artery [PCA] / vertebral artery [VA]). To our knowledge, our study is the first to compare novel volumetric CBF responses to acute exercise in patients with advanced CHF, patients implanted with an LVAD, and healthy subjects, who were age- and sex-matched. Consistently with Cornwell et al.,[25] we found that patients with LVADs had similar CBF to matched healthy controls at rest. Whereas those with CHF (but no LVAD support) had a lowered resting CBF. During exercise, however, we observed that patients with LVADs exhibited impaired anterior and posterior cerebrovascular responses and they did not increase as a function of exercise intensity. Furthermore, exercise-induced shear-stress in the extracranial artery did not cause significant vasodilation in the CHF nor LVAD group. Therefore, while LVAD implantation may normalise cerebral perfusion at rest, it does not fully compensate for the haemodynamic requirements during incremental exercise.

In Chapter 5, we tested whether ET could improve cerebrovascular dysfunction that patients with LVADs experience during exercise. To the best of our knowledge, this is the first study to evaluate this. We found that a supervised and comprehensive 12-week ET program, involving aerobic and resistance exercises, significantly improved cerebrovascular parameters during exercise. At rest, we noted an increased ICA diameter following ET, but not flow, while PCAv decreased. However, the PCAv response during incremental exercise was mitigated following training. Likewise, ET resulted in a ~5-10% increase in ICA blood flow during submaximal exercise (20-60% $\dot{V}O_2$ peak). Our results suggest that ET may improve cerebrovascular endothelial function during exercise, at least in the extracranial arteries. The increase in CBF during exercise was associated with an enhanced $P_{ET}CO_2$ response to exercise. Further research is required to elucidate the relationship of this ventilatory parameter and cerebral haemodynamics during exercise in patients with LVADs. Although no statistically significant relationship was found between the change in $\dot{V}O_2$ peak and CBF parameters, positive correlations were detected at baseline (pre-training) between

$\dot{V}O_2$ peak and CBF parameters (ICA velocity, flow and PCAv) both at rest and during submaximal exercise. The lack of a significant difference may relate to the modest sample size, as four participants were lost to follow-up. Thus, our findings support Brassard's theory[28] which proposes that cerebral hypoperfusion may be a contributing factor for exercise intolerance in patients with CHF.

The underlying mechanisms of cerebral hypoperfusion during exercise for people with CHF and those supported with an LVAD remain unknown. It seems evident that CO is a major determinant, however, CBF regulation is multifactorial, as arterial blood gases, blood pressure, neurovascular metabolism, autonomic neural activity also play a role.[27] Because exercise affects all these factors and their interactions,[29] particularly in the setting of CHF, there are several aspects to consider. Firstly, vascular endothelial cell dysfunction has traditionally been linked to systemic vasoconstriction, which may be aggravated following LVAD implantation.[30,31] This has been attributed to arterial baroreceptor unloading induced by the lack of physiological pulse and LVAD-induced hemolysis.[32,33] It also should be noted that chronic exposure to high blood pressure may promote remodelling of the cerebrovasculature,[32] including vessel hypertrophy and increased cerebrovascular resistance,[34] which may result in impaired vasodilatory capacity. During exercise, the blunted ventilatory response (elevated $\dot{V}E/\dot{V}CO_2$) that these patients commonly experience may further contribute to vasoconstriction of the cerebrovasculature,[28] prompted by diminished partial pressure of carbon dioxide.[29,35] It remains unclear the specific role of increased sympathetic nervous system activation in relation to cerebral perfusion. Given that patients with LVADs have a markedly increased sympathetic tone,[32] it has been proposed that it may provoke vasoconstriction of the cerebral vascular beds,[36,37] and subsequent reduction in CBF. However, animals models have suggested that sympathetic mediated vasoconstriction could also act as a protective mechanism by preventing overdistension of the brain vessels during dramatic acute changes in blood pressure.[38] This notion partially explains why cerebral autoregulation is preserved following LVAD implantation. Thus, whether increased autonomic tone associated with CHF, and even more pronounced in patients with CF-LVADs[32] is beneficial for CBF regulation, and whether it may impact significantly on cerebral haemodynamic during exercise remains to be determined.

Cerebrovascular dysfunction may have important clinical implications for patients with CHF. Because the brain cannot store energy reserves, it is dependent on functional hyperaemia to match the local energetic demands induced by neural activity.[39,40] Thus, any alteration or disruption of CBF may implicate severe damage in the regional cells. Apart from potentially contribute to exercise intolerance, a mounting body of evidence suggests that cerebrovascular alterations may be involved in amyloid-β plaques and hyper-phosphorylated tau peptides accumulation, identified biomarkers in the pathogenesis of vascular cognitive decline.[41-43] Although a recent study[44] found that LVAD implantation improves cognition, and this may be directly related to the improvements in cerebral perfusion from augmentation of cardiac output; the incidence of cognitive decline in this cohort remains relatively high, especially in those supported as destination therapy.[45] Additionally, cerebrovascular dysfunction may account for the development of adverse neurological events, such as ischemic or haemorrhagic stroke, which are a leading cause of death for patients with LVADs.[46] Interestingly, risk factors for vascular cognitive decline and stroke overlap,[47] such as hypertension, smoking, diabetes, obesity and low levels of PA, supporting the concept of a shared predisposition. Of note, Teuteberg et al.[48] observed that having a mean arterial pressure >90 mmHg (at rest) was associated with a higher prevalence of cerebrovascular accidents in patients with CF-LVADs. This finding is not surprising, given that hypertension is also a risk factor of stroke for the general population. Therefore, maintaining mean arterial pressure ≤90 mmHg may be an important mitigation strategy to prevent serious neurological events in patients with LVADs.

Whether the lack of physiological pulse increases the likelihood of adverse neurological events remains a topic of debate.[49,50] While Cornwell[25] argued that brain physiology in patients with LVADs is not dissimilar to healthy individuals with normal pulsatile circulation, because cerebral autoregulation and perfusion is preserved regardless of the pump type used (pulsatile- or continuous-flow); the high occurrence of cerebral microbleeds[51] suggests a problem with the endothelial cell function[32] and/or with the neurovascular coupling.[46] In fact, patient with pulsatile-flow pumps exhibit reduced endothelial dysfunction compared to those with CF devices,[52] which may be reversible with cardiac transplantation,[53] highlighting the relevant role of repetitive physiologic increases in blood flow for vascular reactivity. Another factor that compounds endothelial cell dysfunction and inflammation may be the elevated

shear forces generated by LVADs that utilise rotary pumps, in which haemolysis occurs and platelets activate. This liberates free-haemoglobin and microparticles in plasma, increasing nitric oxide scavenging capacity.[53] These findings suggest that pulsatility may play a vital role in the vascular health and function and may be directly related LVAD complications.

Thus, there might be several factors involved in cerebral complications for these patients, including acquired von Willebrand syndrome, excessive anticoagulation and antiplatelet therapy, chronically elevated arterial pressure, LVAD-induced haemolysis and -related infections.[54,55] The potential interactions between cerebrovascular dysfunction and the pathophysiology of stroke and cognitive decline warrants additional investigation. While there is a lack of understanding and hence lack of treatment, our findings suggest that LVAD therapy coupled with exercise training may mitigate the cerebrovascular alterations that patients with CHF experience. Therefore, long-term exercise programs and incidental PA may be a promising approach to maintain or even improve cerebrovascular health and brain function with a reduction in subsequent adverse clinical outcomes in this patient population.

Lastly, we conducted an RCT to test the effects of different ET intensities in patients with LVADs. For the first time in this clinical cohort, we showed that HIIT was feasible and superior to the conventional approach of MICT for improving $\dot{V}O_2$ peak (17% vs. 6%). This was an interesting finding, and when viewed in concert with previous trials in patients with CHF,[56-58] suggests that HIIT could be applied as a means to further improve aerobic capacity in patients implanted with LVADs. To date, only three RCTs involving an exercise intervention have previously been conducted in patients with LVADs. All of these failed to show a positive effect of the ET intervention on aerobic capacity compared with the control group.[59-61] These findings may have been influenced by small sample sizes, short intervention periods and/or suboptimal training protocols. However, ET has consistently been shown to improve $\dot{V}O_2$ peak, QoL, as well as the risk of all-cause hospitalisation and death in patients with CHF.[62-64] Therefore, although these studies of ET performed to date in patients with LVADs have provided valid and useful data for practice, the question of whether HIIT is more effective in patients with LVADs has not previously been addressed.

For clinically stable patients with CHF, the conventional mode of aerobic exercise prescription has been MICT.[62,65] However, recently, a growing body of evidence has suggested that the magnitude of improvement across a range of physiological measures, including $\dot{V}O_2$ peak, may be dependent on the underlying intensity of the exercise performed.[66,67] In a meta-analysis[68] that compared the effects of three different ET intensities (i.e., high, moderate and low), $\dot{V}O_2$ peak was found to improve by 23%, 16% and 7%, respectively compared with a control group. In keeping with this notion, Udin et al.[69] performed a meta-regression analysis and confirmed that ET intensity was associated with the degree of increase in $\dot{V}O_2$ peak. Furthermore, separate meta-analyses[70-72] of RCTs over recent years have consistently found HIIT to be superior to MICT for improving $\dot{V}O_2$ peak. Taken together, these findings highlight the importance of ET intensity for the rehabilitation of patients with CHF.

