THE EFFECTS OF ACUTE EXERCISE ON CARDIOVASCULAR FUNCTION IN
HUMANS

by

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Abstract

In spite of numerous studies examining cardiac fatigue following acute exercise, there is a significant need for descriptive research that documents the nature and magnitude of this phenomenon in various populations. Accordingly, the aim of this series of studies was to comprehensively investigate the cardiovascular consequences of acute exercise in endurance trained (ET) individuals, normally active (NA) individuals, and heart transplant recipients (HTR). In the first investigation, 25 ET athletes were examined before a 160 km ultra-marathon and were re-assessed immediately following the race using traditional echocardiography, speckle tracking imaging, and cardiac biomarkers. Significant pre to post-race changes in systolic function (ejection fraction (EF): 66.8 ± 3.8 vs. 61.2 ± 4.0 %, $p < 0.05$), and diastolic function (E:A ratio: 1.62 ± 0.37 vs. 1.35 ± 0.33, $p < 0.05$) were observed. The second investigation used cardiac magnetic resonance imaging with tagging to study the impact of interval exercise on biventricular function in nine ET (VO_{2max}: 69 ± 7 mL/kg/min) and nine NA (VO_{2max}: 44 ± 9 mL/kg/min) males. There were no significant changes in RV and LV EF, torsion, rotation rate, strain, or strain rate post-exercise in the NA group. In the ET group, RV and LV EF, untwisting rate, apical rotation rate and circumferential strain were significantly decreased post-exercise. These results suggest that biventricular systolic and diastolic dysfunction occur following 14 min of high intensity exercise in ET athletes, a phenomenon which is not observed in NA individuals. The final investigation examined the cardiovascular responses during incremental and sustained (1 hr) sub-maximal aerobic exercise in 9 clinically stable HTR (age: 63 ± 10 yr; VO_{2peak}: 24.2 ± 10.9 mL/kg/min) and 11 healthy age-matched controls (6 recipient age-matched, RM; age: 60 ± 11 yr; VO_{2peak}: $36.3 \pm$

10.7 mL/kg/min, and 5 donor age-matched, DM; age: 35 ± 8 yr; VO_{2peak}: 51.1 ± 10.4 mL/kg/min) using traditional echocardiography. Despite maintained systolic function during incremental exercise, HTR had significantly reduced peak cardiac output, secondary to blunted heart rate and preload during exercise conditions. These findings provide the basis for future work examining the underlying mechanisms contributing to exercise-induced cardiac fatigue.

Table of Contents

List of Tables

List of Figures

List of Symbols, Nomenclature and Abbreviations

<u>Symbol</u>	<u>Definition</u>
β	Cardiac Beta Receptor
BNP	Brain B-type Natriuretic Peptide
BSA	Body Surface Area
cMRI	Cardiac Magnetic Resonance Imaging
cTnT	Cardiac Troponin T
CVP	Central Venous Pressure
DBP	Diastolic Blood Pressure
DM	Donor Matched
DVI	Diastolic Ventricular Interaction
E:A	Ratio of Early to Atrial Ventricular Filling Velocity
Ea	Effective Arterial Elastance
ECG	Electrocardiogram
EDV	End Diastolic Volume
Ees	End Systolic Elastance
EF	Ejection Fraction
E'	Early Filling Annular Velocity
ESP	End Systolic Pressure
ESV	End Systolic Volume
ET	Endurance Trained
FAC	Fractional Area Change
FFA	Free Fatty Acid

HF	High Frequency
HRV	Heart Rate Variability
HTR	Heart Transplant Recipient
LF	Low Frequency
LV	Left Ventricle
LVM	Left Ventricular Mass
NA	Normally Active
NTproBNP	N-terminal pro-brain natriuretic peptide
Q	Cardiac Output
RM	Recipient Matched
RMSSD	Square Root of the Mean of Squared Differences Between Successive RR intervals
RV	Right Ventricle
SBP	Systolic Blood Pressure
SPECT	Single Photon Emission Computed Tomography
SV	Stroke Volume
SVR	Systemic Vascular Resistance
VO_2	Oxygen Consumption
WS	Wall Stress
WSER	Western States Endurance Run

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CHAPTER ONE: Introduction

It has been almost 45 years since Saltin and Stenberg (93) described the hemodynamic responses of strenuous exercise, and 20 years since the term 'cardiac fatigue' was first coined to refer to the decreases in systolic and diastolic function observed following exercise (25). At the time of its discovery, cardiac fatigue received relatively little attention. While it was understood that individuals with underlying cardiac anomalies had an increased risk of sudden death while exercising (106), it was assumed that healthy individuals with no evidence of underlying cardiovascular pathologies would have no impairments in left ventricular (LV) performance following exercise (25, 66, 95, 111). However, beginning in the 1980s and continuing to an even greater extent in the 1990s, both researchers and clinicians increasingly focused their attention on the impact of exercise-induced cardiac fatigue (75).

Although our knowledge regarding cardiac fatigue has grown dramatically over the past two decades, much of the available information remains descriptive and related to field-based settings. Exercise-induced cardiac fatigue is a multi-faceted entity, and, although a number of hypotheses attempt to explain its mechanism(s) in a given situation, the extent to which these hypotheses can be generalized to all forms of cardiac fatigue (right and left ventricular, systolic and diastolic) remains unclear. Thus, researchers need not only to integrate different, seemingly divergent explanations of the genesis of cardiac fatigue, but also to assess their implications from a broad perspective.

1.2 Statement of the Problem

In spite of numerous studies examining cardiac fatigue, there is significant need for

more deliberate research documenting the nature and magnitude of this phenomenon in various populations. The severe duration of exercise performed during ultra-endurance events (20+ hours) is particularly important, as it is probable that these races require greater cardiac work and thus may result in more extensive changes in ventricular function compared to the previously described changes involving shorter 3-12 hour endurance races (111). Additionally, few studies have examined alterations in cardiac function following brief, high intensity exercise; nor has a comparison been made between the impact of such changes (if any are noted) in normally active individuals and endurance trained athletes. Finally, although the overall duration of exercise incorporated in most cardiac rehabilitation programs is approximately 1 h (50), little research has been conducted on the acute cardiovascular consequences of exercise in clinical populations. Accordingly, the purpose of the following studies is to examine the effects of acute exercise of varying durations on cardiovascular function in endurance trained individuals, normally active individuals, and heart transplant recipients.

   Chapter Two provides a brief review of literature discussing both the cardiovascular consequences of acute exercise in healthy individuals and heart transplant recipients, and the potential underlying mechanisms which contribute to decreases in cardiac function. The third chapter describes an investigation of the cardiovascular consequences of a 160 km ultra-marathon in 25 endurance trained individuals using traditional echocardiography, speckle tracking imaging, cardiac biomarkers, and heart rate variability. Chapter Four discusses a study examining the effects of brief, high intensity exercise on cardiac function using cardiac magnetic resonance imaging in 9 endurance trained and 9 normally active individuals. Chapter Five describes an experiment

assessing the cardiovascular responses during incremental and sustained sub-maximal aerobic exercise in 9 clinically stable heart transplant recipients and 11 healthy age-matched controls (6 recipient age-matched and 5 donor age-matched) using traditional echocardiography. Chapter Six provides an overview of the findings of the series of investigations reported in this dissertation.

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[1]CHAPTER TWO: Review of Literature

2.1 Acute Exercise in Healthy Individuals: Prolonged Exercise

Most studies examining cardiac fatigue have focused on endurance races lasting from 3 (marathon) to 16 (Ironman triathlon) hours. The Ironman World Championship (2.4-mile swim, 112-mile bike ride, and a 26.2-mile run) takes place every year in Hawaii, and a series of experiments have examined how this event affects ventricular function in ultra endurance athletes (25). Two-dimensional and M-mode echocardiography were performed before the event, within 11 minutes after the race, and the day after the triathlon. Compared with baseline measures, prolonged exercise resulted in a significant reduction in end-diastolic cavity diameter and fractional shortening, with no change in end-systolic diameter, mean arterial pressure, or wall stress. The decline in fractional shortening and mean velocity of circumferential fibre shortening, despite no change in

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mean arterial pressure and wall stress, suggests that competing in the Hawaii Ironman is associated with a reduced left ventricular (LV) function in triathletes. It was concluded that preload was not the sole cause of the reduced LV systolic function for the following two reasons: 1) the observation of a non-significant difference between changes in end-diastolic diameter and reduction in fractional shortening and 2) the finding that fractional shortening returned to basal values 28 hours after the triathlon, whereas contractility (systolic blood pressure/end-systolic diameter) remained reduced (25). Since afterload, as measured by end-systolic meridional wall stress, was reduced after exercise, the reduction in fractional shortening may have been due to a decline in myocardial contractility.

The most extensive period of exercise in which cardiac fatigue has been studied previously is 24 hours. Niemela et al. (77) studied 12 endurance runners who completed a 24 hour running race. Left ventricular function was assessed with 2-D echocardiography before, and immediately after the race. Compared with baseline measurements, significant reductions in end-diastolic area, fractional shortening, and mean velocity of circumferential fiber shortening were observed after the race. The decline in these variables occurred despite no change in systolic blood pressure and a significant reduction in wall stress. Similar to the observations by Douglas et al. (25), Niemela et al. (77) noted no significant correlation between changes in end-diastolic diameter and changes in fractional shortening, suggesting that the decline in fractional shortening was not related to alterations in preload. In addition, afterload was significantly reduced during the recovery phase, indicating that the decline in LV performance may be due to, in part, a decline in myocardial contractile function. Bruce

and colleagues (15) provide further supportive data suggesting that LV function is impaired after prolonged exercise. In their case report, the cardiovascular responses during a graded exercise test were measured in a healthy well-trained 24-year-old man before and after running across the United States (40 miles/day for 2.5 months). Compared with baseline values, prolonged exercise resulted in a decline in stroke volume and mean arterial pressure at submaximal and maximal running workloads. This decline was not attributed to hypovolemia since neither heart size nor total blood volume were reduced. These investigations raise the intriguing question as to whether even more prolonged exertion could result in further decreases in systolic and diastolic function into the clinical range.

2.2 Acute Exercise in Healthy Individuals: Brief Exercise

Studies of acute bouts of prolonged (> 3h), moderate intensity exercise have consistently demonstrated that transient decreases in LV systolic and diastolic function are induced in endurance trained athletes (75, 94). Although many studies have supported the evidence in favour of cardiac fatigue, not all authors have found similar declines. In particular, studies examining shorter exercise periods and those involving low intensity exercise have demonstrated little evidence of such dysfunction (37, 84). Whyte et al. (111) examined systolic and diastolic function after half and full Ironman triathlons, and reported that changes in fractional shortening were significantly decreased after the full, but not the half Ironman triathlon. Additionally, several other investigations have found no evidence of cardiac fatigue during brief exercise (with duration ranging from 5-18 min) (30, 54, 102). This suggests there could be a cardiac fatigue "threshold" of duration and/or of intensity of exercise. Indeed, Neilan et al. (74) examined the acute cardiac

changes that occurred following a 2000m ergometer sprint in elite rowers, and reported a reduction in LV diastolic function. Furthermore, Foster and colleagues (33) demonstrated that global LV systolic function is depressed during brief, sudden strenuous exercise (30 s cycling at 400 W). Given the marked RV and LV pressure and volume overload during maximal exercise (100), it is possible that brief, *high intensity* exercise may also result in alterations in cardiac function.

2.3 Acute Exercise in Healthy Individuals: Training Status

The concept that the impact of exercise may be different depending on training status is intriguing, but not currently supported by any investigation. Many studies have simply not recorded the fitness of subjects, thus making it difficult to assess the impact of fitness upon the development of cardiac fatigue. Despite this, decreases in ventricular function have been reported in athletes who completed demanding events such as an Ironman triathlon (25), as well as untrained individuals completing short duration (60 min) cycle ergometry (53). Of note, Niemela et al. (76) reported greater evidence of cardiac fatigue in those athletes who covered greater distances in a run and Douglas and associates (25) reported that the reduction in ventricular shortening tended to be greater in those with the fastest race times. Endurance athletes are often exposed to repeated bouts of maximal exertion; however, the effects of this type of exercise on biventricular function are unknown. Moreover, the clinical ramifications of this type of exercise in normally active individuals have not been investigated. Because normally active individuals seldom experience high cardiac pressure and volume loads, it is possible that they may have significant decreases in biventricular function in response to repeated bouts of high intensity exercise.

2.4 Acute Exercise in Heart Transplant Recipients: Brief Exercise

Over the past 2 decades, heart transplantation, once considered an experimental procedure, has become widely accepted as a life-extending therapy for patients with end-stage heart failure. The dramatic improvements in organ preservation, surgery and immunosuppressive drug management, mean that short term survival is no longer a pivotal issue for most heart transplant recipients (HTR). Rather, a return to functional lifestyle with good quality of life is now the expected procedural outcome. Although the five year survival rate is currently 85%, patients have an ever-present risk of infection and graft rejection. Because of physical inactivity and the severe limitation of cardiac output preoperatively, the initiation of a rehabilitative exercise training program is a vital first step in returning to a functional lifestyle.

Many previous studies of HTR document that peak oxygen uptake is much lower than that of normal adults matched for age, sex and size (14, 18, 48, 51). Consequently, the exercise capacity of these patients is often limited. Similar to the general population, HTR can, however, increase their physical fitness by exercise training, resulting in a 10–30% increase in VO_2 (51, 55, 78).