Notwithstanding the potential benefits of HIIT, it needs to be balanced against the safety risk. Since higher exercise intensity demands higher myocardial oxygen consumption,[73] many health care professionals remain cautious about HIIT. For example, in a systemic review[74] evaluating the safety of a single acute HIIT session in patients with metabolic and cardiovascular disease, including CHF, an adverse response incidence rate of 8% of sessions was reported. Although the majority of these occurrences were not severe (i.e., ventricular bigeminy, self-terminating myocardial ischaemia, asymptomatic atrial tachycardia), it highlights the importance of close supervision during and following this type of training. Conversely, a more recent and larger systemic review that considered safety data of HIIT in patients with coronary artery disease or CHF,[75] found only one serious adverse event out of 11,333 hours of training. Importantly, this adverse event occurred during the participant's first week of training, suggesting it may be prudent for patients have had a lead-in period of moderate-intensity exercise prior to commencing HIIT. In the current project involving patients with LVADs, all participants had undergone at least 8 weeks of standard rehabilitation at up to a moderate-intensity. Although the sample is small, ET was well-tolerated and safe overall, with no serious adverse events occurring in either training group. While this study was not designed or powered to assess the effects of HIIT on clinical events, it suggests that HIIT may be relatively safe to conduct for patients with LVADs within a clinically supervised setting. Future multicentre RCTs

involving a larger sample size are needed to more comprehensively evaluate the safety of HIIT in patients with LVADs, but these findings are promising.

In contrast to the significant effect of HIIT on $\dot{V}O_2$ peak, no statistically significant differences were found between HIIT and MICT on secondary outcomes (cardiac function and structure, endothelial function, submaximal exercise capacity, muscle leg strength, body composition, QoL and biomarkers). Given the relatively small sample size of the study, these findings should be interpreted with caution. However, significant within-group improvements were noted in both training groups, in submaximal exercise capacity, muscular leg strength, vascular endothelial function, QoL domains related to physical health and self-efficacy. These findings highlight the important role of ET for the rehabilitation of patients with LVADs.

There was no improvement in cardiac function or structure suggesting that similar to patients with CHF,[71] training-induced improvements in $\dot{V}O_2$ peak are likely to be predominantly the result of peripheral adaptations. However, future trials are needed to more specifically elucidate the mechanisms of improvement in aerobic capacity with ET in patients with LVADs.

7.4 Limitations

There are several limitations associated with this project that warrant consideration. Although a broad eligibility criteria was applied to all the studies included, our recruitment pool was limited to patients implanted with only three models of CF-LVADs (HeartMate II, HeartMate 3 and HeartWare), and therefore, our findings may not be applicable to patients with other types of LVADs.

It is also important to acknowledge the relatively small sample size in the project, especially in relation to determining the superiority of one ET intervention compared with another. As a consequence, some of the findings, especially those when no significant difference was found, must be interpreted with caution and require replication in larger trials with increased power. However, this was essentially a pilot study to test novel concepts in a unique and relatively small (but growing) patient cohort, which we hope will stimulate further research in the exciting area of rehabilitation of patients implanted with LVADs. A further limitation of the small

sample size was that it was not possible to conduct sub-group analyses between LVAD types, which would have provided an interesting insight with any differences that might exist in the response of different LVADs to exercise.

Specifically for Chapter 3 and 4, we applied a cross-sectional design. The lack of pre-LVAD assessment on daily PA levels or CBF, respectively, limits our understanding of the direct effect of LVAD implantation on these outcomes. However, the feasibility of doing this would have been challenging given that a substantial proportion of patients receive an LVAD as emergency cases, while for others the decision for LVAD implantation is made once the patient is severely ill and hospitalised, or undergoing advanced medical treatment, which limits the patients capacity to participate in trials of the type undertaken in this thesis. Accordingly, a pre-post design would have restricted our recruitment of subjects and further compromised our sample size. It is also important to acknowledge the lack of a control group in Chapter 5, which restricts the interpretation of findings due to the inability to distinguish the impact of ET from the natural course over time.

7.5 Conclusions and future research directions

The findings from the present thesis by research highlight the critical role of LVAD therapy in functional rehabilitation, and the extent to which exercise impacts acutely and chronically on exercise physiology in these patients. In summary, several findings deserve remark.

Firstly, patients supported with an LVAD engage in higher daily PA levels compared with well-matched patients with advanced CHF without mechanical circulatory support, beyond the initial post-surgical recovery period. This seems to be related to an improved $\dot{V}O_2$ peak post-LVAD. Our findings highlight the beneficial role of LVAD implantation for the functional rehabilitation of these patients. In addition to aerobic fitness, improving self-efficacy may be an important target. Future research studies need to perform longitudinal assessments in patients before and after LVAD implantation to clearly determine its impact on PA levels over time. Moreover, a better understanding of the determinants of PA is needed with the aim of developing strategies to optimise PA levels in this clinical cohort.

Secondly, LVAD support may normalise cerebral perfusion at rest. However, during exercise, it is significantly attenuated, and in common with unsupported patients with advanced CHF, there seems to be inadequate compensatory augmentation in CBF to cope with the increasing demands of exercise. These findings suggest that cerebrovascular dysfunction persists despite LVAD support. An integrative assessment of global CBF, monitoring two arteries from the anterior circulation (ICA and MCA) and two from the posterior circulation (PCA and VA), in conjunction with CO and expired gases analyses is needed to formally delineate the precise mechanisms that regulate cerebral perfusion at rest and during different forms of acute exercise (i.e., aerobic and resistance). Since patients with LVADs have a marked increase in sympathetic nervous system activation, future studies are required to examine the extent to which autonomic function affects the brain physiology during exercise and its relation to neurological events. Furthermore, whether added pulsatility *per se* has a direct and beneficial impact on the cerebrovascular and peripheral endothelial function remains unresolved.

Thirdly, ET may improve cerebrovascular function during exercise in patients with LVADs. However, future randomised controlled trials are needed to confirm our preliminary findings. Ideally, these should involve larger samples, longer intervention periods and include peripheral vascular outcomes.

Lastly, we found that for patients with LVADs, HIIT may be feasible, safe and superior to MICT for improving aerobic capacity. While these findings need to be replicated in larger multicentre trials that include longer follow up periods to confirm the effectiveness and safety of this training mode in this clinical cohort, they are encouraging findings. The largest ET study to date in patients with CHF (HF-ACTION),[76] found that a 6% increase in $\dot{V}O_2$ peak conferred a 7% lower risk of all-cause mortality. Although there are currently no studies documenting the prognostic relevance of aerobic capacity in patients with LVADs, it is highly conceivable that patients with a higher $\dot{V}O_2$ peak may have a survival advantage over those with a lower $\dot{V}O_2$ peak.

There continues to be many important objectives and challenges related to understanding exercise physiology in patients with LVADs and how it relates to rehabilitation in this interesting patient cohort. Some of the important issues include:

1. A better understanding of barriers, facilitators and potential limitations for PA in patients with LVADs, and to develop effective strategies to optimise daily PA levels.
2. How time on LVAD support impacts the main physiological paramters (i.e., cardiac function and strcuture, vascular function, skeletal muscle metabolism, etc.).
3. The need to develop exercise prescription recommendations and guidelines specifically for LVAD patients.
4. An improved understanding of the pathophysiology of advanced CHF, how this is improved with LVAD implantation, the residual effects of the 'CHF hangover', and a better understanding of the physiology associated with the low pulsatility environment in patients with LVADs.
5. Mechanistic insight into exercise intolerance and training-induced adaptations, especially in the periphery, in patients with LVADs.

It is hoped the projects undertaken in this thesis will form the foundation for future research in these and other areas, that ultimately lead to improved rehabilitation strategies for patients with LVADs, and help them to live with better physical function and improved QoL.

7.6 References

1. Hu SX, Keogh AM, Macdonald PS, et al. Interaction between physical activity and continuous-flow left ventricular assist device function in outpatients. J Card Fail 2013;19:169-75.

2. Granegger M, Schloglhofer T, Ober H, Zimpfer D, Schima H, Moscato F. Daily life activity in patients with left ventricular assist devices. Int J Artif Organs 2016;39:22-7.

3. Jakovljevic DG, McDiarmid A, Hallsworth K, et al. Effect of left ventricular assist device implantation and heart transplantation on habitual physical activity and quality of life. Am J Cardiol 2014;114:88-93.

4. Rogers JG, Aaronson KD, Boyle AJ, et al. Continuous flow left ventricular assist device improves functional capacity and quality of life of advanced heart failure patients. J Am Coll Cardiol 2010;55:1826-34.

5. Maybaum S, Mancini D, Xydas S, et al. Cardiac improvement during mechanical circulatory support: a prospective multicenter study of the LVAD Working Group. Circulation 2007;115:2497-505.

6. Lahpor J, Khaghani A, Hetzer R, et al. European results with a continuous-flow ventricular assist device for advanced heart-failure patients. Eur J Cardiothorac Surg 2010;37:357-61.

7. Simon MA, Kormos RL, Gorcsan J, 3rd, et al. Differential exercise performance on ventricular assist device support. J Heart Lung Transplant 2005;24:1506-12.

8. Dontje ML, van der Wal MH, Stolk RP, et al. Daily physical activity in stable heart failure patients. J Cardiovasc Nurs 2014;29:218-26.

9. Pandey A, Garg S, Khunger M, et al. Dose–Response Relationship Between Physical Activity and Risk of Heart Failure. Circulation 2015;132:1786-94.

10. Palmisano P, Guerra F, Ammendola E, et al. Physical Activity Measured by Implanted Devices Predicts Atrial Arrhythmias and Patient Outcome: Results of IMPLANTED (Italian Multicentre Observational Registry on Patients With Implantable Devices Remotely Monitored). Journal of the American Heart Association;7:e008146.

11. Conraads Viviane M, Spruit Martijn A, Braunschweig F, et al. Physical Activity Measured With Implanted Devices Predicts Patient Outcome in Chronic Heart Failure. Circulation: Heart Failure 2014;7:279-87.

12. Cattadori G, Segurini C, Picozzi A, Padeletti L, Anzà C. Exercise and heart failure: an update. ESC Heart Fail 2018;5:222-32.

13. Yancy Clyde W, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017;136:e137-e61.

14. Ponikowski P, Voors AA, Anker SD, et al. [2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure]. Kardiol Pol 2016;74:1037-147.

15. Briffa TG, Maiorana A, Sheerin NJ, et al. Physical activity for people with cardiovascular disease: recommendations of the National Heart Foundation of Australia. Med J Aust 2006;184:71-5.

16. Doukky R, Mangla A, Ibrahim Z, et al. Impact of Physical Inactivity on Mortality in Patients With Heart Failure. Am J Cardiol 2016;117:1135-43.