There is ample evidence indicating that both endurance and resistance training are well tolerated in HTR (42). Moreover, there is growing clinical consensus that specific endurance training regimens in HTR are efficacious in the reversal of the pathophysiological consequences (myocardial cell damage, rejection, coronary artery disease) associated with cardiac denervation and antecedent heart failure. While the benefits of exercise for both normally active individuals and HTR are undisputed, there are significant differences in the cardiovascular responses of healthy individuals and

HTR to acute exercise. A healthy individual responds to constant-load exercise with a rapid increase in heart rate (HR), which is initially sustained by the release of the parasympathetic tone and thereafter, by an increase in sympathetic activation (92). The activity of the autonomic nervous system is influenced by a variety of stimuli arising from several regions of the brain, exercising muscles, baroreceptors located in the aortic arch and carotid sinuses, and from mechanical receptors in the respiratory system (92). These reflexes require that both the afferent and efferent branches of the autonomic nervous system be intact.

Denervation of the myocardium, which occurs with cardiac transplantation, results in alterations in autonomic nervous system modulation of the heart. As a consequence, resting HR is higher than in healthy subjects (2, 18, 51), the HR response at the onset of constant-load exercise is delayed and slower than that of healthy individuals (2, 18, 24, 38), peak HR attained at maximal exercise is lower than that observed in age-matched healthy subjects (3, 18, 51, 55), and HR changes during exercise are typically dictated by an increasing plasma catecholamine concentration (3, 24, 87). At the onset of submaximal exercise, stroke volume of denervated HTR increases rapidly, therefore, to a certain extent, counterbalancing the lack of HR response (9, 68). As a consequence of this rapid adaptation, the time course of the cardiac output (Q) readjustment at the onset of a submaximal exercise is almost normal (9) or only slightly slower (38) than in healthy sedentary individuals. Whereas Q at rest and at submaximal exercise is normal or mildly reduced, at peak exercise it is 30–40% lower than that of age-matched controls due to the low peak HR value, which is only ~80% of the predicted value (48). Although

the alterations in cardiovascular responses to short bouts of exercise are well known in HTR, very little is understood about the consequences of continuous exercise (1 h).

2.5 Acute Exercise in Heart Transplant Recipients: Continuous Exercise

Long-term endurance training allows HTR to attain high peak HR and VO_2 levels (169 beats/min and 40 ml/kg/min, respectively), (90) and to achieve remarkable performances such as completing a 20-km race in 146 min (79), a full marathon in just under 6 h (27), a 600 km relay road race (90), and a half Ironman triathlon in 6.5 h (43). With more and more HTR completing endurance events, it has become extremely important to understand the consequences of these prolonged endurance events on the cardiovascular system in this population. Prolonged endurance exercise requires a sustained increase in myocardial work in order to deliver sufficient oxygen to the skeletal muscles. Interestingly, almost twenty years ago, Douglas et al. (27) studied the immediate cardiac effects of an Olympic distance triathlon in a HTR. Following 4 hours of exercise at an average HR of 144 beats/min, they reported a marked decrease in LV cavity size without a change in fractional shortening, as well as a decrease in E:A ratio. These results suggest that HTR may also experience cardiac fatigue following continuous exercise.

2.6 Mechanisms of Post-Exercise Alterations in Systolic Function

2.6.1 Altered Preload/afterload

In any study of ventricular function, it is difficult to separate the influence of changes in loading conditions from intrinsic myocardial contraction and relaxation properties. Acute exercise may result in hypovolemia and/or redistribution of central blood volume which would then decrease preload through a reduction in venous return (66). Several

previous studies on the effects of prolonged exercise on LV function have reported a reduction in end diastolic volume (an index often used to measure preload) (95, 111). It is therefore possible that the change in LV function observed previously represents an altered hemodynamics rather than a true depression in inotropy or intrinsic relaxation properties.

A limited number of studies on cardiac function and exercise have attempted to maintain preload (22, 37, 41). In their examination of LV function before, during, and following prolonged exercise, Dawson et al. (22) carefully maintained preload by regulating central venous pressure (CVP) with intravenous saline infusion. They found that indices of LV function did not change significantly within a 3 h bout of submaximal semi-recumbent cycle ergometry with maintained preload (as indicated by CVP) (22). Although maintenance of LV loading in field studies is difficult, Hassan et al. (41) manipulated the posture during scans by adopting the Trendelenburg position in an attempt to standardize hemodynamic loading conditions during submaximal exercise. Similar to Dawson et al. (22), Hassan et al. (41) found that, with maintenance of preload, the effect of exercise on indices of LV systolic function was negligible.

The lack of alteration in ejection fraction and end systolic pressure/volume ratio after exercise reported by Dawson et al. (22) and Hassan et al. (41) is in contrast with previous research involving exercise durations similar to the Ironman triathlon (25, 111). Several investigations have reported no change in post-exercise preload indices, while clearly outlining decreases in LV systolic function (94, 107) (as demonstrated by significant exercise-induced downward shift in the stress-shortening relationship). Consequently, the lack of any significant changes in LV systolic function during or following prolonged

exercise reported by Dawson et al. (22) and Hassan et al. (41) could be attributed to several factors. Irrespective of the maintenance of LV loading, it is possible the duration and intensity (or both) employed in these studies were not great enough to provoke a pronounced depression in left ventricular contractility (21, 66).

Further, exercise leads to significant changes in peripheral vascular function, including a persistent reduction in total peripheral vascular resistance. This decrease in peripheral vascular resistance often produces post-exercise hypotension, which ultimately reduces afterload on the heart. Most studies have shown a reduction in systolic blood pressure (a surrogate measure of afterload) after exercise (94, 111). Indeed, Hassan et al. (41) suggest that the given changes in loading (increased left ventricular end-diastolic volume and reduced blood pressure), would normally have resulted in a small rise in contractility. The fact that there was not an increase in contractility could, in fact, be interpreted as a decrease in LV contractility. Although the loading conditions of the heart clearly warrant consideration in the transient LV impairment following exercise, the above findings suggest that it may be presumptuous to completely dispel the occurrence of a depression in LV function that is independent of loading after exercise.

2.6.2 Myocardial Ischemia and/or Damage

Alterations in myocardial function, thought to be related to cardiac damage, have been reported in several studies after acute exercise (73, 97). Given the changes in LV function that occur with ischemia and cardiomyocyte damage in cardiovascular diseases, it is plausible that exercise-induced myocardial damage could underpin changes in LV systolic function after acute exercise. It is interesting to note that Rifai et al. (91) and Neilan et al. (73) correlated functional changes with cardiac troponin T (cTnT)

appearance following a marathon run. It should be noted that the association between cardiac biomarker appearance and functional changes is still highly controversial, and many investigations have found no such correlations (36, 96, 110). This is despite a growing evidence base that has described the appearance of markers of cardiomyocyte damage in the circulation after acute exercise.

The release of myocardial cellular proteins could be due to a number of events. Starnes and Bowles (98) suggested that a mechanism for changes in LV function could be brief coronary occlusion and reflow, or what they termed myocardial stunning. Dysfunctional myocardial tissue is now understood to exist on a spectrum from normal to irreversibly infarcted or necrotic. Between these two extremes are the states of stunned myocardium and hibernating myocardium (20). If brief coronary occlusion occurs during prolonged exercise, it is possible that myocardial stunning (or "pseudo-stunning") is an underlying mechanism (alteration in function with near normal flow in the absence of permanent damage), as opposed to myocardial hibernation (decrease in function with low flow). Research has shown that in most cases myocardial stunning is well tolerated, transient in nature, and has no significant long-term impacts; that is, it does not result in necrosis and permanent cellular damage (6).

Blood flow limitation (ischemia) can cause ultrastructural changes of the cardiac myocyte, which are reversible with restoration of normal blood flow (10). Stunned myocardium results in changes in LV function due to reduced coronary blood flow that can be reversed by reducing myocardial oxygen demand (7). It is interesting to note that our laboratory has previously found that myocardial oxygen consumption (measured non-invasively) is significantly increased and myocardial efficiency is significantly

decreased immediately following prolonged exercise, returning to baseline levels after 24 hours (29). Importantly, Vatner and colleagues (104) have shown that, in dogs with left ventricular hypertrophy, exercise can induce both ischemic myocardial dysfunction and post-ischemic myocardial stunning in the absence of any coronary stenosis, implying that myocardial stunning can also occur after high-flow ischemia in which the primary problem is an increase in oxygen demand (relative to flow) rather than a decrease in supply. Vatner et al. (104) hypothesized that the increased oxygen demand reduced LV function in pathologically hypertrophied hearts; however, athletes are well known to have a large LV mass (89), and, as we have recently observed, increased myocardial oxygen demand following prolonged exercise (29). Although it is likely a large leap in our understanding, the above findings may provide indirect support for the occurrence of myocardial stunning or "pseudo-stunning" after prolonged exercise. It must be noted that exercise-induced eccentric-hypertrophy differs greatly from pathological hypertrophy, and the experimental evidence of stunning (particularly in healthy human athletes) is scarce (49, 97). Further investigation is clearly warranted before definitive statements can be made about the prevalence of myocardial stunning and its effects on LV function following acute exercise.

An extensive discussion of the physiology of stunned myocardium (1) is beyond the scope of this chapter, but in order to understand the rationale behind the consequences of myocardial damage on exercise-induced cardiac fatigue, it is valuable to review the key concepts briefly. Two major hypotheses explain this phenomenon: 1) the oxyradical hypothesis, which proposes that oxidant stress impairs LV function (7), and 2) the calcium hypothesis, which postulates that stunning results from disturbed myocyte

calcium homeostasis (Figure 2.1) (60). The oxyradical hypothesis remains controversial, as the exact mechanism whereby oxygen metabolites depress contractile function is speculative. Kumar et al. (59) showed that an acute bout of exhaustive endurance exercise increased the generation of free radical signals in the myocardium of female rats. Venditti et al. (105) also reported that prolonged aerobic exercise (210 min) produced a 22% decrease in overall antioxidant capacity of rat hearts, while exhaustive exercise (444 min) produced a 50% decrease. This finding suggests that a key role in the myocardial damage could be the duration of exercise.

Acute Exercise

Myocardial Stunning

A) Oxidative Stress

B) Calcium Overload

ROS Modification of
Contractile Proteins

Decreased
Calcium
Responsiveness

Apoptosis

Proteolysis of
Contractile
Proteins

**Impairment of
Systolic and Diastolic
Function**
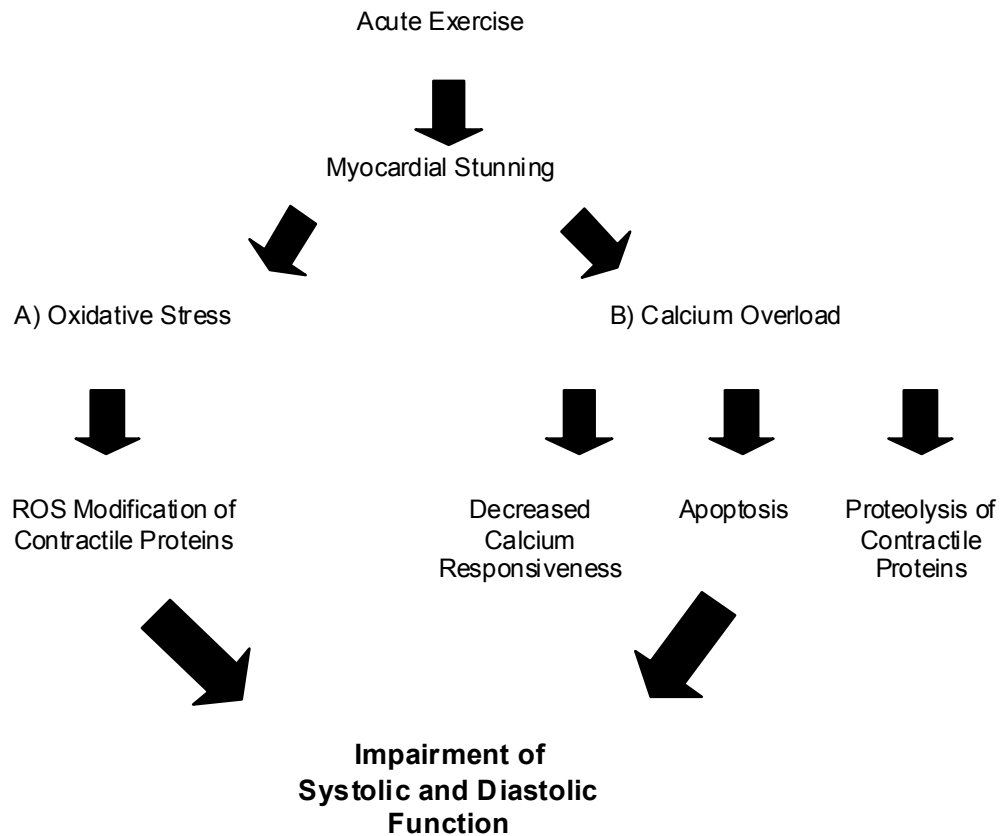
**Figure 2.1 Illustration of the proposed mechanisms of stunning induced alterations
in systolic and diastolic function.**
Exercise induced stunning of the myocardium results in oxidative stress and/or calcium
overload. Pathway A: the increase in reactive oxygen species (ROS) during exercise
alters contractile proteins, ultimately impairing systolic and diastolic function. Pathway
B: the overload of intracellular calcium results in a decrease in myofilament calcium
responsiveness, apoptosis, and/or proteolysis of contractile proteins, ultimately
decreasing systolic and diastolic function.

Interestingly, Whyte et al. (110) reported a significant increase in reactive oxygen species following a marathon run; however, this rise in free radical production was unrelated to alterations in LV function or appearance of cardiac troponins. It is important to note that the free radical measures used in that investigation were global biological measures that may not be specific to that of the cardiomyocyte. Clearly, further research examining the effects of free radicals and antioxidants on exercise-induced cardiac fatigue is warranted.