17. Grandes G, Sanchez A, Sanchez-Pinilla RO, et al. Effectiveness of Physical Activity Advice and Prescription by Physicians in Routine Primary Care: A Cluster Randomized Trial. JAMA Internal Medicine 2009;169:694-701.

18. Choi BR, Kim JS, Yang YJ, et al. Factors associated with decreased cerebral blood flow in congestive heart failure secondary to idiopathic dilated cardiomyopathy. Am J Cardiol 2006;97:1365-9.

19. Loncar G, Bozic B, Lepic T, et al. Relationship of reduced cerebral blood flow and heart failure severity in elderly males. The aging male : the official journal of the International Society for the Study of the Aging Male 2011;14:59-65.

20. Fraser KS, Heckman GA, McKelvie RS, Harkness K, Middleton LE, Hughson RL. Cerebral hypoperfusion is exaggerated with an upright posture in heart failure: impact of depressed cardiac output. JACC Heart Fail 2015;3:168-75.

21. Caldas JR, Panerai RB, Haunton VJ, et al. Cerebral blood flow autoregulation in ischemic heart failure. Am J Physiol Regul Integr Comp Physiol 2017;312:R108-R13.

22. Ono M, Joshi B, Brady K, et al. Cerebral blood flow autoregulation is preserved after continuous-flow left ventricular assist device implantation. Journal of cardiothoracic and vascular anesthesia 2012;26:1022-28.

23. Bozkurt S. Effect of Cerebral Flow Autoregulation Function on Cerebral Flow Rate Under Continuous Flow Left Ventricular Assist Device Support. Artif Organs 2018;42:800-13.

24. Brassard P, Jensen AS, Nordsborg N, et al. Central and peripheral blood flow during exercise with a continuous-flow left ventricular assist device: constant versus increasing pump speed: a pilot study. Circ Heart Fail 2011;4:554-60.

25. Cornwell WK, 3rd, Tarumi T, Aengevaeren VL, et al. Effect of pulsatile and nonpulsatile flow on cerebral perfusion in patients with left ventricular assist devices. J Heart Lung Transplant 2014;33:1295-303.

26. Fu TC, Wang CH, Hsu CC, Cherng WJ, Huang SC, Wang JS. Suppression of cerebral hemodynamics is associated with reduced functional capacity in patients with heart failure. Am J Physiol Heart Circ Physiol 2011;300:H1545-55.

27. Smith KJ, Ainslie PN. Regulation of cerebral blood flow and metabolism during exercise. Experimental Physiology 2017;102:1356-71.

28. Brassard P, Gustafsson F. Exercise Intolerance in Heart Failure: Did We Forget the Brain? Can J Cardiol 2016;32:475-84.

29. Ogoh S, Ainslie PN. Cerebral blood flow during exercise: mechanisms of regulation. Journal of applied physiology 2009;107:1370-80.

30. Hasin T, Matsuzawa Y, Guddeti RR, et al. Attenuation in Peripheral Endothelial Function After Continuous Flow Left Ventricular Assist Device Therapy Is Associated With Cardiovascular Adverse Events. Circulation Journal 2015;79:770-77.

31. Witman MA, Garten RS, Gifford JR, et al. Further Peripheral Vascular Dysfunction in Heart Failure Patients With a Continuous-Flow Left Ventricular Assist Device: The Role of Pulsatility. JACC Heart Fail 2015;3:703-11.

32. Purohit Suneet N, Cornwell William K, Pal Jay D, Lindenfeld J, Ambardekar Amrut V. Living Without a Pulse. Circulation: Heart Failure 2018;11:e004670.

33. Hayward CS, Fresiello L, Meyns B. Exercise physiology in chronic mechanical circulatory support patients: vascular function and beyond. Curr Opin Cardiol 2016;31:292-8.

34. Cornwell William K, Ambardekar Amrut V, Tran T, et al. Stroke Incidence and Impact of Continuous-Flow Left Ventricular Assist Devices on Cerebrovascular Physiology. Stroke 2019;50:542-48.

35. Willie CK, Tzeng YC, Fisher JA, Ainslie PN. Integrative regulation of human brain blood flow. J Physiol 2014;592:841-59.

36. Francis GS. The relationship of the sympathetic nervous system and the renin-angiotensin system in congestive heart failure. Am Heart J 1989;118:642-8.

37. Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. J Am Coll Cardiol 1992;20:248-54.

38. Busija DW, Heistad DD, Marcus ML. Effects of sympathetic nerves on cerebral vessels during acute, moderate increases in arterial pressure in dogs and cats. Circulation Research 1980;46:696-702.

39. Iadecola C. The Neurovascular Unit Coming of Age: A Journey through Neurovascular Coupling in Health and Disease. Neuron 2017;96:17-42.

40. Iadecola C, Duering M, Hachinski V, et al. Vascular Cognitive Impairment and Dementia. JACC Scientific Expert Panel 2019;73:3326-44.

41. Sauve MJ, Lewis WR, Blankenbiller M, Rickabaugh B, Pressler SJ. Cognitive impairments in chronic heart failure: a case controlled study. Journal of cardiac failure 2009;15:1-10.

42. Hammond Christa A, Blades Natalie J, Chaudhry Sarwat I, et al. Long-Term Cognitive Decline After Newly Diagnosed Heart Failure. Circulation: Heart Failure 2018;11:e004476.

43. Fendler Timothy J, Spertus John A, Gosch Kensey L, et al. Incidence and Predictors of Cognitive Decline in Patients with Left Ventricular Assist Devices. Circulation: Cardiovascular Quality and Outcomes 2015;8:285-91.

44. Pavol MA, Willey JZ, Wei Y, et al. Does cognition improve following LVAD implantation? General Thoracic and Cardiovascular Surgery 2018;66:456-63.

45. Fendler TJ, Spertus JA, Gosch KL, et al. Incidence and predictors of cognitive decline in patients with left ventricular assist devices. Circulation Cardiovascular quality and outcomes 2015;8:285-91.

46. Acharya D, Loyaga-Rendon R, Morgan CJ, et al. INTERMACS Analysis of Stroke During Support With Continuous-Flow Left Ventricular Assist Devices: Risk Factors and Outcomes. JACC Heart Fail 2017;5:703-11.

47. Sharma M. Preventing Alzheimer's Disease. Some Light in the Darkness 2019;74:1924-25.

48. Teuteberg JJ, Slaughter MS, Rogers JG, et al. The HVAD Left Ventricular Assist Device: Risk Factors for Neurological Events and Risk Mitigation Strategies. JACC Heart Fail 2015;3:818-28.

49. Cornwell III WK, Tarumi T, Lawley J, Ambardekar AV. Rebuttal from William K. Cornwell III, Takashi Tarumi, Justin Lawley and Amrut V. Ambardekar. The Journal of Physiology 2019;597:363-64.

50. Cornwell WK, 3rd, Ambardekar AV, Tran T, et al. Stroke Incidence and Impact of Continuous-Flow Left Ventricular Assist Devices on Cerebrovascular Physiology. Stroke 2019;50:542-48.

51. Yoshioka D, Okazaki S, Toda K, et al. Prevalence of Cerebral Microbleeds in Patients With Continuous-Flow Left Ventricular Assist Devices. J Am Heart Assoc 2017;6.

52. Amir O, Radovancevic B, Delgado RM, et al. Peripheral Vascular Reactivity in Patients With Pulsatile vs Axial Flow Left Ventricular Assist Device Support. The Journal of Heart and Lung Transplantation 2006;25:391-94.

53. Sansone R, Stanske B, Keymel S, et al. Macrovascular and microvascular function after implantation of left ventricular assist devices in end-stage heart failure: Role of microparticles. J Heart Lung Transplant 2015;34:921-32.

54. Moazami N, Dembitsky WP, Adamson R, et al. Does pulsatility matter in the era of continuous-flow blood pumps? The Journal of Heart and Lung Transplantation 2015;34:999-1004.

55. Boyle AJ, Jorde UP, Sun B, et al. Pre-Operative Risk Factors of Bleeding and Stroke During Left Ventricular Assist Device Support. An Analysis of More Than 900 HeartMate II Outpatients 2014;63:880-88.

56. Wisloff U, Stoylen A, Loennechen JP, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. Circulation 2007;115:3086-94.

57. Fu TC, Wang CH, Lin PS, et al. Aerobic interval training improves oxygen uptake efficiency by enhancing cerebral and muscular hemodynamics in patients with heart failure. Int J Cardiol 2013;167:41-50.

58. Freyssin C, Verkindt C, Prieur F, Benaich P, Maunier S, Blanc P. Cardiac Rehabilitation in Chronic Heart Failure: Effect of an 8-Week, High-Intensity Interval Training Versus Continuous Training. Archives of Physical Medicine and Rehabilitation 2012;93:1359-64.

59. Laoutaris ID, Dritsas A, Adamopoulos S, et al. Benefits of physical training on exercise capacity, inspiratory muscle function, and quality of life in patients with ventricular assist devices long-term postimplantation. European Journal of Cardiovascular Prevention & Rehabilitation 2011;18:33-40.

60. Hayes K, Leet AS, Bradley SJ, Holland AE. Effects of exercise training on exercise capacity and quality of life in patients with a left ventricular assist device: a preliminary randomized controlled trial. J Heart Lung Transplant 2012;31:729-34.

61. Kerrigan DJ, Williams CT, Ehrman JK, et al. Cardiac rehabilitation improves functional capacity and patient-reported health status in patients with continuous-flow left ventricular assist devices: the Rehab-VAD randomized controlled trial. JACC Heart Fail 2014;2:653-9.

62. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-200.

63. Taylor RS, Long L, Mordi IR, et al. Exercise-Based Rehabilitation for Heart Failure: Cochrane Systematic Review, Meta-Analysis, and Trial Sequential Analysis. JACC Heart Fail 2019;7:691-705.

64. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1439-50.

65. Selig SE, Levinger I, Williams AD, et al. Exercise & Sports Science Australia Position Statement on exercise training and chronic heart failure. J Sci Med Sport 2010;13:288-94.

66. Haykowsky MJ, Daniel KM, Bhella PS, Sarma S, Kitzman DW. Heart Failure: Exercise-Based Cardiac Rehabilitation: Who, When, and How Intense? Can J Cardiol 2016;32:S382-S87.

67. Kuehn BM. Evidence for HIIT Benefits in Cardiac Rehabilitation Grow. Circulation 2019;140:514-15.

68. Ismail H, McFarlane JR, Nojoumian AH, Dieberg G, Smart NA. Clinical Outcomes and Cardiovascular Responses to Different Exercise Training Intensities in Patients With Heart Failure: A Systematic Review and Meta-Analysis. JACC: Heart Failure 2013;1:514-22.

69. Uddin J, Zwisler A-D, Lewinter C, et al. Predictors of exercise capacity following exercise-based rehabilitation in patients with coronary heart disease and heart failure: A meta-regression analysis. European journal of preventive cardiology 2016;23:683-93.

70. Gomes Neto M, Duraes AR, Conceicao LSR, Saquetto MB, Ellingsen O, Carvalho VO. High intensity interval training versus moderate intensity continuous training on exercise capacity and quality of life in patients with heart failure with reduced ejection fraction: A systematic review and meta-analysis. Int J Cardiol 2018;261:134-41.

71. Haykowsky MJ, Timmons MP, Kruger C, McNeely M, Taylor DA, Clark AM. Meta-analysis of aerobic interval training on exercise capacity and systolic function in patients with heart failure and reduced ejection fractions. Am J Cardiol 2013;111:1466-9.

72. Ballesta Garcia I, Rubio Arias JA, Ramos Campo DJ, Martinez Gonzalez-Moro I, Carrasco Poyatos M. High-intensity Interval Training Dosage for Heart Failure and Coronary Artery Disease Cardiac Rehabilitation. A Systematic Review and Meta-analysis. Rev Esp Cardiol (Engl Ed) 2019;72:233-43.

73. Gobel FL, Norstrom LA, Nelson RR, Jorgensen CR, Wang Y. The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. Circulation 1978;57:549-56.

74. Levinger I, Shaw CS, Stepto NK, et al. What Doesn't Kill You Makes You Fitter: A Systematic Review of High-Intensity Interval Exercise for Patients with Cardiovascular and Metabolic Diseases. Clinical Medicine Insights Cardiology 2015;9:53-63.

75. Wewege MA, Ahn D, Yu J, Liou K, Keech A. High-Intensity Interval Training for Patients With Cardiovascular Disease-Is It Safe? A Systematic Review. J Am Heart Assoc 2018;7:e009305.

76. Swank AM, Horton J, Fleg JL, et al. Modest increase in peak VO2 is related to better clinical outcomes in chronic heart failure patients: results from heart failure and a controlled trial to investigate outcomes of exercise training. Circ Heart Fail 2012;5:579-85.

Appendix A Attribution statements

A.1 Study 1

	Conception and Design	Acquisition of Data and Method	Data Conditioning and Manipulation	Analysis and Statistical Method	Interpretation and Discussion	Final Approval
Ignacio Moreno Suarez		X	X	X	X	X
Ignacio Moreno Suarez acknowledgment: I acknowledge that these represent my contribution to the above research output. 15/06/2020						
Sylvia Liew		X				X
Sylvia Liew acknowledgment: I acknowledge that these represent my contribution to the above research output. Date: 19/06/2020						
Lawrence Dembo					X	X
Lawrence Dembo acknowledgment: I acknowledge that these represent my contribution to the above research output. Date: 18/06/2020						
Robert Larbalestier					X	X
Robert Larbalestier acknowledgment: I acknowledge that these represent my contribution to the above research output. 2/07/2020						
Andrew Maiorana	X	X			X	X
Andrew Maiorana acknowledgment: I acknowledge that these represent my contribution to the above research output. Date:18/06/2020						

A.2 Study 2

	Conception and Design	Acquisition of Data and Method	Data Conditioning and Manipulation	Analysis and Statistical Method	Interpretation and Discussion	Final Approval
Ignacio Moreno Suarez	X	X	X	X	X	X
Ignacio Moreno Suarez acknowledgment: I acknowledge that these represent my contribution to the above research output. date: 12/12/2019						
Kurt Smith	X	X	X	X	X	X
Kurt Smith acknowledgment: I acknowledge that these represent my contribution to the above research output. date: 12/12/2019						
Anna Scheer		X				X
Anna Scheer acknowledgment: I acknowledge that these represent my contribution to the above research output. date: 19/06/2020						
Lauren Chasland		X				X
Lauren Chasland acknowledgment: I acknowledge that these represent my contribution to the above research output. date: 17/06/2020						
Hannah J. Thomas		X				X
Hannah J. Thomas acknowledgment: I acknowledge that these represent my contribution to the above research output. date: 18/06/2020						
Marilia A. Correia		X				X
Marilia A. Correia acknowledgment: I acknowledge that these represent my contribution to the above research output. date: 19/06/2020						
Louise H Naylor	X				X	X
Louise H Naylor acknowledgment: I acknowledge that these represent my contribution to the above research output. Date: 18/06/2020						
Andrew Maiorana	X	X			X	X
Andrew Maiorana acknowledgment: I acknowledge that these represent my contribution to the above research output.						

18/06/2020						
Lawrence Dembo					X	X
Lawrence Dembo I acknowledge that these represent my contribution to the above research output. Date: 18/06/2020						
Daniel Green	X				X	X
Daniel Green acknowledgment: I acknowledge that these represent my contribution to the above research output. 18 June 2020						

A.3 Study 3

	Conception and Design	Acquisition of Data and Method	Data Conditioning and Manipulation	Analysis and Statistical Method	Interpretation and Discussion	Final Approval
Ignacio Moreno Suarez	X	X	X	X	X	X
Ignacio Moreno Suarez acknowledgment: I acknowledge that these represent my contribution to the above research output. date: 12/12/2019						
Kurt Smith	X	X	X	X	X	X
Kurt Smith acknowledgment: I acknowledge that these represent my contribution to the above research output. date: 12/12/2019						
Anna Scheer		X				X
Anna Scheer acknowledgment: I acknowledge that these represent my contribution to the above research output. 19/06/2020						
Louise H Naylor	X				X	X
Louise H Naylor acknowledgment: I acknowledge that these represent my contribution to the above research output. 18/06/2020						
Lawrence Dembo					X	X
Lawrence Dembo I acknowledge that these represent my contribution to the above research output. date: 18/06/2020						
Andrew Maiorana	X	X			X	X
Andrew Maiorana acknowledgment: I acknowledge that these represent my contribution to the above research output. 18/06/2020						
Daniel Green	X				X	X
Daniel Green acknowledgment: I acknowledge that these represent my contribution to the above research output. 18 June 2020						

Appendix B Ethical and site-specific assessment authorisation at Fiona Stanley Hospital

B.1 Ethical approval

Government of **Western Australia**
Department of **Health**
South Metropolitan Health Service

Royal Perth Hospital
Human Research Ethics Committee

4 December 2015

A/Prof Andrew Maiorana
Department of Allied Health
Fiona Stanley Hospital

Dear Andrew

Project Title: The effects of different intensity exercise training in patients with left ventricular assist devices: a multicentre, randomized, control trial.

HREC Reference: REG 15-164

The ethics application for the project referenced above has been approved by the RPH Human Research Ethics Committee (HREC).

Approved documents:
PISCF Study 1
PISCF Study 2
Research Proposal

This approval is valid to **4 December 2018 and on the basis of compliance with the 'Conditions of HREC Approval for a Research Project' (attached).**

The nominated participating site(s) in this project is/are:

- **Fiona Stanley Hospital**

If additional sites are recruited prior to the commencement of, or during the research project, the Coordinating Principal Investigator is required to notify the HREC. Notification of withdrawn sites should also be provided to the HREC in a timely fashion.

This letter constitutes ethical approval only. This project cannot proceed at any site until separate site authorisation has been obtained from the CE, or delegate, of the site following Site Specific Assessment by a Research Governance Officer.

The RPH HREC is registered with the Australian Health Ethics Committee and operates according to the NHMRC National Statement on Ethical Conduct in Human Research and International Conference on Harmonisation – Good Clinical Practice.

Should you have any queries about the HREC's consideration of your project, please contact the **HREC Administrative Officer on 6151 1180. The HREC's Terms of Reference, Standard Operating** Procedures, membership and standard forms are available from the SIRO Research Ethics & Governance Unit or from the website http://smhs.hdwa.health.wa.gov.au/ServicesFacilitiesLocator/sa/ethics/aboutus.asp?v=0.

Southern Integrated Research Organisation (SIRO)
Locked Bag 100, PALMYRA DC WA 6961
Telephone: 08 6151 1180
Email: SMHS.REG@health.wa.gov.au
www.southmetropolitan.health.wa.gov.au

Yours sincerely

PROF FRANK VAN BOCKXMEER
CHAIRMAN ROYAL PERTH HOSPITAL HUMAN RESEARCH ETHICS COMMITTEE

B.2 Site-specific assessment authorisation

Government of **Western Australia**
Department of **Health**

FIONA STANLEY hospital

Enquiries : (08) 6151 1180

Associate Professor Andrew Maiorana
Advanced Heart Failure and Transplant Service
Fiona Stanley Hospital
11 Robin Warren Drive
MURDOCH WA 6150

Dear Associate Professor Maiorana

Project Title: The effects of different intensity exercise training in patients with left ventricular assist devices: a multicentre, randomized, control trial.
Protocol No: Version 2D
HREC Reference: 2015-164

On behalf of Fiona Stanley Hospital, I give authorisation for your research project to be conducted at Fiona Stanley Hospital.