As opposed to the oxyradical hypothesis, the calcium hypothesis is more complex and has several postulated mechanisms (for review see (7)). Calcium plays two distinct roles in myocardial stunning: 1) as the chemical activator of contraction, calcium overload could be a major determinant in the physiology of the decrease in function; and 2) as an agent of injury, calcium may contribute to the pathogenesis of stunning. In response to stunning, a transient calcium overload has been demonstrated to result in an impairment in myofilament calcium responsiveness (70). This decrease in calcium responsiveness, in turn, produces mechanical and metabolic abnormalities (57). It is possible that calcium overload may ultimately contribute to the decreases in LV function observed after exercise.

Increased intracellular calcium concentration due to alterations in calcium homeostasis in the ischemic or otherwise stressed heart, also activates a calcium dependant protease (calpain), which results in degradation of target proteins, such as troponin I and troponin T. The regulatory function of the troponins is therefore disturbed, resulting in a sustained elevation of end-systolic pressure and volume (indicators of depressed diastolic and systolic function), traits which are often observed following prolonged exercise. Several investigators have also demonstrated that calpain activation may promote myocardial

apoptosis (19). Calcium overload has been shown to contribute to myocardial apoptosis in a variety of cardiovascular diseases (39); and it is possible that calcium overload triggered by acute exercise could induce apoptosis (Figure 2.1).

Although transient ischemia can occur in the absence of significant changes in ECG, there is limited direct evidence of any myocardial ischemia in any exercise-induced cardiac fatigue studies (111). Osbakken and Locko (83) employed stress-redistributed thallium scans and reported possible evidence of myocardial perfusion defects in trained athletes after 40 ± 7 minutes of fatigue-limited submaximal bicycle exercise. They suggested that this might be caused by ischemia or coronary vasospasm. However, the lack of any other evidence of decreases in cardiac function led them to conclude that the changes may be due to uneven ventricular hypertrophy resulting from the pressure and volume loads imposed by exercise. Furthermore, Neilan et al. (73) suggested that due to a lack of evidence of LV wall motion abnormalities suggestive of ischemia, it is unlikely that cTnT elevations are due to coronary ischemia.

2.6.3 Altered Beta-receptor Function

A desensitization of cardiac β1-receptors, yet another mechanism proposed to result in a decreased inotropic state, has recently received significant attention (30, 94, 107). To date, this mechanism has received the greatest experimental support in healthy humans following prolonged exercise. In clinical populations, such as those patients with chronic heart failure, investigators have long observed that prolonged exposure of β1-receptors to increased concentrations of catecholamines results in desensitization of these receptors (11, 103). Vanoverschelde et al. (102) suggested that because of the increased exposure to catecholamines during prolonged exercise, a downregulation of β1-receptor

responsiveness may occur, prompting the decline in LV contractility in healthy athletes. Following an endurance run, Maron et al. (65) reported a 5-fold increase in catecholamines from resting levels, an increase which has also been observed following a marathon (23), a 100 km ultra-marathon (80), and a prolonged run to exhaustion (95). Given that prolonged exercise provides a lengthy exposure to these elevated catecholamines, it is possible that there is a desensitization of β1-receptors (23). This appears to be true in dogs, where prolonged dynamic exercise produced a significant decrease in sensitivity to the effects of β1-receptor stimulation (34). A reduced chronotropic response to the β1-receptor agonist isoproterenol has been demonstrated following prolonged exercise in both untrained (30) and trained subjects (26). More recent investigations in humans have also revealed that prolonged exercise alters β1-receptor responsiveness (26, 30, 94, 107). For example, Welsh et al. (107) demonstrated that following a half Ironman triathlon, the chronotropic and inotropic response to the β1-receptor agonist dobutamine is blunted. Our group has also recently shown that there are gender differences in LV function and cardiac β1-receptor responsiveness following a single bout of prolonged exercise (94). Scott et al. (94) examined β1-receptor desensitization following a single bout of prolonged exercise, and demonstrated not only that LV function was reduced following prolonged exercise, but also that this reduction was closely related to a decreased sensitivity to exogenous β1-receptor stimulation (Figure 2.2).
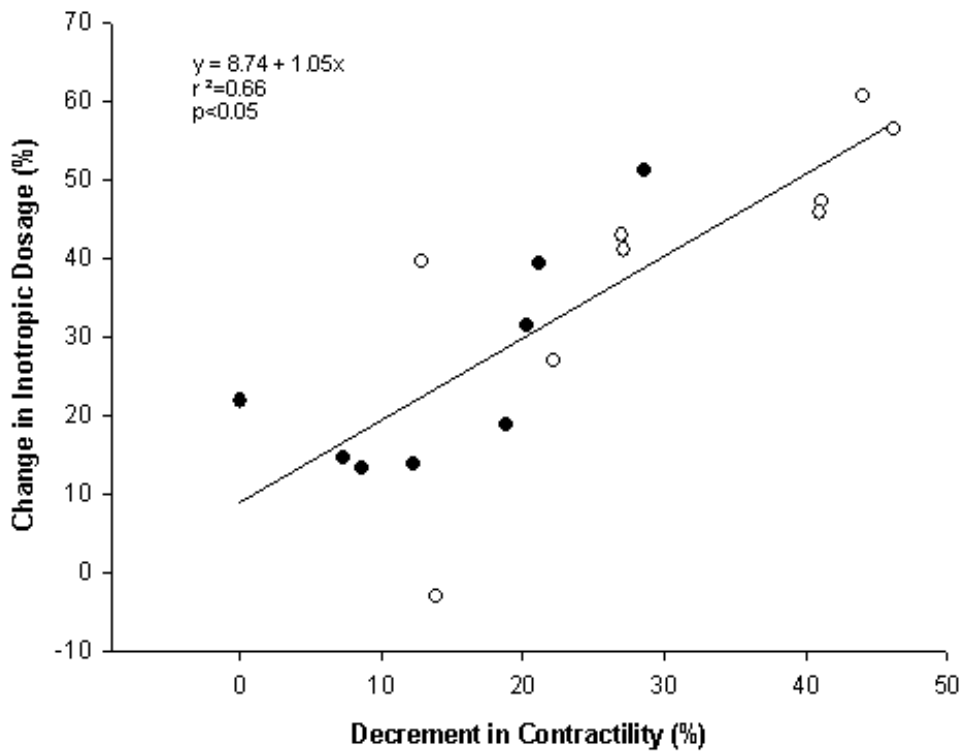
Figure 2.2. Relationship between magnitude of decrease in contractility and magnitude of increase in dobutamine dosage
Dobutamine dosage necessary to increase contractility by 10 mmHg·cm^{-2} in males (clear circles) and females (filled circles). In general, participants requiring greater dobutamine dosages to induce a 10 mmHg·cm^{-2} change in inotropy experienced greater decreases in contractility following prolonged exercise. All data represent changes from data obtained pre-race to those obtained post-race.

The shift of sarcolemmal β1-receptors to an intracellular location following exercise has been demonstrated in rats, suggesting that acute exercise may result in β1-receptor downregulation, in addition to β1-receptor desensitization. Werle et al. (108) investigated the cardiac β1-receptor adaptation to physical activity in four groups of rats and reported a decrease in the number of cardiac β1-receptors by 26% in the maximal training group, 13% in the endurance-training group, and 17% in the acute endurance group (108). An early investigation by Butler et al. (16) into β1-receptor function in human athletes reported that the decreases in sympathetic nervous system responsiveness which were noted following physical training, were related to decreases in lymphocyte β1-receptor density. They hypothesized that the reductions in receptor density at higher levels of physical fitness were a protective mechanism against the chronic exposure to high concentrations of catecholamines. Human lymphocytes contain β1-receptors that are regulated by changes in circulating catecholamines, and many investigations have utilized this non-invasive approach for studying cardiac β1-receptor regulation (12, 71). Eysmann et al. (30) also examined lymphocyte β1-receptor density following prolonged exercise, but reported no differences between pre- and post-exercising levels. These contradictory results may be due to the unreliability of using lymphocytes β1-receptors as a surrogate to cardiac β1-receptors, as several investigations have demonstrated that total β1-receptor density in the heart is significantly lower than that measured in peripheral lymphocytes (13, 109). It is interesting to note that a desensitization or downregulation of β1-receptors could also be linked to alterations in calcium handling. In diabetic rat hearts, Op den Buijs et al. (82) demonstrated that an impaired responsiveness

to β1-receptor stimulation was associated with alterations in cardiac calcium handling. Given the evidence of altered β1-receptor responsiveness observed following prolonged exercise (40, 94), future research should examine if the impaired contractile responsiveness to β1-receptor stimulation is associated with alterations in cardiac calcium handling in athletes.

During heart transplantation, the extrinsic branches of the vagal nerve and the cardiac plexus supplying the donor heart are sectioned, resulting in both efferent and afferent decentralization (5). Therefore, the hearts of HTR rely primarily on circulating catecholamines to increase HR and contractility during exercise. Ferretti et al. (32) reported both higher resting catecholamine levels and peak exercise values in HTR compared to controls, which confirmed previous observations (3, 52). With these higher levels of catecholamines, it is possible HTR may experience greater decreases in β-receptor sensitivity compared to controls. Leenen et al. (62) evaluated the HR responses to cycle exercise in HTR and patients with essential hypertension on placebo and β-blocker. Non-selective β-blockade decreased the peak exercise HR response by 60% in HTR, but only by 10% in the hypertensive group. The results from Leenen and associates (62) clearly demonstrate the importance of intact β-receptor function during exercise for HTR, and illustrate the potential for systolic dysfunction following acute exercise in HTR if β-receptor function is altered.

2.6.4 Cardiac Autonomic Modulation

It is possible that changes in the set point, operating point, or gain of parasympathetic tone and a variety of autonomic reflexes, including the arterial baroreflex and carotid chemoreflex could also result in changes in the inotropic state (21). An increase in vagal

tone and the resulting cardiac muscarinic receptor stimulation cause a decrease in chronotropic and inotropic activity (17). It is plausible that the mechanism underlying decreased LV function following acute exercise could be caused by strong vagal reactivation after exercise (46). However, this rationale has been refuted by several investigations. In their study involving dogs, Friedman et al. (34) found that the functional desensitization following exercise was evident both with and without pretreatment with atropine, suggesting that the phenomenon was unrelated to changes in vagal tone. Recently, Hart et al. (40) also reported a persistent decrease in contractility following prolonged exercise, regardless of vagal inhibition (via glycopyrrolate). Furthermore, several other investigations have demonstrated that there is a delayed vagal reactivation following exercise in highly trained males and females (4, 85). Heart rate variability data also suggests there may be attenuated cardiac vagal modulation and a sympathetic predominance following prolonged exercise in both males and females (94). Therefore, it is likely that the observed decrease in LV systolic function can be attributed to factors other than a large parasympathetic influence following acute exercise.

2.7 Mechanisms of Post-Exercise Alterations in Diastolic Function

Because diastolic function is complex and relatively poorly understood compared to systolic function (63), the mechanisms underlying alterations in diastolic function after acute exercise are more difficult to elucidate. There are, however, several mechanisms that may contribute to the occurrence of impaired LV diastolic function such as the gradient between the atrium and the ventricle, and LV relaxation and compliance (8).

2.7.1 LV Pressure Gradients

Early rapid filling may be the phase of diastole that is the most affected by exercise. Normal early diastolic pressure gradient has two components: a relatively higher left atrial pressure and a lower minimum left ventricular pressure. Although it is possible that a decrease in left atrial pressure could result in alterations in diastolic function following exercise, it is unlikely, given that most investigations have reported little or no change in preload (35, 69). Furthermore, Dawson et al. (22) maintained preload during a 3 hour bout of exercise and still observed a post-exercise drop in diastolic function. Without direct catheterization it is not possible to provide a clear explanation of changes in left atrial and LV pressure and the resultant pressure gradients throughout diastole, although several studies have attempted to describe pressures using non-invasive indices. Using TDI, both George et al. (35) and Neilan et al. (75) found that prolonged exercise had a significant impact upon diastolic TDI myocardial velocities at all segments post-race (35), and further reported that the ratio E/E', a non-invasive indicator of left atrial pressure (72, 81), did not change pre to post race. This indicates that the alterations in diastole may be due to an elevated minimum LV pressure, and ultimately lead to a decrease in the pressure gradient (44). Prolonged exercise is typically associated not only with a significant decline in systolic function and wall stress, but also with a concomitant increase in end-systolic volume (66). Elevated end-systolic volume has also been shown to be related to increases in minimum LV pressure (101).

An increase in LV filling pressures with exercise has been repeatedly observed in HTR, and may contribute to the lower than normal exercise tolerance after heart transplantation (99). This increase in LV filling pressures has been attributed mainly to the blunted heart

rate response, and the consequential reliance on preload reserve during exercise to raise cardiac output (45). Elevated LV filling pressures during exercise could result not only from abnormal passive diastolic LV properties but also from altered LV relaxation kinetics (86). Paulus et al. (86) compared the response of LV relaxation to exercise in HTR and in normal control subjects exercised to the same heart rate, and found that HTR had a smaller acceleration of LV relaxation than the control group. Given that HTR have decreased diastolic function following brief exercise, it is possible that continuous exercise could induce even greater decreases.