The documents approved for use at site are those approved by the HREC in the letter dated 25 August 2016:

Approved document(s)
• Research Protocol Version 2D • Fiona Stanley Hospital Site Participant Information and Consent Form Version 2e dated 29 August 2016 based on Master Participant Information Sheet and Consent Form Version 2d

This authorisation is based on the approval from the Royal Perth Hospital Human Research Ethics Committee and the review from the Research Governance Office. This authorisation is valid subject to the ongoing approval from the HREC, and on the basis of compliance with the 'Conditions of Site Authorisation to Conduct a Research Project' (attached) and with the compliance of all reports as required by the Research Governance Office and approving HREC. Noncompliance with these requirements could result in the authorisation being withdrawn.

The responsibility for the conduct of this project remains with you as the Principal Investigator at the site.

Yours sincerely

[redacted]

Dr Paul Mark
A/EXECUTIVE DIRECTOR
31 August 2016

11 Robin Warren Drive
Murdoch WA 6150
Telephone: (08) 6152 2222

Locked Bag 100
Palmyra DC, WA 6961
www.fsh.health.wa.gov.au

B.3 Extension approval

15 October 2018

Assoc Professor Andrew Maiorana
Advanced Heart Failure and Transplant Service
Fiona Stanley Hospital

Dear Assoc Professor Maiorana

Project Title:	***The effects of different intensity exercise training in patients with left venticular assist devices: a multicentre, randomized, control trial.***
REG Number:	**2015-164**
HREC:	**Royal Perth Hospital Human Research Ethics Committee (EC00270)**
Site:	**Fiona Stanley Hospital**

The following **amendment/s (and associated documents)** have been **approved** by the HREC:

Amendment/Documents
Extension of Approval: **New Approval Date: 04/12/2021**

Please submit a copy of this approval letter to the Research Governance Office at participating sites.

Yours sincerely

[redacted]

SUE WALLACE
Delegate of the Chair
Royal Perth Hospital HREC

Research Ethics & Governance
Level 2 Kirkman House, Royal Perth Hospital, GPO Box X2213 Perth WA 6847
Telephone: (08) 9224 2260 / (08) 9224 2292
Email: EMHS.REG@health.wa.gov.au

B.4 Curtin University reciprocal approval

MEMORANDUM

Curtin University

To.	A/Prof Andrew Maiorana School of Physiotherapy and Exercise Science
CC:	Nacho Moreno Suarez
From	Professor Peter O'Leary, Chair HREC
Subject	Reciprocal ethics approval Approval number: HR13/2016
Date	20-Jan-16

Office of Research and Development
Human Research Ethics Office

TELEPHONE 9266 2784
FACSIMILE 9266 3793
EMAIL hrec@curtin.edu.au

Thank you for your application submitted to the Human Research Ethics Office for the project: 5244
The effects of different intensity exercise in patients with left ventricular assist devices: a multicentre, randomized, control trial.

Your application has been approved through Curtin University Human Research Ethics Committee (HREC) through a reciprocal approval process with the lead HREC:
RPH Human Research Ethics Committee EC00270
The lead HREC for this project has been identified as

Approval number from the lead HREC is noted as: REG 15-164

Please note the following conditions of approval:

1. Approval is granted from **21-Jan-16** to **04-Dec-18**
2. Research must be conducted as stated in the approved protocol.
3. Any amendments to the approved protocol must be approved by the Ethics Office.
4. An annual progress report must be submitted to the Ethics Office annually, on the anniversary of approval.
5. All adverse events must be reported to the Ethics Office.
6. A completion report must be submitted to the Ethics Office on completion of the project.
7. Data must be stored in accordance with WAUSDA and Curtin University policy.
8. The Ethics Office may conduct a randomly identified audit of a proportion of research projects approved by the HREC.

Should you have any queries about the consideration of your project please contact the Ethics Support Officer for your faculty, or the Ethics Office at hrec@curtin.edu.au or on 9266 2784. All human research ethics forms and guidelines are available on the ethics website.

Yours sincerely,

[redacted]

Professor Peter O'Leary
Chair, Human Research Ethics Committee

Appendix C Ethical and site-specific assessment authorisation at participating sites

C.1 Ethical approval at Alfred Hospital Human Research Ethics Committee

theAlfred

ETHICS COMMITTEE CERTIFICATE OF APPROVAL

This is to certify that

Project No: HREC/16/Alfred/119 (Local Reference: Project 297/16)

Project Title: The effects of different intensity exercise training in patients with left ventricular assist devices: A multicentre, randomized control trial

(Coordinating) Principal Researchers: Ms Louise Fuller & A/Prof Andrew Maiorana

was considered under the Consultative Council for Clinical Trial Research (CCCTR) National Mutual Acceptance (NMA) scheme by the Ethics Committee on 25-Aug-2016, meets the requirements of the National Statement on Ethical Conduct in Human Research (2007) and was APPROVED on 25-Oct-2016.

It is the Principal Researcher's responsibility to ensure that all researchers associated with this project are aware of the conditions of approval and which documents have been approved.

The Principal Researcher is required to notify the Secretary of the Ethics Committee, via amendment or progress report, of

- Any significant change to the project and the reason for that change, including an indication of ethical implications (if any);
- Serious adverse effects on participants and the action taken to address those effects;
- Any other unforeseen events or unexpected developments that merit notification;
- The inability of the Principal Researcher to continue in that role, or any other change in research personnel involved in the project;
- Any expiry of the insurance coverage provided with respect to sponsored clinical trials and proof of re-insurance;
- A delay of more than 12 months in the commencement of the project; and,
- Termination or closure of the project.

Additionally, the Principal Researcher is required to submit

- A Progress Report on the anniversary of approval and on completion of the project *(forms to be provided)*;

The Ethics Committee may conduct an audit at any time.

All research subject to the Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).

The Alfred Hospital Ethics Committee is a properly constituted Human Research Ethics Committee in accordance with the National Statement on Ethical Conduct in Human Research (2007).

APPROVED DOCUMENTS

Documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Protocol	1	29-Jul-2016
Master Invitation Letter	1	24-Aug-2016
Master Participant Information & Consent Form	5	24-Aug-2016
Heart Disease Self Efficacy Scale (modified)	-	-
SF-12 Health Survey	-	-

APPROVED SITES

Approval is given for this research project to be conducted at the following sites and campuses:

- Alfred Hospital (VIC)
- St Vincent's Hospital, Sydney (NSW)

The Alfred Hospital Ethics Committee has approved the study but does not take responsibility for research governance processes at the participating sites. It is the responsibility of each participating site to create and implement research governance practices to adequately authorise, monitor and oversee the conduct of the study at their site.

Site-Specific Assessment (SSA)
SSA authorisation is required at all sites participating in the study. SSA must be authorised at a site before the research project can commence.

The completed Site-Specific Assessment Form and a copy of this ethics approval letter must be submitted to the Research Governance Officer for authorisation by the Chief Executive or delegate. This applies to each site participating in the research.

The HREC wishes you and your colleagues every success in your research.

SIGNED:

Chair, Ethics Committee (or delegate)

Please quote project number and title in all correspondence

C.2 Site-specific assessment authorisation at the Alfred Hospital

Dr Angela Henjak
Manager, Office of Ethics & Research Governance
Alfred Health

Ms Louise Fuller
Senior Physiotherapist
The Alfred Hospital
Heart and Lung Transplant Unit
Alfred Hospital
Commercial Road
Melbourne, VIC 3004

20 February 2017

Dear Ms Fuller

Study title: The effects of different intensity exercise training in patients with left ventricular assist devices: a multicentre, randomized, control trial.

HREC Reference Number: HREC/16/ALFRED/119
SSA Reference Number: SSA/16/Alfred/191
Protocol version: 1.0
Protocol date: 29-Jul-2016

Thank you for submitting a Site Specific Assessment Form for authorisation of the above project at Alfred Health.

I am pleased to inform you that authorisation has been granted for this project to be conducted.

Reviewed and authorised documents

Documents reviewed and authorised were:

Document	*Version*	*Date*
Master Patient Information Sheet & Consent Form (Alfred Health – Local Governance Date 19-Aug-2016)	5	24-Aug-2016

If you have any matters that arise regarding conduct of the research at this site, please ensure you contact the Research Governance Officer.

Alfred Health wishes you and your colleagues every success in your research.

Yours sincerely

Angela Henjak
Manager, Office of Ethics & Research Governance
Alfred Health

C.3 Site-specific assessment authorisation at St Vincent's Hospital

St Vincent's Hospital

A facility of St Vincent's & Mater Health Sydney

St Vincent's Hospital Sydney Ltd
ABN 77 054 038 872
390 Victoria Street
Darlinghurst NSW 2010
Australia

T + 61 2 9362 4111
F + 61 2 9332 4142
www.stvincents.com.au

3 March 2017

Prof Christopher Hayward
The Victor Chang Cardiac Research Institute
Darlinghurst NSW 2010

Dear Christopher,

SVH File Number: 16/256
Project Title: The effects of different intensity exercise training in patients with left ventricular assist devices: a multicentre, randomized, control trial.
Short Title: SSA_Exercise training in patients with LVADs.
HREC reference: HREC/16/Alfred/119
SSA reference: SSA/16/SVH/351

Thank you for submitting an application for authorisation of this project. I am pleased to advise that the Director of Research on **1 March 2017**, has granted site authorisation for the above project to commence at

- **St Vincent's Hospital, Sydney**

Documents to be used at this site are:

- SVH Participant Information Sheet and Consent form, Version 5.2, dated 13 December 2016
- Protocol, Version 1, Alfred, dated 29 July 2016
- SVH Invitation Letter, Version 1.1, dated 10 October 2016
- Heart Disease Self Efficacy Scale (modified)
- SF-12 Health Survey

The SSA form reviewed was: **AU/2/8BA23**

Site authorisation will cease on the date of HREC expiry (**25 October 2021**).

Please note that it is not considered best practice to store research data on personal hardware. No identifiable participant data can leave a site. There always needs to be data security measures in place and a clear plan for permanent destruction of data needs to be adhered to at completion of the project.