Another potential factor influencing minimum LV pressure is the right side of the heart. The ventricles share a common interventricular septum and, therefore, the compliance of one ventricle is influenced by changes in the volume, pressure or compliance of the other, or a combination of these elements. This phenomenon has been termed diastolic ventricular interaction (DVI). The relatively non-distensible pericardium further substantially increases ventricular interaction, since a rise in pressure within one ventricle will be transmitted to the other ventricle. In healthy individuals, when upright at rest, the effect of DVI is minor. However, if RV end-diastolic pressure, volume, or both are raised, the interaction can have major physiologic consequences (28). Pulmonary pressures are also elevated during exercise and the consequences may even include acute pulmonary edema (67). High pulmonary circulatory pressures and/or pulmonary edema may be exacerbated by reductions in RV systolic function and elevated LV end diastolic pressure. A rise in pressure in the pulmonary circulation could also have important implications for the RV. High RV afterload may result in "fatigue" in the right side of the heart. Several investigators have shown suppressed RV systolic function and elevated

RV end-diastolic cavity areas following acute exercise (61, 75). It is plausible that an enlarged, fatigued RV could decrease LV suction via the interventricular septum and diastolic ventricular interaction (28, 58).

2.7.2 Alterations in Cardiac Metabolism

Although difficult to measure in humans, changes in diastolic function with acute exercise could also be caused by mechanisms that are related to cellular metabolism. These include changes in biochemical homeostasis caused by 1) elevated levels of free fatty acids (FFA); 2) alterations in myofilament sensitivity to calcium; and 3) abnormal sarcoplasmic reticulum calcium reuptake caused by a decrease in sarcoplasmic reticulum calcium ATPase. Changes in any of these processes can result in increased cytosolic diastolic calcium concentration, and delayed and slowed diastolic decline in cytosolic calcium concentration (112). In myocardium from failing hearts, alterations in calcium homeostasis have been shown to impede early rapid filling and to limit cardiac pumping ability (8), symptoms commonly observed following prolonged exercise (21).

High levels of FFA can reduce LV systolic pressure and increase heart rate, classic symptoms of exercise-induced cardiac fatigue (64). Although no studies have correlated levels of FFA with decreases in diastolic or systolic function, several investigations have reported significantly elevated levels of FFA along with decreases in systolic and diastolic function (47, 95). Elevated FFA levels have also been shown to have detrimental mechanical and metabolic effects in the animal model following exercise, where FFA may act to uncouple electron transport, ultimately reducing mitochondrial respiration (64).

The sensitivity of the myofilament to calcium is regulated by the sarcomeric proteins as

well as regulatory thin filaments, notably troponin-I. Cyclic AMP decreases calcium binding availability, assisting a decline in force as calcium falls. In animal models of acute heart failure, diastolic dysfunction is related to decreased myofilament sensitivity to calcium (88). Accumulation of calcium at the onset of diastole may decrease LV diastolic relaxation and early LV diastolic filling (8). There is also a strong positive correlation between myocardial relaxation abnormalities and end-diastolic calcium concentrations (88). Failure of the sarcoplasmic reticulum calcium pump to sequester calcium from the cytosol results in delayed ventricular relaxation (31). Elevated end-diastolic calcium concentrations have also been shown to be associated with increases in LV end-diastolic pressure (56). There is clearly a lack of information related to the impact of acute exercise on intracellular metabolic control and homeostasis and further research examining the effects of calcium sensitivity on exercise-induced cardiac fatigue is necessary.

2.8 Conclusions

Exercise-induced cardiac fatigue represents a condition where systolic and/or diastolic ventricular function is transiently reduced. In spite of numerous studies examining cardiac fatigue, there is significant need for research that documents the nature and magnitude of this phenomenon in various populations. The severe duration of exercise performed during ultra-endurance events (20+ hours) is particularly important, as it is possible that these races require greater cardiac work and thus may result in more extensive changes in ventricular function compared to the previously described changes involving shorter 3-12 hour endurance races (111). Additionally, few studies have examined alterations in cardiac function following brief, high intensity exercise; nor has

a comparison been made between the impact of such changes (if any are noted) in normally active individuals and endurance trained athletes. Finally, although the overall duration of exercise incorporated in most cardiac rehabilitation programs is approximately 1 h (50), little research has been conducted on the acute cardiovascular consequences of exercise in clinical populations. Despite some specific areas of progress towards an understanding of the likely multifactorial mechanisms underlying changes in ventricular function, researchers have not yet reached consensus on a definitive explanation for this phenomenon. The numerous mechanisms proposed to contribute to changes in ventricular systolic function with exercise include altered loading conditions, myocardial ischemia/damage, altered β1-receptor responsiveness, and altered cardiac autonomic modulation. Although less well understood, the potential mechanisms contributing to changes in LV diastolic function with acute exercise include changes in left ventricular pressure gradients, and alterations in intrinsic myocardial properties. The major challenges for the future will be to unravel these mechanisms, and assess their impact on LV systolic and diastolic function following acute exercise.

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[1]CHAPTER THREE: Cardiovascular Consequences of Completing a 160 km Ultra-marathon

3.1 Introduction

There is a growing body of evidence suggesting that prolonged exercise may induce a transient reduction in left ventricular (LV) function (17). Recent scientific and media interest in this issue has heightened concern in endurance athletes, coaches, scientists and clinicians alike. With well over 100 ultra-marathon events held annually in North America, the increasing popularity of extreme endurance exercise necessitates a clear understanding of the cardiovascular consequences associated with such races. The severe duration of exercise performed during ultra-endurance events (20+ hours) is particularly important, as it is possible that these races require greater cardiac work and thus may

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result in more extensive changes in LV function compared to the previously described changes involving shorter endurance races (3-12 hours) (39). Although several studies have examined cardiovascular function following ultra-endurance events (22, 23), these investigations were conducted over 20 years ago, and furthermore, utilised only global measures of LV function. Newer techniques such as speckle tracking assessment of tissue strain and strain rates may provide a much more sensitive assessment of both regional and global LV function.

Prolonged exercise has also been linked to the appearance of cardiac-specific biomarkers such as cardiac troponin T (cTnT), B-type natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-pro-BNP) (29). Investigations involving shorter endurance events such as marathons and Ironman triathlons have reported up to 86.5% (36) of finishers with detectable levels of cTnT. Interestingly, in the few studies involving ultra-endurance exercise, cTnT was detectable in only 21% of athletes who completed a 100 km run (37) and levels of cTnT were undetectable in athletes who completed a 216 km run (28). Similar incongruities exist regarding BNP release. König et al. (14) examined professional cyclists during a 5-day cycling race and observed BNP to remain within the normal range, while Ohba et al. (25) described BNP increases of up to 500% following a 100 km ultra-marathon. Further cardiac biomarker data is clearly required from ultra-endurance events in order to understand the connection between exercise duration and the release of biomarkers.

Understanding of the mechanism(s) contributing to decreases in LV function is limited. One theory suggests that if myocardial damage occurs with prolonged exercise (evidenced by biomarker release), as in clinical scenarios, this damage would result in a

decrease in LV function. Several studies have recently reported that exercise-induced decreases in LV function are associated with increased post-exercise levels of cardiac biomarkers (15, 19). However, these findings remain controversial as they often appear to be influenced greatly by one or two outliers and other confounding variables such as alterations in plasma volume. Moreover, evidence of myocardial damage has not been demonstrated using SPECT or cMRI (30, 33), and other investigations examining biomarkers and LV function following prolonged exercise have failed to confirm an association (10). It is apparent that additional research is required to elucidate a potential relationship between alterations in LV function and myocardial damage.

It is also possible that alterations in LV function after prolonged activity may be caused by decreases in cardiac receptor responsiveness (13) or a sudden post-exercise gain in parasympathetic tone (4). Due to the increased exposure to catecholamines during prolonged exercise (8), a downregulation of β1-receptor responsiveness may occur, prompting the decline in LV contractility in healthy athletes (13). An increase in vagal tone and the resulting cardiac muscarinic receptor stimulation may cause a decrease in chronotropic and inotropic activity (34). Evidence to support this theory is limited and indeed some investigations have demonstrated a delayed vagal reactivation following exercise in highly trained athletes (3). As a result of these discrepancies, it is still unclear if the observed decrease in LV systolic function can be attributed to a large parasympathetic influence following prolonged exercise.

Therefore, this study was designed with two objectives. The first aim was to assess the cardiovascular consequences of a 160 km (100 mile) ultra-marathon using traditional echocardiography, speckle tracking imaging, cardiac biomarkers, and heart rate

variability (HRV). Secondly, in order to examine possible mechanisms contributing to exercise induced decreases in LV function, the relationship between changes in LV function, changes in cardiac biomarkers and changes in cardiac autonomic regulation were assessed. We hypothesized that 1) as a result of ultra-endurance exercise athletes would demonstrate decreases in cardiac function (measured by traditional echocardiography and speckle tracking imaging), and 2) the changes in cardiac function following ultra-endurance exercise would be related to changes in cardiac biomarkers and/or cardiac autonomic regulation.

3.2 Methods

3.2.1 Participants

Thirty five athletes (25 male, 10 female) competing in the 2007 Western States 100 mile Endurance Run (WSER) (start: Squaw Valley, California, finish: Auburn, California) were recruited to participate in this study. A questionnaire was completed to obtain demographic data, training history, ultra-endurance competition history, and details of cardiovascular risk factors. The participants who volunteered for this investigation were well conditioned male and female amateur athletes (see table 1 for characteristics). This study was approved by the Western States Endurance Run Research Committee (United States) and the University of British Columbia. Written informed consent was obtained from each participant.

3.2.2 General Protocol

Participants underwent two separate testing days: 1) pre-race assessment of LV function, cardiac biomarkers, cardiac autonomic modulation, and body mass assessment one day prior to WSER, and 2) post-race assessment of LV function, cardiac biomarkers,

cardiac autonomic modulation, and body mass assessment immediately following WSER. For the post-race assessment subjects were asked to attend a testing tent adjacent to the finish area as soon as possible after completion of the race. All subjects were advised to abstain from hard training within the 48-h period before pre-testing.

3.2.3 Assessment of LV Function

Traditional Echocardiographic Measurements

   Participants underwent two-dimensional transthoracic and pulsed-Doppler imaging by use of a commercial ultrasound system (Vivid-*i*, GE Healthcare). Images were obtained by a single, experienced sonographer in the parasternal long axis, short axis and apical 4 chamber views according to the American Society of Echocardiography guidelines (16). Left ventricular systolic function was evaluated using fractional area change (FAC), ejection fraction (EF), end-systolic pressure volume relationship (systolic blood pressure/end systolic volume (SBP/ESV)) and stroke volume (SV). End-diastolic LV dimensions were used to calculate LV mass (9). Pulsed Doppler recordings were employed to assess diastolic filling; in particular, early (E) and atrial (A) peak mitral inflow velocities were measured and the ratio of early to late diastolic filling velocity (E:A) was calculated. Left ventricular end-diastolic volume (EDV; modified Simpson's rule from 4 chamber view) and end-systolic meridional wall stress (27) (WS) [WS (g·cm^{-2}) = 0.334·SBP·end-systolic diameter/end-systolic posterior wall thickness·(1+end-systolic posterior wall thickness)/end-systolic diameter] were estimated as indices of preload and afterload, respectively. Images were analyzed off-line by a single experienced technician. Based on the HR differences before and after the race, it was not

possible to blind the technician to this aspect of analysis. A minimum of three consecutive cardiac cycles were measured and averaged.

Speckle Tracking Imaging

Radial and circumferential strain data were derived from a parasternal short axis view imaged at the basal level. Specifically, this was at the level of the first appearance of the superior surface of the papillary muscle when imaged down from the mitral valve to provide a reproducible anatomical landmark for repeat scans. The focal point was positioned close to the centre of the LV cavity to provide optimum beam width whilst reducing the effects of divergence. The apical window was utilised for longitudinal assessment incorporating apical 2 and 4 chamber orientations. The focal point was positioned at the level of the mitral valve. In both orientations frame rates were maximised (>40 and <90 frames per second). Using the original two-dimensional images, a single experienced technician performed offline measurements of the longitudinal, radial, and circumferential planes using a dedicated software package (Echopac, GE Healthcare). This system tracks acoustic markers within the myocardium, frame-by-frame, over the entire cardiac cycle. The spatial displacement of an acoustic marker indicates local tissue movement. A tracking setting was selected with a width between endocardium and epicardium to include as much myocardium as possible. The software automatically scores the tracking quality of each segment on a scale from 1.0, for optimal, to 3.0, for unacceptable. Segments with scores greater than 2.0 were excluded from the analysis. Due to limitations in scanning time as well as occasional image quality problems we report data for basal wall segments. Sonographer specific coefficient of variation data ranged from 4.9 to 7.1% for strain and strain rate derived in

radial and circumferential planes. This rose slightly to 7.1 to 12.7% for indices derived in the longitudinal plane. Based on the HR differences before and after the race, it was difficult to blind the technician to this aspect of analysis. A minimum of three consecutive cardiac cycles were measured and averaged.

3.2.4 Assessment of Cardiac Biomarkers

For each blood sample, 5 mL of whole blood was drawn from an antecubital vein and collected in serum-gel tubes. Blood samples were left to clot, centrifuged, and the serum drawn off and stored (-80°C) for subsequent analysis of cTnT and NT-pro-BNP. cTnT was analysed using the third generation TROP T STAT assay by ECLIA technology, employed within the Elecsys 1010 automated batch analyzer (Roche Diagnostics,Lewes,UK). Assay imprecision was 5.5% at 0.32 μg/L and 5.4% at 6 μg/L, with a detection limit of 0.01 μg/L. NT-pro-BNP concentrations were determined with an Elecsys proBNP electrochemiluminescent immunoassay (ECLIA) on the Roche Elecsys 1010 (Roche Diagnostics), with an analytical range of 5–35 000 ng/L and intra-assay and inter-assay imprecision of 0.7–1.6 and 5.3–6.6%, respectively.

3.2.5 Assessment of Cardiac Autonomic Modulation

In order to provide an indication of autonomic modulation pre and post-race, HRV was assessed during 10 minutes of supine rest. HRV was sampled at 1000 samples per second with an A/D converter (Powerlab/16SP ML 795; ADInstruments, Colorado Springs, CO, USA) from ECG to computer. The ECG segment was then evaluated according to previously established guidelines (1). Both frequency domain and time domain measures were analysed. In order to assess frequency domain measures, the power spectra were estimated using a 1024-point linear fast Fourier transform algorithm. The power spectra

were then analyzed for total power (0.0 – 0.4 Hz), as well as low (LF; 0.04 – 0.15 Hz) and high (HF; 0.15 – 0.4 Hz) frequency power. HF power is almost entirely mediated by the vagal activity in the sinoatrial node, whereas LF power reflects the mixed modulation of vagal and sympathetic activities (1). HF and LF values at each specific frequency range were also normalized by dividing by the total spectral power (HFnu and LFnu) to minimize the effect of the changes in total power on the LF and HF components (11). The square root of the mean of squared differences between successive RR intervals (RMSSD) was also computed as another index of cardiac parasympathetic activity (11).

3.2.6 Statistical Analysis

Cardiovascular variables were compared before and after the race using paired Student's t tests. The change in LV functional measures from pre to post race (delta scores) were correlated with age, finishing time, average training volume, as well as delta scores for HR, HRV indices, estimates of preload and afterload and NT-pro-BNP by Pearson product-moment correlations. Because of the nature of cTnT data we assessed the association with changes in cardiac function on a case-by-case basis. The level of significance was set *a priori* at $p<0.05$. Data are presented as means ± the standard deviation at pre-race and post-race respectively. Data analysis was performed using statistical computer software (Statistica; Statsoft Ltd, Tulsa, Oklahoma, USA).

3.3 Results

3.3.1 Prolonged Exercise

Twenty five athletes (20 male, 5 female) successfully completed the race with an average finish time of 25.5 hours ± 3.2 hours. Participant characteristics are shown in Table 3.1. All 25 athletes had blood drawn for the assessment of cardiac biomarkers,

whilst 18 (15 male, 3 female) completed post-race echocardiography assessment, and 16 (13 male, 3 female) completed post-race cardiac autonomic assessment. All athletes were assessed within 30 minutes of cessation of exercise.

Variable (n=25)	
Age (yr)	41.2 ± 4.7
Height (cm)	178.7 ± 7.1
Mass (kg)	69.4 ± 9.3
Average Training (hours·week^{-1})	13.1 ± 1.2
Average Training (miles·week^{-1})	53.8 ± 16.7
BMI (kg·m^2)	21.7 ± 2.0
BSA (m^2)	1.90 ± 0.15
LVM (g)	200.9 ± 36.4
LVM/BSA (g·m^2)	104.9 ± 16.8

Table 3.1 Participant characteristics

BMI, body mass index; BSA, body surface area; LVM, left ventricular mass. (means ± SD).

3.3.2 Traditional Echocardiographic Measurements

Table 3.2 summarises the echocardiographic data. There were no changes in body mass and SBP, although there was a significant increase in HR after the race. There were no significant changes in left ventricular WS (afterload). EDV, EF, FAC, and SV fell significantly post-race (p<0.05, Table 3.2), with no change in cardiac output (pre: 4.3 ± 0.7 l·min^{-1}; post: 4.8 ± 1.0 l·min^{-1}). SBP/ESV was reduced post race (-8 ± 18%), but this did not reach statistical significance (P=0.09). The peak early (E) transmitral filling velocity decreased significantly (p<0.05, Table 1.2), whereas peak late (A) transmitral filling velocity remained unchanged after the race. This resulted in a significantly lower E/A ratio after the race. There were no significant correlations between changes in LV function and any alteration in loading conditions, HR, age, average training (miles/week) or finish time (Table 3.3).

Variable (n=18)	Pre-race	Post-race	p value
Mass (kg)	72.1 ± 9.3	71.8 ± 8.5	0.52
Loading			
HR (beats·min^{-1})	57 ± 8	77 ± 12	< 0.05
SBP (mmHg)	119 ± 10	112 ± 12	0.07
DBP (mmHg)	75 ± 8	74 ± 10	0.96
EDV (mL)	114 ± 22	104 ± 24	< 0.05
LV WS	44 ± 16	43 ± 18	0.71
Systolic function			
SV (mL)	77 ± 12	64 ± 13	< 0.05
LV EF (%)	67 ± 4	60 ± 4	< 0.05
LV FAC (%)	55 ± 3	50 ± 3	< 0.05
SBP·ESV^{-1} (mmHg·mL^{-1})	3.18 ± 0.89	2.95 ± 1.04	0.09
Diastolic function			
E (cm·s^{-1})	0.74 ± 0.13	0.62 ± 0.13	< 0.05
A (cm·s^{-1})	0.46 ± 0.09	0.47 ± 0.12	0.66
E:A	1.66 ± 0.36	1.35 ± 0.33	< 0.05

Table 3.2 Selected cardiovascular variables before and after exercise

HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; EDV, end diastolic volume; LV WS, left ventricular wall stress; SV, stroke volume; LV EF, left ventricular ejection fraction; LV FAC, left ventricular fractional area change; SBP·ESV^{-1}, end-systolic pressure volume relationship; E, early diastolic filling velocity; A, late diastolic filling velocity (means $\pm$ SD).

Variable	Age	Finish Time	Average Training	Δ EDV	Δ HR	Δ WS
Δ EF						
r	0.37	0.05	0.38	-0.05	0.11	0.53
p	0.13	0.90	0.22	0.83	0.67	0.05
Δ SBP·ESV^{-1}						
r	0.40	-0.24	0.30	-0.30	-0.23	0.72
p	0.22	0.47	0.34	0.37	0.50	< 0.05
Δ E:A						
r	-0.15	0.15	0.33	0.18	0.07	0.13
p	0.53	0.55	0.30	0.49	0.79	0.72

Table 3.3 Selected correlations for changes in cardiac function

Δ EF, difference between pre-and post-race ejection fraction; Δ SBP·ESV^{-1}, difference between pre-and post-race end-systolic pressure volume relationship; Δ E:A, difference between pre-and post-race early and late atrial filling; Δ EDV, difference between pre-and post-race end diastolic volume; Δ HR, difference between pre-and post-race heart rate; Δ WS, difference between pre-and post-race wall stress (data are Pearson's correlation coefficients).

3.3.3 Speckle Tracking Imaging

Twelve participants who completed the race had echocardiographic images that were suitable for speckle tracking analysis (tracking quality better than 2.0). Basal radial and basal longitudinal (septum and lateral wall) displacements were significantly reduced post-race ($p < 0.05$, Table 3.4). Longitudinal myocardial velocity during systole and early diastole in both the basal septum and basal lateral wall were also reduced following the race ($p < 0.05$, Table 3.4). Peak radial and circumferential basal strain were diminished post-race ($p < 0.05$, Table 3.4), while peak longitudinal strain was only reduced in the basal septum but not the lateral wall (Table 3.4). Neither systolic nor early diastolic strain rates were consistently altered in a given plane of motion, although several pre vs. post-race differences existed (Table 3.4). The largest relative percent reduction in peak strain was seen in the circumferential plane, followed closely by reductions in radial strain, with relatively small changes longitudinally (Figure 3.1). Changes in strain and strain rates were generally not associated with changes in EDV, WS, HR, age, average training (miles/week), or finish time. However, change in septal longitudinal strain was negatively correlated with finish time and positively correlated to average training – such that those with the greatest training volume (miles/week) and those who finished the fastest had the greatest decreases in septal longitudinal strain (Table 3.5).

Plane	Variable (n=12)	Pre Race	Post Race	p value
Longitudinal	Basal Septum Displacement (mm)	19.1 ± 2.7	13.7 ± 3.1	<0.05
	Basal Lateral Wall Displacement (mm)	15.1 ± 3.6	10.2 ± 3.6	<0.05
	Basal Septum S velocity (cm•s^{-1})	7.9 ± 1.3	7.1 ± 1.8	<0.05
	Basal Lateral Wall S velocity (cm•s^{-1})	8.1 ± 1.7	6.6 ± 2.1	<0.05
	Basal Septum E velocity (cm•s^{-1})	-10.3 ± 1.1	-9.0 ± 1.8	<0.05
	Basal Lateral Wall E velocity (cm•s^{-1})	-9.2 ± 1.5	-6.8 ± 2.2	<0.05
	Basal Septum Strain (%)	-21.2 ± 3.5	-19.8 ± 4.7	<0.05
	Basal Lateral Wall Strain (%)	-22.3 ± 4.5	-20.7 ± 3.9	0.15
	Basal Septum S Strain Rate (%•s^{-1})	-1.6 ± 0.3	-1.5 ± 0.5	<0.05
	Basal Lateral Wall S Strain Rate (%•s^{-1})	-1.8 ± 0.4	-1.6 ± 0.5	0.13
	Basal Septum E Strain Rate (%•s^{-1})	1.9 ± 0.4	1.5 ± 0.5	<0.05
	Basal Lateral Wall E Strain Rate (%•s^{-1})	2.2 ± 0.5	2.4 ± 0.5	0.49
Radial	Basal Displacement (mm)	6.6 ± 2.6	3.9 ± 1.7	<0.05
	Basal strain (%)	41.7 ± 10.2	29.9 ± 15.8	<0.05
	Basal S Strain Rate (%•s^{-1})	4.2 ± 3.1	3.5 ± 3.0	0.30
	Basal E Strain Rate (%•s^{-1})	-1.4 ± 0.4	-1.3 ± 0.8	0.52
Circumferential	Basal Strain (%)	-17.7 ± 1.9	-11.9 ± 3.8	<0.05
	Basal S Strain Rate (%•s^{-1})	-1.7 ± 0.3	-1.6 ± 0.4	0.37
	Basal E Strain Rate (%•s^{-1})	1.6 ± 0.2	1.4 ± 0.2	<0.05

Table 3.4 Speckle tracking derived indices of cardiac function
E, early diastole; S, systole (means ± SD).

Variable		Age	Finish Time	Average Training	Δ EDV	Δ HR	Δ WS
Δ LS (S)	r	-0.48	-0.67	0.66	0.30	-0.12	0.13
	p	0.16	<0.05	<0.05	0.28	0.78	0.81
Δ L SRS	r	0.33	-0.12	0.15	-0.26	-0.43	0.12
	p	0.47	0.98	0.67	0.58	0.33	0.80
Δ L SRE	r	-0.80	-0.56	-0.04	0.53	0.26	-0.57
	p	< 0.05	0.91	0.91	0.23	0.57	0.18
Δ RS	r	0.27	-0.34	0.05	0.18	-0.13	0.30
	p	0.95	0.37	0.89	0.73	0.74	0.57
Δ R SRS	r	0.40	0.42	-0.51	-0.08	0.14	-0.01
	p	0.37	0.35	0.13	0.87	0.77	0.99
Δ R SRE	r	-0.60	0.08	0.02	0.36	-0.49	-0.69
	p	0.15	0.86	0.95	0.43	0.26	0.08
Δ CS	r	0.07	-0.17	-0.44	-0.56	-0.19	0.39
	p	0.85	0.66	0.21	0.25	0.62	0.44
Δ C SRS	r	0.51	-0.22	0.44	-0.33	0.04	0.78
	p	0.24	0.64	0.20	0.48	0.94	< 0.05
Δ C SRE	r	0.48	-0.15	0.66	0.36	-0.29	0.21
	p	0.28	0.75	0.06	0.43	0.49	0.65

Table 3.5 Selected correlations for changes in myocardial strain

Δ LS (S), difference between pre-and post-race septal longitudinal strain; Δ RS, difference between pre-and post-race radial strain; Δ CS, difference between pre-and post-race circumferential strain; SRS, strain rate systole; SRE, strain rate early diastolic filling; Δ EDV, difference between pre-and post-race end diastolic volume; Δ HR, difference between pre-and post-race heart rate; Δ WS, difference between pre-and post-race wall stress (data are Pearson's correlation coefficients).
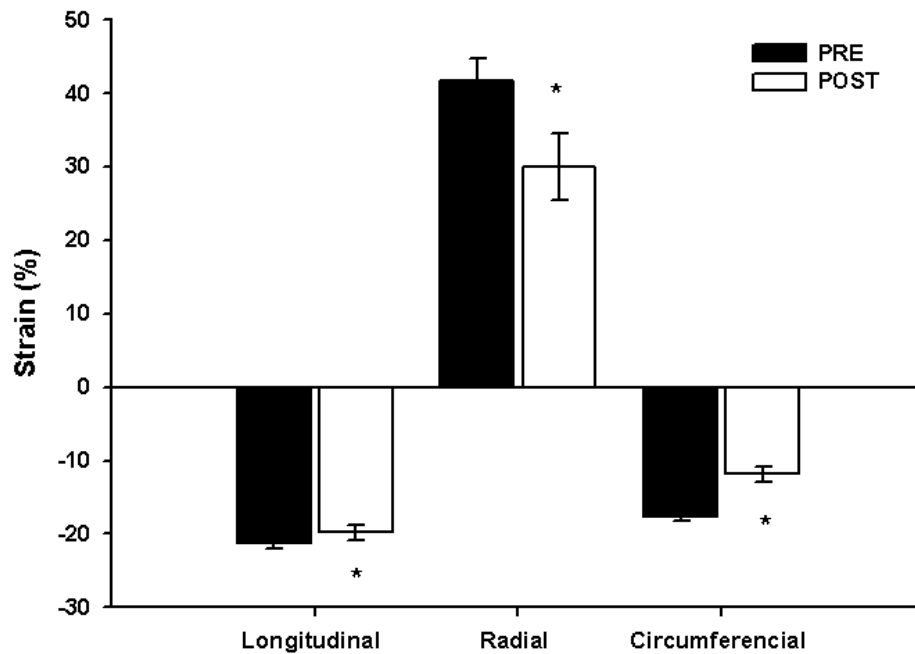
Figure 3.1 Three planes of myocardial strain before and after exercise
There were significant differences before and after the race in all three planes of motion. The greatest relative change was found in the circumferential plane (32.3%), followed by the radial plane (27.3%) with the smallest relative change in the longitudinal plane (7.1%). Radial and circumferential measures were taken at the basal level and the longitudinal data is from the basal septum. * $p < 0.05$

3.3.4 Cardiac Biomarkers

Concentrations of serum cTnT were <0.01 ng/mL in all participants at baseline. After the race, an increase in cTnT of >0.01 ng/mL was recorded in 5 athletes (20%), ranging from 0.01 to 0.05 ng/L. Out of the five participants who had elevated levels of cTnT post-race, only two completed post-race echocardiography. One participant with elevated cTnT and echocardiographic measures was a 36 year old male, and the other was a 35 year old female. These two athletes had moderate decreases in EF (-4.5% and -4.6% vs. group: -6.1 ± 2.1%) and longitudinal strain (2.5% and 0.7% vs. group: 1.3 ± 3.2).