Please find enclosed the following documents:

- Medicines Australia Clinical Trial Research Agreement (x2)

The following conditions apply to this research project. These are additional to those conditions imposed by the Human Research Ethics Committee that granted ethical approval:

1. The Principal Investigator must provide the St Vincent's Hospital Research Governance Officer via email (SVHS.Research@svha.org.au) with the following OHMR/MoH Imposed Metrics:
   - Within 45 calendar days of the date that the delegate of the institution has granted site authorisation for this project, report the date on which the first participant was enrolled to the clinical trial by this site. If at least one participant was not enrolled within 40 calendar days, a reason for the delay in enrolment also must be reported to the Research Governance Officer.
   - Within 15 days of site closure to enrolment, report the total number of participants enrolled in the clinical trial at the above site and report whether the minimum enrolment target as per the CTRA was reached. If the enrolment target was not reached, provide an explanation.

2. An annual progress report will be provided to the Research Governance Officer acknowledged by the LEAD HREC beginning in **October 2017**.
3. Proposed amendments to the research protocol or conduct of the research which may affect the ethical acceptability of the project, and are submitted to the lead HREC for review, are copied to the Research Governance Officer prior to implementation of the amendment on site.
4. All proposed amendments to the research protocol or conduct of the research which may affect the ongoing site acceptability of the project are to be submitted via email to the Research Governance Officer for review.
5. The relevant University HREC may require notification for projects that are undertaken by investigators holding an academic appointment (including conjoint appointments) or by students as part of a University course. This is the responsibility of the investigators.

Please note that only an electronic copy of this letter will be provided, if you require the original signed letter please contact the Research Office and we will be happy to provide this.

Should you have any queries about your project please contact the Research Office, Ph 8382 4960, email SVHS.Research@svhs.org.au. The HREC Terms of Reference, Standard Operating Procedures, *National Statement on Ethical Conduct in Human Research* (2007) and the *CPMP/ICH Note for Guidance on Good Clinical Practice* and standard forms are available on the Research Office website to be found at: https://svhs.org.au/home/research-education/research-office

Please quote **SVH file reference 16/256** and **HREC reference HREC/16/Alfred/119** in all correspondences.
The SVH Research Office wishes you every success in your research.

Yours sincerely,

[redacted]

Dr Sabine Giesebrecht
Research Governance Officer
St Vincent's Hospital Research Office
Translational Research Centre, 97-105 Boundary Street

Cc: Clare Coates
TRIM REF: D/2017/22895

Appendix D Participant information sheet and consent forms

D.1 Study 1

Government of Western Australia
Department of Health

FIONA STANLEY hospital

PARTICIPANT INFORMATION AND CONSENT FORM

The impact of left ventricular assist device implantation on physical activity levels in patients with advanced chronic heart failure

Principal Investigator: Dr Andrew Maiorana, Advanced Heart Failure and Cardiac Transplant Service, Fiona Stanley Hospital

This information sheet explains a study being undertaken at Fiona Stanley Hospital (FSH) and describes what will be involved should you decide to participate. Please read the information carefully and ask any questions you might have. You may also wish to discuss the study with a relative or friend.

Background and aim
A left ventricular assist device (LVAD) is a small pump that is implanted into the heart of people with severely impaired heart function to help circulate blood around the body. One of the objectives of LVAD implantation is to improve exercise tolerance and enable recipients to lead more active lifestyle. However, to date, few studies have directly investigated the effects of LVAD implantation on physical activity levels.

The aim of this study is to evaluate whether patients with a history of heart failure who have LVADs, undertake more physical activity than people with heart failure but who have not received an LVAD. This study will also assess the relationship between how much physical activity someone does and their level of confidence in performing exercise, their quality of life and their fitness.

Improving an understanding of physical activity levels in people with heart failure, with and without LVADs, will improve the understanding of the impact LVADs have on peoples' lives and the potential benefits on exercise and physical activity.

What participation in the study involves
If you choose to participate, you will be asked to undergo an exercise test, complete two questionnaires and wear a monitor that measures the amount of physical activity you perform over seven days. Some participants will also be provided with a second activity monitor that gives you feedback on the amount of activity you perform.

Assessments:
An assessment session will be conducted at FSH and will take approximately two hours. Firstly, you will be required to complete two questionnaires. The first questionnaire contains questions that relate to your confidence to perform different activities. The second questionnaire is used to assess how your heart condition affects your ability to cope with your day to day life. You will then undergo an exercise test on a treadmill in order to measure your heart and lung fitness by determining the amount of oxygen you consume during exercise. Electrodes will be placed on your chest to monitor your heart and you will be required to breath through a mouthpiece so the air that you exhale can be collected and analysed. The treadmill test will commence with walking slowly then every 3 minutes the speed and slope of the treadmill will be gradually increased making the exercise become progressively harder until you are unable to continue.

Questionnaires:
The first questionnaire poses 16 statements, each describing a different physical act. You will be required to rate each activity from 0 to 100 based on your confidence for undertaking that activity ("0" describes an activity that you "cannot do at all" and "100" is an activity you rate as "absolutely certain I can do".
The second questionnaire poses 36 questions about how your heart condition impacts upon your physical and mental health. If the researcher administering the questionnaire identifies that your mental health is being significantly impacted by your heart condition, we will advise you and offer you a referral to a Psychiatrist or Clinical Psychologist for follow up.

FSH PICF version 2 dated 2 April 2017; based on:
Master RPH PICF version 1

Physical activity level assessment:
At the conclusion of the assessment session you will be provided with a physical activity monitor (Actiheart) that you will be asked to wear for the next 7 days. The activity monitor is small (about the size of a 20 cent piece) and is worn under clothing, so isn't noticeable to others. It attaches to two standard ECG dots on your chest. If you wish, you can take the monitor off when sleeping and showering/bathing, however it is important to put it back on immediately after these activities. If you have an allergic reaction to ECG dots, let the researchers know and the activity monitor can be attached to a strap that is worn around the chest. You will be provided with a stamped post pack to return the device to RPH at the end of seven days so that the data it has collected can be reviewed. After the initial physical activity assessment, some participants will be provided with a different type of activity monitor (called a Fitbit) that is worn around the wrist and gives you feedback on the amount of activity you're doing via a mobile phone, so you can keep informed about your physical activity.

During the 7 days of assessment with the Actiheart device, you will also receive follow up phone calls from an investigator to monitor how you are managing with the device and your usual daily activities. You will also be able to contact the investigators at any stage if you need advice. For the people who are allocated the Fitbit, after several weeks using this device, you will be required to wear the Actiheart for a further 7 days.

Risks
Maximal exercise testing is commonly used in clinical practice and is associated with a very low risk of adverse events in people with heart conditions, less than 1 complication in 1,000 tests. You will be carefully monitored throughout and appropriately trained staff will be present at all times to ensure your safety. There is also a risk you may experience some muscle soreness after exercise testing, however this should resolve within 48-72 hours.

Because you will be required to undertake your usual activities during the 7 days of physical activity assessment, you should not experience any symptoms different to those that you would experience if you weren't being monitored.

Some people experience skin irritation from wearing the ECG electrodes for the extended period required for the study. If you have a history of skin irritation due to ECG electrodes, or if irritation occurs during the course of the study please inform the researchers immediately. In the case where skin irritation occurs, you will be provided with a chest strap to wear that the activity monitor can be attached.

Possible benefits
Regular physical activity is important in the management of patients with heart failure, including those with LVADs. Information derived from this study will provide valuable knowledge to improve the care of people with heart failure in the future.

Privacy and confidentiality
The information gathered about you by the investigator or obtained during this study will be held by the investigator in strict confidence. All the people who handle your information will adhere to traditional standards of confidentiality and will also comply with the Privacy Act 1988. If the results of the trial are published in a medical journal, as is intended, no reader will be able to identify individual patients.

What if something goes wrong?
In the event that you suffer an expected or unexpected side effect or medical accident during this study that arises from your participation, you will be offered all full and necessary treatment by Fiona Stanley Hospital. The Ethics Committee has approved this study on the basis (amongst others) that the reported risk of such an event is either small or acceptable in terms of the risk you face as a result of your current illness.

Costs to participation
There will be no costs incurred as a result of participation in this study. You will not be paid for participation, however expenses you incur associated with parking will be reimbursed at your request.

Voluntary Participation and withdrawal

Participation in this study is entirely voluntary. You do not have to participate if you do not want to and your decision to participate or not will in no way affect your current or future care at RPH. You are also free to withdraw from the study at any time without reason or justification.

Contact Information
If you have questions about this study, please contact Dr Maiorana on (08) 6152 2222. This study has been approved by the Royal Perth Hospital Ethics Committee. If you have any concerns about the conduct of the study or your rights as a research participant, please contact Prof Frank van Bockxmeer, Chairman of the RPH Ethics Committee, on (08) 9224 2244 and quote the ethics approval number (13-122).

FSH PICF version 2 dated 2 April 2017; based on:
Master RPH PICF version 1

Government of Western Australia
Department of Health

FIONA STANLEY hospital

CONSENT FORM

The impact of left ventricular assist device implantation on physical activity levels in patients with advanced chronic heart failure

Principal Investigator: Dr Andrew Maiorana, Advanced Heart Failure and Cardiac Transplant Service, Fiona Stanley Hospital

I, ... agree to participate in the above study. I have read and understood the attached information sheet and I have retained a copy of the signed document. I have been given the opportunity to ask questions about the study by the Investigator. I understand that I may withdraw from the study at any time without affecting any future medical treatment, or the treatment of the condition which is the subject of the study.

Signed ..... Date .....

Signature of Investigator ..... Date .....

FSH PICF version 2 dated 2 April 2017; based on:
Master RPH PICF version 1

D.2 Study 2

Government of Western Australia
Department of Health

FIONA STANLEY hospital

PARTICIPANT INFORMATION SHEET

A comparison of acute haemodynamic responses to exercise in people with ventricular assist devices compared with chronic heart failure & healthy individuals

Principal Investigator: Dr Andrew Maiorana, Allied Health Dept. and Cardiac Transplant Service, FSH

Fiona Stanley Hospital (FSH) and Curtin University are investigating exercise responses in people who receive ventricular assist devices (VADs), people who have heart failure but don't receive a VAD and healthy individuals. The following information describes what will be involved should you decide to participate in this research project. Please read the information about this study carefully and ask any questions you may have. You may also wish to discuss the study with a relative or friend.