At baseline mean NT-pro-BNP was 28 ± 17.1 ng/L; following the WSER, NT-pro-BNP levels were significantly higher (795 ± 823 ng/L (p<0.05)), with a post-race range of NT-pro-BNP concentrations from 212 to 3427 ng/L). Pre-race one athlete had NT-pro-BNP concentrations which exceed the upper reference limit for healthy subjects (125 ng/L) and was excluded from NT-pro-BNP analyses. All participants had levels of NT-pro-BNP above the upper limit of normal for exclusion of heart failure post-race (35). Changes in NT-pro-BNP were not significantly associated with LV mass (r = 0.07), average training volume (r = -0.05), age (r = -0.29), or finish time (r = 0.09). Changes in NT-pro-BNP were not associated with changes in most measures of LV function (Table 3.6). However, there was a significant correlation between change in radial strain and change in NT-pro-BNP (p<0.05; Table 3.6). Interestingly, changes in NT-pro-BNP were significantly associated with changes in HFnu (p<0.05; Figure 3.2).

3.3.5 Cardiac Autonomic Modulation

Mean RR interval was significantly decreased post-race when compared to pre-race (pre-race 1081 ± 161 ms vs. post-race 800 ± 123 ms; p<0.05). Parasympathetic indices

(RMSSD: pre-race 88.9 ± 48.9 ms vs. post-race 72.8 ± 92.5 ms and HFnu: pre-race 40.4 ± 10.9 nu vs. post-race 32.3 ± 11.7 nu) were reduced following prolonged exercise, although these changes were not statistically different. The sympathetic index LFnu (pre-race 55.5 ± 16.2 nu vs. post-race 42.9 ± 27.2 nu) was also decreased post-race, although not significantly so. There was also a non-significant increase in LF:HF ratio post-race with respect to pre-exercise values (pre-race: 1.6 ± 1.0 vs. post-race 2.6 ± 3.5). Change in HFnu was not associated with LV mass (r = 0.29), average training volume (r = 0.10), age (r = -0.09), or finish time (r = -0.37). Changes in the parasympathetic index HFnu were also not associated with most changes in LV function (Table 3.6). However, there was a significant correlation between change in radial strain and change in HFnu (p<0.05; Table 3.6).

Variable		Δ NT-proBNP	Δ HFnu
Δ EF	r	0.50	0.32
	p	0.21	0.44
Δ E:A	r	0.25	-0.09
	p	0.54	0.82
Δ LS (S)	r	0.24	-0.12
	p	0.54	0.77
Δ L SRS	r	-0.33	-0.25
	p	0.39	0.55
Δ L SRE	r	-0.19	-0.39
	p	0.62	0.34
Δ RS	r	0.83	0.77
	p	< 0.05	<0.05
Δ R SRS	r	0.36	0.20
	p	0.34	0.63
Δ R SRE	r	-0.56	-0.57
	p	0.12	0.08
Δ CS	r	0.06	0.08
	p	0.88	0.85
Δ C SRS	r	0.26	0.29
	p	0.50	0.48
Δ C SRE	r	0.15	-0.07
	p	0.71	0.86

Table 3.6 Selected correlations for changes in LV function

Δ EF, difference between pre-and post-race ejection fraction; Δ E:A, difference between pre-and post-race early and late atrial filling; Δ LS (S), difference between pre-and post-race septal longitudinal strain; Δ RS, difference between pre-and post-race radial strain; Δ CS, difference between pre-and post-race circumferential strain; SRS, strain rate systole; SRE, strain rate early diastolic filling; Δ NT-proBNP, difference between pre-and post-race NT-proBNP; Δ HFnu, difference between pre-and post-race high frequency normalized units (data are Pearson's correlation coefficients).
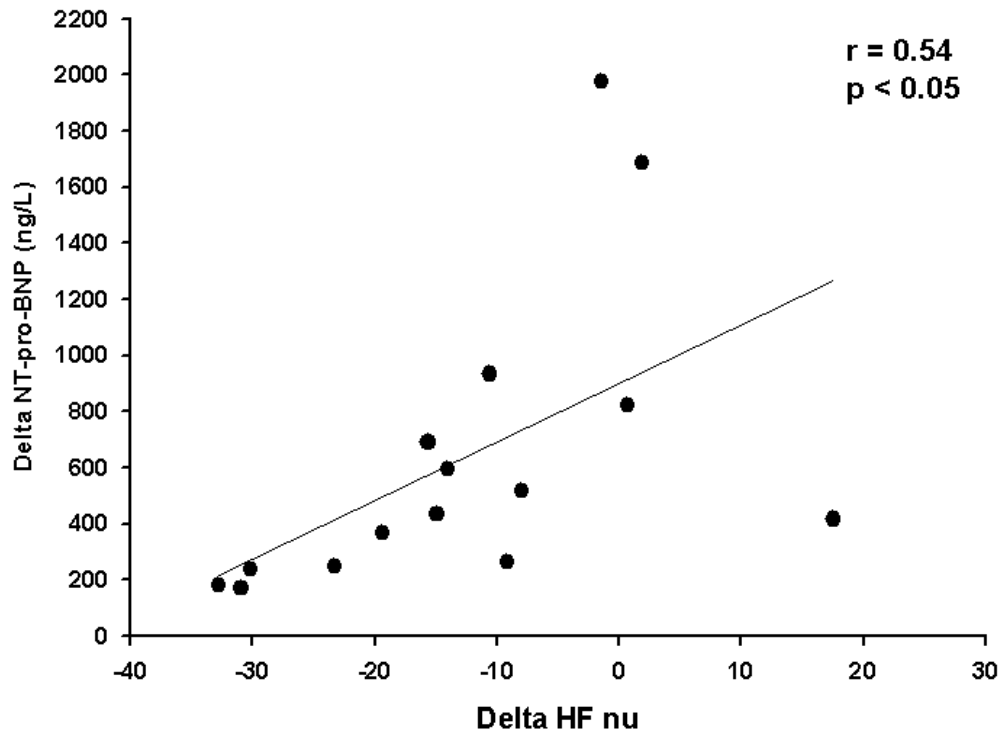
Figure 3.2 Relationship between NT-pro-BNP and parasympathetic index
There was a significant and positive linear correlation found between delta NT-pro-BNP and delta high frequency normalized units (HFnu; an indicator of parasympathetic cardiac activation).

3.4 Discussion

The present study comprehensively examined the cardiovascular consequences of ultra-endurance exercise (25.5 ± 3.2 hours) using traditional echocardiography, speckle tracking imaging, cardiac biomarkers and HRV. This investigation represents the first comprehensive use of speckle tracking imaging after ultra-endurance exercise and describes regional alterations in cardiac function. Confirming previous studies (22, 23), we also found a significant reduction in both LV systolic and diastolic function post-race using standard two dimensional echocardiography measures. Relatively few athletes demonstrated increases in cTnT following the race but there was a significant increase in plasma NT-pro-BNP in all athletes. Finally, in contrast with several recent studies (15, 19) we report that echocardiographic evidence of decreases in LV function were not associated with alterations in cardiac biomarkers, or cardiac autonomic regulation.

3.4.1 Left Ventricular Function

Traditional Echocardiographic Measurements

The present data support the findings of Niemela et al. (23), suggesting that the completion of an ultra-endurance event results in a reduction in LV systolic function and an alteration in diastolic filling. Previous investigations have suggested that decreases in LV function are related to alterations in loading conditions (12), and acute reductions in preload such as during the Valsalva maneuver have been shown to alter diastolic and systolic parameters (18). However, the general lack of significant correlation between LV function and HR, preload and afterload in this investigation (Table 3.3) suggests that an alteration in intrinsic LV function occurred post-race. Furthermore, although recent studies have indicated that decreases in LV function are associated with training volume

(19), and/or age (14), our data would suggest that both of these variables had little impact on LV function in the current cohort.

Speckle Tracking Imaging

Our results also support the findings of Neilan et al. (20), who reported decreases in both peak systolic strain and strain rate following a marathon run. However, Neilan et al. (20) used tissue Doppler derived strain and strain rate, which is even more angle-dependent than Doppler flow measures (24). We have used speckle tracking imaging, which is less dependent on transducer orientation, and found both strain and strain rate to be decreased following a 100 mile running race. Importantly, there were also differential alterations in the basal longitudinal, radial, and circumferential planes of motion following the race. The largest relative percent reduction in peak strain was seen in the circumferential plane (32.3 %), followed closely by reductions in radial strain (28.3 %), with relatively small changes longitudinally (7.1%) (Figure 3.1). This is interesting to note considering that Notomi et al. (24) have recently shown that with exercise the largest proportional increase in myocardial velocity from rest to exercise occurs in the circumferential plane, followed by the radial and lastly, changes in the longitudinal plane. Therefore, it is possible that the planes of myocardial contraction which increase the most during exercise will result in the greatest impairments of function following prolonged exercise.

Although our results indicate that age, finish time and training volume had little impact on both traditional echocardiography and most speckle tracking derived measures, finish time and training volume were related to changes in longitudinal strain. That is, the more miles an individual ran per week in training, the faster they finished the race, and the

greater their reduction in longitudinal strain. This finding may be suggestive of an intensity dependent contribution to the decrease in LV function. Whilst speculative, this point requires further study.

3.4.2 Cardiac Biomarkers

In the present investigation, cTnT results were negative in all subjects pre-race, while post-race, five runners (20%) presented with cTnT values above the lower detection limit of the assay. This percentage of positive cTnT levels is lower than data obtained from studies involving exercise ranging from 3 to 12 hours, which revealed percentages of 56% to 86.5% (15). Similar to our results, other investigations involving extreme endurance events (over 20 hours) have reported few, if any, cases of positive cTnT values (28, 37). It is possible that troponin release is related to exercise intensity, as athletes in shorter endurance events may exercise at higher intensities than those racing for 20 or more hours. Interestingly, Neilan et al. (19) reported that post-exercise alterations in cardiac biomarkers were strongly influenced by the level of preparation undertaken by participants; such that the majority of the most marked abnormalities in cardiac structure or function, as well as cardiac biomarker changes, were seen in those athletes training less than 35 miles/week before a marathon race. Although George et al. (10) found no such relationship in a diverse group of recreational runners, it is possible that high training volumes could act to prevent myocardial damage and the release of cardiac troponins. Participants in the present investigation trained an average of 53.8 ± 16.7 miles/week, and this high training volume may account for the relatively low percentage of athletes who demonstrated cTnT levels above the assay detection limit.

The fact that the majority of participants exhibited reduced LV function despite non-detectable troponin release, coupled with only moderate decreases in LV function observed in two athletes with elevated cTnT, together suggest that the decline in LV function after prolonged exercise is due to mechanisms other than myocardial damage. A remaining question becomes what causes the post-exercise biomarker release? Several authors (21, 29, 30) have theorized that an exercise-induced overload of free radicals caused by long-term oxidative stress may involve cardiomyocyte-membrane leakage, leading to the leakage of cytosolic cTnT into the circulation. The concept of cytosolic leakage fits with the low levels of cTnT present in the circulation as well as their rapid appearance and clearance compared to clinical cases (21, 29, 30).

Previous investigations have reported increases in BNP levels following prolonged exercise. König et al. (14) examined professional cyclists during a 5-day cycling race and observed BNP to remain within the normal range, with post-exercise increases of just 37%. Differing results were revealed by Ohba et al. (25), who described BNP increases of up to 500% following a 100-km ultra-marathon. Similar to Ohba et al. (25), there was an even more pronounced increase in NT-pro-BNP in the current investigation. We found nearly a 30-fold increase in NT-pro-BNP immediately after exercise. In contrast with several other investigations (14, 19), we found no associations between changes in NT-pro-BNP and athletes' ages or finish times.

The cause of the observed dramatic increase in NT-pro-BNP is intriguing. NT-pro-BNP is a hormone produced by the ventricles in response to pressure and volume load and works as a counter-regulatory mechanism against the renin-angiotensin-aldosterone system (6). The renin-angiotensin-aldosterone system is elevated in situations of

increased central blood volume, such as during exercise (5). Since renal blood flow is dependent on the duration and intensity of exercise (32), pronounced reductions in renal blood flow would be expected to occur, particularly given the duration (20 + hours) of exercise used in this study. Therefore, it is possible that the increase in NT-pro-BNP observed following exercise in the present investigation could in fact be part of a regulatory response to significant increases in sympathetic activity and renin secretion (21). This would suggest that these responses are purely physiological and regulatory and not of any pathological relevance. It is interesting to note that although NT-pro-BNP was unrelated to changes in systolic and diastolic function, it was significantly related to indices of vagal tone (Figure 3.2). Our results demonstrate that following an ultra-endurance run, those with the greatest increase in parasympathetic indices also have the greatest increase in NT-pro-BNP. Further research is required to elucidate this possible link.

3.4.3 Cardiac Autonomic Modulation

There has been relatively little information on the recovery of cardiovascular autonomic function after various types of physical exercise. Arai et al. (2) assessed the dynamics of autonomic nervous activity during and after a maximal bicycle exercise test with HRV, and reported both HF and LF variables returned to baseline within few minutes after exercise. We also found no significant differences between pre-race and post-race HRV indices. Some investigators have suggested that a decreased LV function following prolonged exercise could be caused by strong vagal reactivation after exercise (34). However, unlike these recent reports involving shorter endurance events, we found little evidence of association between alterations in echocardiographic measures and

changes in cardiac biomarkers or changes in cardiac autonomic modulation. Given this

lack of relationship following the WSER, it is likely that factors other than myocardial

damage or strong vagal reactivation contributed to post-exercise decreases in LV

function (7). A number of other underlying mechanisms have been presented in the

literature which may have contributed to the decreases in LV function. These

mechanisms could include: a downregulation of cardiac β1-receptors mediated by

elevated catecholamines during prolonged exercise (13, 31), changes in biochemical

homeostasis caused by elevated levels of free fatty acids (38), alterations in myofilament

sensitivity to calcium (26), and abnormal sarcoplasmic reticulum calcium reuptake

caused by a decrease in sarcoplasmic reticulum calcium ATPase (40).

3.5 Limitations

Several limitations should be considered when interpreting the results of the present

study. This study included ultra-endurance athletes under the age of 50. With the

increasing number of older individuals participating in ultra-endurance events, future

studies should aim to investigate the impact of age on alterations in cardiovascular

function following ultra-endurance races. Additionally, although our results provide

more support for the role of an extraordinarily prolonged duration (e.g., greater than 20

hours), as being pivotal in the development of decreases in LV function, the interplay and

importance of exercise duration, intensity, and volume on the development of decreases

in LV function requires further research.

3.6 Conclusions

Evidence from the present study indicates that, based on traditional echocardiography and novel speckle tracking imaging, both systolic and diastolic function are mildly reduced immediately following a 100 mile ultra-endurance race. Furthermore, levels of NT-pro-BNP are increased in all participants, whereas levels of cTnT are increased in very few athletes. Although we found no association between traditional echocardiography, strain, NT-pro-BNP and cTnT, further study is needed to confirm these data possibly in older athlete groups. It appears that factors other than myocardial damage or strong vagal reactivation contributed to post-exercise decreases in LV function following an ultra-marathon.

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CHAPTER FOUR: Biventricular Dysfunction Following Brief High Intensity Exercise in Endurance Trained Individuals

4.1 Introduction

Recent evidence suggests that more cardioprotective benefits result from high intensity (>90% peak heart rate) rather than moderate intensity exercise (<75% peak heart rate) (20, 26, 40, 65, 72). Public health recommendations support this belief by focussing on the value of high intensity exercise training for improving cardiovascular health and reducing the risk of coronary artery disease (22). Although several investigations report that this type of training is a powerful stimulus for improving overall health (38, 65), few have examined the impact of an acute bout of high intensity exercise on right (RV) and left ventricular (LV) systolic and diastolic function.

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Studies of acute bouts of prolonged (> 5h), moderate intensity exercise have clearly demonstrated that transient decreases LV systolic and diastolic function are induced in endurance trained athletes (21, 59). Given the marked RV and LV cardiac pressure and volume overload during maximal exercise (25, 63), it is possible that brief, high intensity exercise may also result in alterations in cardiac function. Indeed, Neilan et al. (48) examined the acute cardiac changes that occurred following a 2000m ergometer sprint in elite rowers, and reported an attenuation in LV diastolic function. Furthermore, Foster and colleagues (14, 15) demonstrated that LV systolic function is depressed during brief, sudden strenuous exercise. Endurance athletes are often exposed to repeated bouts of maximal exertion; however, the effects of this type of exercise on biventricular function are unknown. Moreover, the clinical ramifications of this type of exercise in normally active individuals have not been investigated. Because normally active individuals seldom experience high cardiac pressure and volume loads, it is possible that they may have significant decreases in biventricular function in response to repeated bouts of high intensity exercise.

While the decline in LV systolic and diastolic function has been well established following prolonged, low intensity exercise, limited information exists regarding the impact of exercise on the RV. This is partially due to difficulties in obtaining reliable and accurate data in non-invasive imaging studies with the use of echocardiography. With the complex shape of the RV, excessive trabeculation, and the inability to image in numerous planes, it is difficult to accurately provide RV volumetric models (12, 36, 55). As a result of the inherent limitations of 2D and conventional Doppler assessment, cardiovascular magnetic resonance imaging (cMRI) has become the "gold standard" in

the assessment of RV and LV volumes and function (33, 44). Additionally, myocardial tagging with cMRI allows for evaluation of detailed systolic LV function such as torsion, strain and strain rate, as well as diastolic indices such as untwisting rate, early filling velocity, and annular velocity (19).

The aim of this study was to evaluate the consequences of repeated bouts of maximal intensity exercise on biventricular systolic and diastolic function in endurance trained and normally active individuals using cMRI. We hypothesized that interval exercise would result in biventricular decreases in systolic and diastolic function in both groups, with greater decreases in function occurring in the normally active group.

4.2 Methods

4.2.1 Participants

Nine healthy, normally active (NA) males who were not participating in a regimented aerobic exercise program (VO$_2$max < 50 ml·kg^{-1}·min^{-1}) and nine endurance-trained (ET) males who trained in excess of 10 h/wk (VO$_2$max > 60 ml·kg^{-1}·min^{-1}) were recruited for this study. This investigation was approved by the University of Alberta Health Research Ethics Board, and informed consent was provided by all participants before testing. All testing was conducted in accordance with the Declaration of Helsinki.

4.2.2 General Protocol

Participants reported to the Alberta Cardiovascular and Stroke Research Centre at the Mazankowski Alberta Heart Institute on two occasions separated by a minimum of 48 h. Subjects were asked to refrain from vigorous exercise for 24 h and caffeine for 12 h prior to each testing session. On day 1, subjects underwent basic anthropometric measures and an incremental cycle test to exhaustion to determine maximal aerobic power (VO$_2$max).

On day 2, subjects underwent a baseline cMRI assessment. They then performed a high intensity interval exercise session on a cycle ergometer followed by two additional cMRI assessments.

4.2.3 Incremental Exercise Test (day 1)

An incremental exercise test was performed on an electronically braked cycle ergometer (Ergometrics er800s; Ergoline, Bitz, Germany) to assess VO_2max and determine the exercise workloads for the second experimental day. After a brief rest period, the workload increased by 20 W every two minutes until reaching the ventilatory threshold (68), thereafter power output increased by 20 W each minute until exhaustion. Heart rate (HR; Polar heart rate, Kempele, Finland), and expired gas analysis (Parvomedics, Salt Lake City, UT) were obtained at rest and throughout exercise.

4.2.4 High Intensity Exercise (day 2)

Following a 15 min self-selected warm-up, subjects were instructed to perform fifteen 1 min workloads at 100% of the power output achieved at VO_2max separated by 2 min of active recovery. Subjects were verbally encouraged throughout the entire exercise session. Average and peak power output and HR were recorded for each work interval, and subjects were encouraged to drink water *ad libitum*.

4.2.5 Magnetic Resonance Imaging Acquisition

All examinations were performed using a 1.5 T Siemens Sonata MRI scanner (Erlangen, Germany) using a 5 element cardiac array for signal reception. Short axis cines covering the RV and LV (10 to 12 slices) were used to measure end systolic volumes (ESV), end diastolic (EDV) volumes, stroke volumes (SV), and ejection fractions (EF). Image parameters were TE=1.5 ms; TR=3.0 ms; flip angle=60°; slice

thickness=8 mm; matrix=256x192; field of view=300 to 380 mm; and 10 views per

segment with 30 reconstructed phases. E and A wave blood velocities, at the level of the

mitral leaflet tips, and E' tissue velocities, at the mitral annulus, were measured from

short axis through-plane phase contrast cines. Typical image parameters were TE=2.5

ms; TR=5.0 ms; flip angle=15°; slice thickness=8 mm; matrix=128x96; field of

view=300 to 380 mm; GRAPPA factor = 2; V_{enc} = 100 cm/s for E/A and 50 cm/s for E';

and 3 views per segment with 50 reconstructed phases. Myocardial tagging was used to

measure peak torsion and untwisting rate, and circumferential strain and strain rate. Five

short axis slices from base to apex provided full heart coverage. Typical image

parameters were TE=2.2 ms; TR=4.0 ms; flip angle=12°; slice thickness=8 mm;

matrix=192x128; field of view=300 to 380 mm; and 5 views per segment with 20 ms

temporal resolution. All image acquisitions were ECG-gated and acquired during breath

holds. The data was acquired in the order listed above and took approximately 20

minutes. HR (electrocardiogram) and blood pressure (automated cuff

sphygmomanometer) were also monitored throughout acquisition.

4.2.6 Magnetic Resonance Imaging Analysis

Assessment of LV and RV volumes was performed by manual segmentation of short-

axis cine images at end diastole and end systole (Argus; Siemens Medical Systems). LV

and RV EDV and ESV were calculated using Simpson's rule (54), from which SV and

EF were determined. Papillary muscles were included to the ventricular cavity and were

not considered for calculation of mass (29).

Image processing and data analysis of phase contrast and tagged images were

performed using a custom designed software package. Tag analysis was fully automated

using an image morphing algorithm to determine the spatial deformation field of all images with respect to a reference image. User input was limited to tracing the endo and epicardium at a single cardiac phase for each slice. The center of mass for each slice was calculated for each frame as a moving reference for the calculation of rotation, torsion and circumferential strain. Torsion was calculated as the difference between the clockwise rotation at the base and the counterclockwise rotation at the apex, yielding a measure of the total base-to-apex deformation. The rate of untwisting was calculated as the time derivative of the torsion. Circumferential strain was measured as the fractional change in circumferential length between a given cardiac phase and a reference phase at diastasis, and the strain rate is the time derivative of this value. Circumferential values were averaged over the 5 slices. All analyses were repeated for endocardium (inner third of myocardium), epicardium (outer 1/3rd of myocardium) and for the full thickness. All parameters were plotted as a function of time from the QRS and peak values were selected manually and stored with the times of the peak values. A normalized untwisting value was calculated by dividing the peak rate of untwisting by the peak torsion.

4.2.7 Statistical Analysis

A non-parametric test (Freidman ANOVA ranks test) was used to make comparisons within groups, while between-group differences were calculated using the Mann-Whitney U-test (Statistica; Statsoft Ltd, Tulsa, Oklahoma, USA). The change in LV and RV EF from pre to post exercise (delta scores) was correlated with age, VO$_2$max, as well as delta scores for HR, and estimates of preload (EDV) and afterload (wall stress) using Pearson's correlation coefficient. Data are presented as means ± SD and the significant level was set *a priori* at p<0.05.

4.3 Results

4.3.1 Participant Characteristics

Participant characteristics are shown in Table 4.1. There were no statistical group differences in age, height, or body surface area. The NA group had significantly greater body mass, and lower absolute LVM and LVM indexed to body surface area$^{1.5}$ compared to the ET group (Table 4.1). By study design, peak VO$_2$ was significantly lower in NA versus ET.

	Normally Active (n=9)	Endurance Trained (n=9)
Age (years)	35 ± 7	29 ± 6
Height (cm)	177 ± 7	180 ± 11
Weight (kg)	84 ± 6*	73 ± 9
Body surface area (m^2)	2.0 ± 0.1	1.9 ± 0.2
VO_2 (ml/kg/min)	43.9 ± 8.7*	68.7 ± 6.6
Left ventricular mass (g)	152 ± 23*	173 ± 19
Left ventricular mass/body surface area$^{1.5}$ (g/m^3)	53.2 ± 8.1*	65.5 ± 10.2

Table 4.1 Participant characteristics
* $p < 0.05$ vs. Endurance Trained (means ± SD).

4.3.2 Performance During High Intensity Exercise

Table 4.2 summarizes the mean exercise performance data during the high intensity interval exercise session. The average combined duration of all intervals was 14.0 ± 0.1 min. The average duration of the entire exercise session, including the warm-up, intervals, and recovery between intervals was 58.7 ± 0.08 min. Both groups completed an average of 14 intervals at 93 ± 4 % of maximal HR. There was no change in body mass following exercise.

	Normally Active (n=9)	Endurance Trained (n=9)
Number of Intervals	14 ± 2	14 ± 1
Interval Heart Rate (beats/min)	169 ± 9	174 ± 7
% of Maximal Heart Rate (%)	93 ± 4	93 ± 4
Recovery Heart Rate (beats/min)	133 ± 13	135 ± 7
% of Maximal Heart Rate (%)	73 ± 6	72 ± 4
Interval Power Output (Watts)	291 ± 81*	402 ± 76
% of Maximal Power Output (Watts)	97 ± 11	99 ± 6
Recovery Power Output (Watts)	66 ± 26*	95 ± 40
% of Maximal Power Output (%)	21 ± 6	21 ± 9

Table 4.2 Performance during high intensity exercise
 * $p < 0.05$ vs. Endurance Trained (means ± SD).