BACKGROUND

Ventricular assist device (VAD) implantation is associated with improved survival, exercise capacity and quality of life. A key goal of VADs is to improve physical function, facilitating the return to activities of daily living as soon as possible. Exercise training plays an important role in this, and is currently a vital component of patients' clinical management. However, little is known about the contribution of VADs during exercise and the responses of the circulatory system.

WHAT IS THE PURPOSE OF THE STUDY?

The aim of this study is to compare brain blood flow at rest and during exercise between people with VADs, chronic heart failure and healthy people. This will provide new information about how VADs contribute to brain blood flow during exercise.

WHAT WILL PARTICIPATION INVOLVE?

If you agree to take part in the study, you will first be asked to attend an **initial screening appointment** at FSH, which will take about approximately half an hour. The following will occur at the initial appointment:

1. We will review this Information Sheet, answer any questions you have and, if you agree to continue, ask you to sign the attached Consent Form. We will document your medical history and demographic information. Some of this may be recorded in your medical records, so we are requesting your permission to access these details. We may need to confirm some of this information or seek further information from you, but obtaining the information already available in your medical record will save time and ensure accuracy.
2. You will perform a maximal strength test on a leg press resistance machine. This will involve testing how much weight you are able to lift just once.

At least 48 hours later, you will be asked to attend a second appointment at FSH to complete the main study tests. This appointment will take approximately 2 hours.

1. Blood vessel function test: This assessment involves non-invasive ultrasound of an artery in your arm. The test measures the change in blood vessel size prior to and following occlusion of blood flow by a blood pressure cuff for five minutes.

2. You will be asked to perform a cycling test and weight lifting test while blood flow to your brain is measured. The order of these tests will be randomised and separated by a 20 minute recovery period.

Prior to the first test we will set up the equipment and get you to rest quietly for 20 minutes. We will then take resting measurements of your blood flow to the brain:

The cycling test will be performed on a semi-recumbent bike in order to measure your heart and lung fitness by determining the amount of oxygen you consume during exercise. Electrodes will be placed on your chest to monitor your heart and you will be asked to breathe through a mask so the air that you exhale can be collected and analysed. The exercise test will start by pedalling at a low workload. Every two minutes the pedal's resistance will be gradually increased, making the cycling become progressively harder until you are unable to continue. While you are completing the exercise test, blood flow to the brain will be examined non-invasively via ultrasound. Small ultrasound probes (similar to those used to monitor unborn babies) will be mounted on a head frame, which resembles a bicycle helmet, and will sit in front of your ears so we can examine the speed of blood flowing through an artery in your brain. Neck blood flow with be measured using a vascular ultrasound probe applied to the side of you neck and held in place by an experienced sonographer throughout the exercise protocols.

Arterial blood pressure: Blood pressure will be recorded using a blood pressure monitoring cuff device attached to your finger. There are no side effects to this technique.

Respiratory gas exchange: Oxygen and carbon dioxide will be assessed while breathing face mask throughout the cycling exercise. There are no side effects to this technique.

You will be asked to perform two sets of lower body lifting exercises (leg press). The weight for each stage of this test will be based on your lifting capacity previously recorded during your first visit. We will be measuring your brain blood flow and cardiorespiratory measures with the same devices as described above. Each stage of testing will be separated by a 5-minute rest period to allow brain blood flow to return to resting levels.

- First set of resistance exercise: 50% of maximum lifting capacity for 10-15 repetitions.

- Second set of resistance exercise: 75% of maximum lifting capacity for 5-10 repetitions.

SUMMARY OF VISITS AND TIME COMMITMENT

The table below lists the visit and test schedule.

Appointment	Procedure	Timing
Visit 1: Screening	-Introduction to the study	**15 min**
	-Review of information sheet, medical history and demographic information - Weight lifting capacity test (1-RM)	**20 min**
Visit 2: Experimental Protocol *(About 1 week after screening)*	- Vascular function test - Resting brain blood flow (ultrasound) -Exercise brain blood flow during the cycling and lifting tests	**30 minutes** **1,30 hours**

WHAT ARE THE POSSIBLE DISADVANTAGES AND RISK OF TAKING PART?

Maximal exercise testing is commonly used in clinical practice and is associated with a very low risk of adverse events in people with advanced heart conditions, with less than 1 complication in every 1,000 tests. While there is a transient increase in the risk of a cardiovascular event with exercise, recent studies have found exercise testing and training to be safe for people with VADs and have recommended exercise training from 3 weeks after the surgery. *To minimise any risks with testing and training you will be carefully monitored by appropriately trained staff at all times to ensure your safety and ECG monitoring will be used during the exercise test.*

There is also a risk you may experience some muscle soreness after exercise testing, however this should resolve within 48-72 hours.

During some sessions you may be asked to exercise at an intensity which is higher than you are used to, this may result in moderate fatigue. However, as the exercise intensity will be participant controlled (i.e. will involve your rating of how hard you find the exercise), we expect this discomfort will be minimal.

POSSIBLE BENEFITS

All participants will receive an individualised comprehensive fitness test with full expired breath analysis. While this may lead to individual benefits for you, this cannot be guaranteed.

WHAT ARE THE COSTS OF BEING IN THIS STUDY?

There are no financial costs associated with participating in the study. You will not be paid for participation, however expenses you incur associated with travel and parking to attend study specific visits will be reimbursed.

PRIVACY AND CONFIDENTIALITY

The information gathered about you by the investigator or obtained during this study will be held by the investigator in strict confidence. All the people who handle your information will adhere to traditional standards of confidentiality and will also comply with the Privacy Act 1988. Your research data will initially be identified only by a unique study code and held separately from a link that matches the code to your name. No identifiable data (i.e. with your name attached) will leave FSH. Once the study is completed, the data will be anonymised, by deleting the link that matches the code to your name. If the results of the trial are published in a medical journal, as is intended, no reader will be able to identify individual patients.

WHAT IF SOMETHING GOES WRONG?

In the event that you suffer an expected or unexpected side effect or medical accident during this study that arises from your participation, you will be offered all full and necessary treatment by Fiona Stanley Hospital.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Participation in this study is voluntary. You do not have to participate and, if you decide to participate, you can stop at any time without explanation. Your decision to participate or not, or to later withdraw from the study, will in no way affect your current or future care at Fiona Stanley Hospital.

CONTACT INFORMATION

If you have questions about this study, please contact Associate Professor Andrew Maiorana on (08) 61521692 or alternatively Nacho Suarez on 0403 243 221.

This study has been approved by the Royal Perth Hospital Human Research Ethics Committee. If you have any concerns about the conduct of the study or your rights as a research participant, please contact the RPH Ethics Committee on (08) 6151 1180 or SMHS.REG@health.wa.gov.au and quote the ethics approval number (REG 15-164).

CONSENT FORM

The acute haemodynamic responses to exercise in individuals with ventricular assist devices

Principal Investigator: Dr Andrew Maiorana, Cardiac Transplant Service, FSH

I, ... agree to participate in the above study. I have read and understood the attached information sheet and I have retained a copy of the signed document. I have been given the opportunity to ask questions about the study by the Investigator. I understand that I may withdraw from the study at any time without affecting any future medical treatment, or the treatment of the condition which is the subject of the study.

Signed _____ **Date** _____

Signature _____ **Date** _____

of person obtaining consent

Name _____

of person obtaining consent

D.3 Studies 3 & 4

Government of **Western Australia**
Department of **Health**

FIONA STANLEY hospital

PARTICIPANT INFORMATION SHEET

The effects of different intensities of exercise training in patients with ventricular assist devices

Principal Investigator: Dr Andrew Maiorana, Allied Health Dept. and Advanced Heart Failure and Cardiac Transplant Service, FSH

You are being invited to participate in a study investigating the benefits of moderate and high intensity exercise programs on patients who have a ventricular assist device (VAD) because you are scheduled to have a VAD inserted at Fiona Stanley Hospital (FSH). This project is being undertaken and leading by FSH and Curtin University, as well as other hospitals in Australia.

This information sheet describes what will be involved should you decide to participate. Please read the information carefully and ask any questions you might have. You may also wish to discuss the study with a relative or friend.

BACKGROUND

Exercise training is an important and beneficial component of cardiac rehabilitation. For people who have ventricular assist devices (VADs), moderate-intensity continuous exercise is the current clinical standard. However, based on recent research in people with cardiac conditions, exercise at an increased intensity, performed in shorter duration intervals, may be a more effective and time-efficient method of exercise for improving fitness.

WHAT IS THE PURPOSE OF THE STUDY?

The aim of this project is to compare the effects of 12 weeks of high-intensity interval exercise training (HIT) with the current clinical standard exercise of moderate-intensity continuous training (MIT) on fitness, heart and blood vessel function and 'quality of life' in individuals supported with VADs. We anticipate that the findings of the study will be used to refine exercise training protocols for people following VAD implantation.

Participants will be randomly allocated (as if by the toss of a coin) to either the high intensity (HIT) or moderate intensity (MIT) group.

- Participants in the **HIT group** will complete 3-4 minute bouts of relative high-intensity aerobic exercise training on a treadmill, interspersed with 3-4 minutes of active recovery at a low-moderate intensity.
- Participants in the **MIT group** will be asked to perform continuous aerobic exercise training on a treadmill at a moderate intensity for up to 30 minutes per session.

Exercise training in both groups will be performed three times a week. Both groups will also receive a standard, moderate intensity resistance (weights) exercise rehabilitation program for a period of 6 weeks following VAD implantation and prior to being randomly assigned to one of the study groups.

WHAT WILL PARTICIPANT INVOLVE?

If you agree to take part in the study you will be asked to attend an **initial study appointment** which will take less than 1 hour and will occur during one of your routine visits to FSH.

The following will occur at your initial study appointment:

1. We will review this Information Sheet, answer any questions you have and, if you agree to continue, ask you to sign the attached Consent Form.

2. We will document your medical history and demographic information. Much of this will be recorded in your medical records, so we are requesting your permission to access these details. We may need to confirm some of this information or seek further information from you, but obtaining the information already available in your medical record will save time and ensure accuracy.

3. You will be asked to complete two questionnaires for the study. The first questionnaire measures your confidence in undertaking different types of physical activity and in different settings. The second questionnaire poses questions about how your heart condition impacts upon your physical and mental health. If the researcher administering the questionnaires identifies that your mental health is being significantly impacted by your heart condition, we will advise you and offer you a referral to a Psychiatrist or Clinical Psychologist for follow up.

Assessment Visit 1: Measurement of heart function and exercise oxygen consumption

1. Heart function: An experienced sonographer will perform echocardiography assessments of the heart to measure the size and pumping ability of the heart's chambers before and after the exercise test described below.

2. You will be asked to complete an exercise test on a treadmill or bike in order to measure your heart and lung fitness by determining the amount of oxygen you consume during exercise. Electrodes will be placed on your chest to monitor your heart and you will be required to breathe through a mouthpiece so the air that you exhale can be collected and analysed. Before the test your breathing will be measured at rest. The exercise test will then commence at a low workload, then every 2 minutes the workload will be gradually increased making the exercise become progressively harder until you are unable to continue.

Assessment Visit 2: Peripheral blood flow, heart and daily functional capacity assessment

1. A blood sample will be taken following at least 8 hours of fasting (no food nor caffeine allowed). Approximately 30mL of blood will be collected to assess full blood picture, cholesterol, markers of inflammation and the health of blood vessels and different organs in the body (heart, liver, kidneys, etc.). *Note: The blood sample will only be used for this study, after which any leftover blood will be destroyed.*

2. You will be asked to have a dual x-ray absorptiometry (DEXA) scan to measure your body fat, muscle mass and mineral bone density. This involves a low level of radiation (described below).

3. Blood vessel function test. This assessments involves non-invasive ultrasound of an artery in your arm. The first test measures the change in blood vessel size prior to and following occlusion of blood flow by a blood pressure cuff for five minutes.

4. You will be asked to perform the Six-Minute Walk Test (6MWT), in order to evaluate your functional capacity. This test measures the distance that you can quickly walk on a flat, hard surface in a period of 6 minutes. It reflects the functional exercise level for daily life activities.

Assessment Visit 3: Brain blood flow measurement during exercise
You will be asked to return to Fiona Stanley Hospital to complete a cycling test and weight lifting test while blood flow to your brain is measured. These will be conducted in a randomised order, with a 20 minute recovery period between each test.

The cycling exercise test will start with a light intensity workload, which will progressively increase in intensity every 2 minutes until you are unable to continue. .

a. While you are completing the exercise test, blood flow to the brain will be examined via ultrasound. Small ultrasound probes (similar to those used to monitor unborn babies) will be mounted on a head frame, which resembles a bicycle helmet, and will sit in front of your ears so we can examine the speed of blood flowing through an artery in your brain. Neck blood flow with be measured using a vascular ultrasound probe applied to the side of you neck and held in place by an experienced sonographer throughout the exercise protocols.
b. Arterial blood pressure: Blood pressure will be recorded using non-invasive blood pressure monitoring device attached to your finger. This device involves the placement of a small blood pressure cuff around your finger. There are no side effects to this technique.
c. Respiratory gas exchange: Oxygen and carbon dioxide will be assessed non-invasively while breathing through a mouthpiece throughout the cycling exercise. There are no side effects to this technique.

The weight lifting test will involve performing a series of lower body lifting exercises (leg press). The weight for each stage of this test will be based on your lifting capacity previously recorded during your training assessments as part of your rehabilitation. We will be measuring your brain blood flow and cardiorespiratory measures with the same devices used in Assessment Visit 2. Each stage of testing will be separated by a 10 minute rest period to allow cerebral blood flow to return to baseline.

Stages:

a. 50% of maximum lifting capacity for 10-15 repetitions
b. 75% of maximum lifting capacity for 5-10 Repetitions

Once all the tests have been completed you will be notified which group you have been randomly allocated to; either moderate-intensity continuous training (MIT) or high-intensity interval training (HIT).

Exercise training intervention (12 weeks):
It is estimated that you will need to attend FSH three times a week for 12 weeks for approximately one hour per session. The first week will be used to familiarise you with the exercises to be completed during the training program. All exercise intensities will be prescribed according to your fitness level achieved on the exercise test performed at the start of the study. Each session will begin and end with a five-minute warm-up and cool down.

Follow-up Visits
At the conclusion of the 12 week exercise program, we will ask you to attend three follow-up visits that will repeat the tests undertaken in the initial set of Assessment Visits.

SUMMARY OF VISITS AND TIME COMMITMENT
The table below lists the visit and test schedule.

Time period	Procedures	Time commitment
Initial study appointment	-Review of information sheet, medical history and demographic information. -Completing questionnaire	<1hour
Baseline Visit 1	-echocardiogram -Maximal exercise test	1.5 hour
Baseline Visit 2	-fasting blood sample -DEXA scan -blood vessel function (ultrasound) -6 minute walk test	2.0 hours
Baseline Visit 3	-Cycling and lifting test -Brain blood flow (ultrasound)	2.0 hours
12 week exercise program (randomised to either HIT or MIT) (3 x 1 hour sessions a week)		36 hours

Follow-up Visit 1	-Review of recent medical history -Completing questionnaires -Echocardiogram -Maximal exercise test	1.5 hours
Follow-up Visit 2	-fasting blood sample -DEXA scan -blood vessel function (ultrasound) -6 minute walk test	2.0 hours
Follow-up Visit 3	-Cycling and lifting test -Brain blood flow (ultrasound)	2.0 hours

WHAT ARE THE POSSIBLE DISADVANTAGES AND RISK OF TAKING PART?

Maximal exercise testing is routinely used in clinical practice and is associated with a very low risk of adverse events in people with advanced heart failure, with less than 1 complication in every 1,000 tests. While there is a transient increase in the risk of a cardiovascular event with exercise, recent studies have found exercise testing and training to be safe for people with VADs and have recommended exercise training from 3 weeks after the surgery. *To minimise any risks with testing and training you will be carefully monitored by appropriately trained staff at all times to ensure your safety and ECG monitoring will be used during the exercise test.*

There is also a risk you may experience some muscle soreness after exercise testing and training, however this should resolve within 48-72 hours.

As well, this research study involves exposure to a very small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose from this study is about 0.01 mSv. At this dose level, no harmful effects of radiation have been demonstrated as any effect is too small to measure. The risk is believed to be minimal.

During some sessions, you may be asked to exercise at an intensity which is higher than you are used to. This may result in moderate fatigue; however, as all exercise intensity will be participant controlled (i.e. based on a level of perceived exertion), we expect this discomfort will be minimal.

It is possible that you may experience bleeding, bruising or pain at the blood sampling site, similar to that experienced with routine blood tests.

POSSIBLE BENEFITS

All participants will receive an individualised, supervised exercise training program, as well as comprehensive body composition analysis and fitness test with full expired breath analysis. While this may lead to individual benefits for you, this cannot be guaranteed.

WHAT ARE THE COSTS OF BEING IN THIS STUDY?

There are no financial costs associated with participating in the study. You will not be paid for participation, however expenses you incur associated with travel and parking to attend study specific visits will be reimbursed.

PRIVACY AND CONFIDENTIALITY

The information gathered about you by the investigator or obtained during this study will be held by the investigator in strict confidence. All responses to the questionnaires and tests as well as information provided by you will be held in de-identified format and stored in a locked cabinet or on a password protected computer at FSH. Only members of the research team will have access to the information. All the people who handle your information will adhere to traditional standards of confidentiality and will also comply with the Privacy Act 1988. If the results of the trial are published in a medical journal, as is intended, no reader will be able to identify individual patients.

WHAT IF SOMETHING GOES WRONG?

In the event that you suffer an expected or unexpected side effect or medical accident during this study that arises from your participation, you will be offered all full and necessary treatment by Fiona Stanley Hospital.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Participation in this study is voluntary. You do not have to participate and, if you decide to participate, you can stop at any time without explanation. Your decision to participate or not, or to later withdraw from the study, will in no way affect your current or future care at Fiona Stanley Hospital.

CONTACTS FOR FURTHER INFORMATION

If you have questions about this study, please contact Associate Professor Maiorana on (08) 61521692 or alternatively Nacho Suarez on 0403243221.

This study has been submitted by the Royal Perth Hospital Human Research Ethics Committee. If you have any concerns about the conduct of the study or your rights as a research participant, please contact the RPH Ethics Committee on (08) 6151 1180 or SMHS.REG@health.wa.gov.au and quote the ethics approval number (REG 15-164).

CONSENT FORM

The effects of different intensities of exercise training in patients with ventricular assist devices

Principal Investigator: Dr Andrew Maiorana, Cardiac Transplant Service, FSH

I, ... agree to participate in the above study. I have read and understood the attached information sheet and I have retained a copy of the signed document. I have been given the opportunity to ask questions about the study by the Investigator. I understand that I may withdraw from the study at any time without affecting any future medical treatment, or the treatment of the condition which is the subject of the study.

Signed _____ **Date** _____

Signature _____ **Date** _____

of person obtaining consent

Name _____

of person obtaining consent

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Wolters Kluwer

Physical Activity Is Higher in Patients with Left Ventricular Assist Device Compared with Chronic Heart Failure

Author: IGNACIO MORENO-SUAREZ, SYLVIA LIEW, LAWRENCE DEMBO, et al
Publication: Medicine & Science in Sports & Exercise
Publisher: Wolters Kluwer Health, Inc.
Date: Jan 1, 2020

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Cerebral blood flow responses to exercise are enhanced in left ventricular assist device patients after an exercise rehabilitation program

Author: Kurt J. Smith, Ignacio Moreno-Suarez, Anna Scheer, et al
Publication: Journal of Applied Physiology
Publisher: The American Physiological Society
Date: Jan 1, 2020

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Thank you for your order.

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