4.3.3 Cardiac Magnetic Resonance Imaging Volume Assessment

The first post-exercise (post 1) cMRI assessment began 6.2 ± 2.6 min following completion of the last interval, and the second assessment (post 2) began 38.4 ± 3.8 min post-exercise. Table 4.3 summarizes the hemodynamic data (HR and BP averaged). Heart rates were significantly greater in the NA group vs. ET group pre-exercise (65 ± 6 vs. 55 ± 6 bpm). There were no statistical differences in systolic (123 ± 9 vs. 121 ± 12 mmHg), diastolic (74 ± 11 vs. 71 ± 7 mmHg), or mean (90 ± 9 vs. 88 ± 8 mmHg) arterial blood pressures pre-exercise between NA and ET respectfully. Pre-exercise LVEDV (178 ± 36 vs. 205 ± 40 mL), LVESV (68 ± 16 vs. 80 ± 20), RVEDV (193 ± 42 vs. 216 ± 53 mL), RVESV (83 ± 23 vs. 96 ± 26), LVSV (110 ± 20 vs. 126 ± 23 mL), RVSV (110 ± 21 vs. 121 ± 28 mL) were all lower in NA vs. ET respectively (all p's > 0.05). Compared to pre-exercise, there was a significant increase in HR, and a significant decrease in LV wall stress at post 1 and post 2 in both groups. SBP and MAP were significantly decreased post 2 in both groups compared to pre-exercise (p<0.05; Table 4.3). In the NA group, LVEDV and LVSV were significantly decreased post 1 and post 2 compared to pre-exercise, while LVESV was significantly decreased post 1 only. In the ET group there were no differences post-exercise in LVESV, while LVEDV was significantly lower post 1 only and LVSV was lower post 1 and post 2 (p< 0.05). LVEF fell significantly post 1 and post 2 in the ET group (p<0.05, Table 4.3), whereas no change in LVEF occurred in the NA group. In the ET group, RVEDV was significantly decreased post 1 only, while RVSV was decreased post 1 and post 2 and there were no changes in RVESV compared to pre-exercise. RVEF was significantly decreased compared to pre-exercise at post 1 and post 2 in the ET group. In the NA group, RVEDV, RVSV and

RVEF were lower post 1 and post 2 compared to pre-exercise (all p's > 0.05). At post 2 LVEF and RVEF were significantly lower, and ESV significantly higher in the ET group compared to the NA group. The E/A ratio was significantly decreased post-exercise in both groups; however, only the ET group demonstrated a significantly decreased E' at post 1 and post 2 ($p < 0.05$; Table 4.3). There were no significant differences post-exercise in E/E'. There were no significant correlations between changes in LVEF and age, VO_2max, exercise power output normalized to body mass, LVEDV, HR, or LVWS (Table 4.4). Similarly, no significant correlations were found between changes in RVEF and age, exercise power output normalized to body mass, VO_2max, RVEDV, or HR (Table 4.4).

Variable	Pre-exercise		Post 1		Post 2	
	NA	ET	NA	ET	NA	ET
HR (beats/min)	65 ± 6†	55 ± 6	96 ± 13*	87 ± 8*	84 ± 13*	73 ± 8*
SBP (mmHg)	123 ± 9	121 ± 12	120 ± 12	118 ± 6	115 ± 9*	109 ± 7*
DBP (mmHg)	74 ± 11	71 ± 7	75 ± 7	69 ± 6	72 ± 8	67 ± 8
MAP (mmHg)	90 ± 9	88 ± 8	90 ± 7	85 ± 5	86 ± 8*	81 ± 6*
LVWS	85 ± 15	89 ± 20	70 ± 16*	82 ± 20*	67 ± 13*	76 ± 18*
SBP·LVESV^{-1} (mmHg·mL^{-1})	1.9 ± 0.4	1.6 ± 0.4	2.3 ± 0.7	1.7 ± 0.5	1.9 ± 0.4	1.4 ± 0.4
LV Volumes						
LVEDV (mL)	178 ± 36	205 ± 40	155 ± 36*	180 ± 42*	161 ± 30*	195 ± 40
LVESV (mL)	68 ± 16	80 ± 20	57 ± 17*	74 ± 22	62 ± 13	81 ± 20†
LVSV (mL)	110 ± 20	126 ± 23	98 ± 22*	106 ± 22*	99 ± 19*	112 ± 24*
LVEF (%)	62 ± 3	62 ± 4	63 ± 5	59 ± 4*	61 ± 3†	58 ± 4*
RV Volumes						
RVEDV (mL)	193 ± 42	216 ± 53	171 ± 40	189 ± 46*	177 ± 33	202 ± 43
RVESV (mL)	83 ± 23	96 ± 26	71 ± 17*	88 ± 25	79 ± 19	94 ± 24
RVSV (mL)	110 ± 21	121 ± 28	100 ± 25	101 ± 23*	99 ± 19	108 ± 21*
RVEF (%)	58 ± 4	56 ± 3	58 ± 5	54 ± 4*	56 ± 5†	54 ± 3*
LV Diastolic Indices						
E/A	1.9 ± 0.5	2.1 ± 0.5	1.2 ± 0.3*	1.5 ± 0.4*	1.2 ± 0.4*	1.6 ± 0.5*
Lateral E' (m·s^{-1})	0.15 ± 0.04	0.16 ± 0.02	0.13 ± 0.03	0.13 ± 0.02	0.13 ± 0.02*	0.13 ± 0.03*
E/E'	4.5 ± 1.2	4.1 ± 0.9	5.0 ± 2.8	4.5 ± 1.1	4.4 ± 1.9	4.8 ± 1.6

Table 4.3 Selected cardiovascular variables before and after high intensity exercise

NA, normally active; ET, endurance trained; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; LVWS, left ventricular wall stress; LV, left ventricular; EDV, end diastolic volume; SV, stroke volume; EF, ejection fraction; SBP·LVESV^{-1}, end-systolic pressure volume relationship; RV, right ventricular. * $p < 0.05$ vs. pre-exercise; † $p < 0.05$ vs. Endurance Trained (means ± SD).

Variable	Age		VO$_2$ max		PO/body weight		Δ EDV		Δ HR	
	NA	ET	NA	ET	NA	ET	NA	ET	NA	ET
Δ LVEF post 1										
r	0.29	0.51	0.00	-0.43	0.08	-0.41	-0.04	-0.29	0.62	-0.39
p	0.45	0.16	0.99	0.25	0.83	0.27	0.91	0.45	0.08	0.32
Δ LVEF post 2										
r	0.50	0.06	0.07	0.06	0.20	0.09	-0.27	-0.50	0.21	-0.06
p	0.17	0.23	0.86	0.89	0.61	0.81	0.50	0.18	0.56	0.89
Δ RVEF post 1										
r	-0.04	-0.11	0.36	-0.65	0.23	-0.61	0.04	0.10	-0.12	-0.04
p	0.91	0.78	0.35	0.06	0.56	0.08	0.92	0.80	0.76	0.91
Δ RVEF post 2										
r	0.45	-0.33	0.25	-0.43	0.29	-0.65	-0.44	0.28	0.17	0.46
p	0.23	0.39	0.51	0.25	0.45	0.06	0.23	0.46	0.66	0.21

Table 4.4 Selected correlations for changes in cardiac function

NA, normally active; ET, endurance trained; PO, power output; LV, left ventricular; RV, right ventricular; Δ EF, difference between pre-and post-exercise ejection fraction; Δ EDV, difference between pre-and post-exercise end diastolic volume; Δ HR, difference between pre-and post-exercise heart rate (data are Pearson's correlation coefficients).

4.3.4 Cardiac Magnetic Resonance Imaging Tagging Assessment

cMRI tagging data are presented in Table 4.5. There were no significant differences between groups in any variable at any time point (pre-exercise, post 1, or post 2). Following exercise there were no significant changes in torsions, rotation rates, strain, or strain rates in the NA group. In the ET group all (global, subendocardial and subepicardial) untwisting rates, apical rotation rates and circumferential strains were significantly decreased at post 2 (p<0.05; Table 4.5). There was no change in torsions, basal rotation rates and circumferential strain rates post-exercise in the ET group. Torsion was not related to LVEF, LVESV or LVEDV at any time point. Untwisting rate was significantly related to torsion at all time points (r = pre: 0.81; post 1: 0.92; post 2: 0.79; p<0.05). Normalized untwisting rate (untwisting rate/torsion) was significantly decreased post 1 and post 2 in the ET group, but no differences post-exercise were observed in the NA group (Figure 4.1). Timing of peak torsion (pre: 0.34 ± 0.02 s; post 1: 0.37 ± 0.03 s; post 2: 0.35 ± 0.03 s), untwisting rate (pre: 0.42 ± 0.03 s; post 1: 0.44 ± 0.03 s; post 2: 0.43 ± 0.03 s), apical rotation rate (pre: 0.41 ± 0.03 s; post 1: 0.45 ± 0.04 s; post 2: 0.42 ± 0.03 s) were significantly longer post 1 in the ET group, with no differences in the NA group. There was no difference post-exercise in the NA group in time between peak untwisting rate and circumferential strain rate (pre: 0.07 ± 0.02 s; post 1: 0.06 ± 0.02 s; post 2: 0.06 ± 0.02 s); however, this index was significantly decreased post 1 and post 2 in the ET group (pre: 0.07 ± 0.02 s; post 1: 0.04 ± 0.03 s; post 2: 0.05 ± 0.02 s). See Figure 4.2 for representative tracings of peak untwisting rate and circumferential strain rate in NA and ET individuals.

Variable	Pre-exercise		Post 1		Post 2	
	NA	ET	NA	ET	NA	ET
Torsion (deg)	-10.3 ± 3.2	-10.4 ± 2.8	-13.4 ± 4.0	-12.4 ± 3.4	-10.4 ± 2.6	-9.5 ± 2.8
Subendocardial Torsion (deg)	-11.8 ± 3.9	-12.2 ± 3.3	-15.6 ± 4.8	-14.1 ± 3.9	-12.0 ± 3.3	-11.0 ± 3.2
Subepicardial Torsion (deg)	-8.8 ± 2.6	-8.6 ± 2.4	-11.1 ± 3.5	-10.6 ± 2.9	-8.9 ± 2.2	-7.9 ± 2.5
Untwisting Rate (deg·sec^{-1})	139.7 ± 42.5	149.0 ± 30.6	155.5 ± 46.4	142.8 ± 40.8	136.1 ± 38.5	124.2 ± 36.9*
Subendocardial Untwisting Rate (deg·sec^{-1})	159.7 ± 55.5	168.1 ± 37.0	174.7 ± 55.7	163.2 ± 43.3	151.9 ± 42.3	138.2 ± 38.7*
Subepicardial Untwisting Rate (deg·sec^{-1})	119.2 ± 33.0	129.1 ± 25.6	135.6 ± 38.5	121.9 ± 38.6	119.6 ± 35.6	109.4 ± 36.0*
Basal Rotation Rate (deg·sec^{-1})	-49.0 ± 9.8	-53.9 ± 18.7	-57.5 ± 27.0	-48.1 ± 25.6	-50.6 ± 13.1	-44.5 ± 25.5
Subendocardial Basal Rotation Rate (deg·sec^{-1})	-53.3 ± 11.7	-60.9 ± 20.3	-61.5 ± 29.4	-53.4 ± 28.1	-55.3 ± 15.5	-50.8 ± 27.3
Subepicardial Basal Rotation Rate (deg·sec^{-1})	-44.2 ± 8.2	-46.5 ± 17.8	-53.0 ± 25.1	-42.3 ± 22.6	-45.6 ± 11.2	-37.9 ± 24.0
Apical Rotation Rate (deg·sec^{-1})	110.9 ± 44.9	108.8 ± 36.8	111.5 ± 37.2	108.9 ± 39.5	101.6 ± 38.5	85.4 ± 33.5*

Table 4.5 (cont. on next page)

Variable	Pre-exercise		Post 1		Post 2	
	NA	ET	NA	ET	NA	ET
Subendocardial Apical Rotation Rate (deg·sec^{-1})	128.3 ± 56.4	122.7 ± 45.9	127.9 ± 43.9	126.1 ± 42.3	115.1 ± 46.1	95.2 ± 36.7*
Subepicardial Apical Rotation Rate (deg·sec^{-1})	93.4 ± 35.2	94.7 ± 29.1	95.1 ± 32.3	92.0 ± 37.3	87.7 ± 32.0	75.0 ± 31.8*
Circumferential Strain	-0.18 ± 0.02	-0.18 ± 0.03	-0.18 ± 0.02	-0.17 ± 0.02	-0.17 ± 0.02	-0.16 ± 0.02*
Subendocardial Circumferential Strain (%)	-0.21 ± 0.03	-0.21 ± 0.03	-0.21 ± 0.02	-0.20 ± 0.03	-0.20 ± 0.03	-0.19 ± 0.02*
Subepicardial Circumferential Strain (%)	-0.15 ± 0.02	-0.15 ± 0.02	-0.14 ± 0.03	-0.14 ± 0.02	-0.14 ± 0.02	-0.13 ± 0.02*
Circumferential Strain Rate (%•s^{-1})	1.57 ± 0.24	1.52 ± 0.29	1.59 ± 0.21	1.50 ± 0.21	1.48 ± 0.23	1.41 ± 0.31
Subendocardial Circumferential Strain Rate (%•s^{-1})	1.86 ± 0.33	1.77 ± 0.37	1.90 ± 0.26	1.75 ± 0.27	1.74 ± 0.31	1.65 ± 0.35
Subepicardial Circumferential Strain Rate (%•s^{-1})	1.29 ± 0.18	1.27 ± 0.22	1.28 ± 0.21	1.26 ± 0.17	1.22 ± 0.17	1.17 ± 0.27

Table 4.5 cMRI tagging derived indices of cardiac function
* $p < 0.05$ vs. pre-exercise (means ± SD).
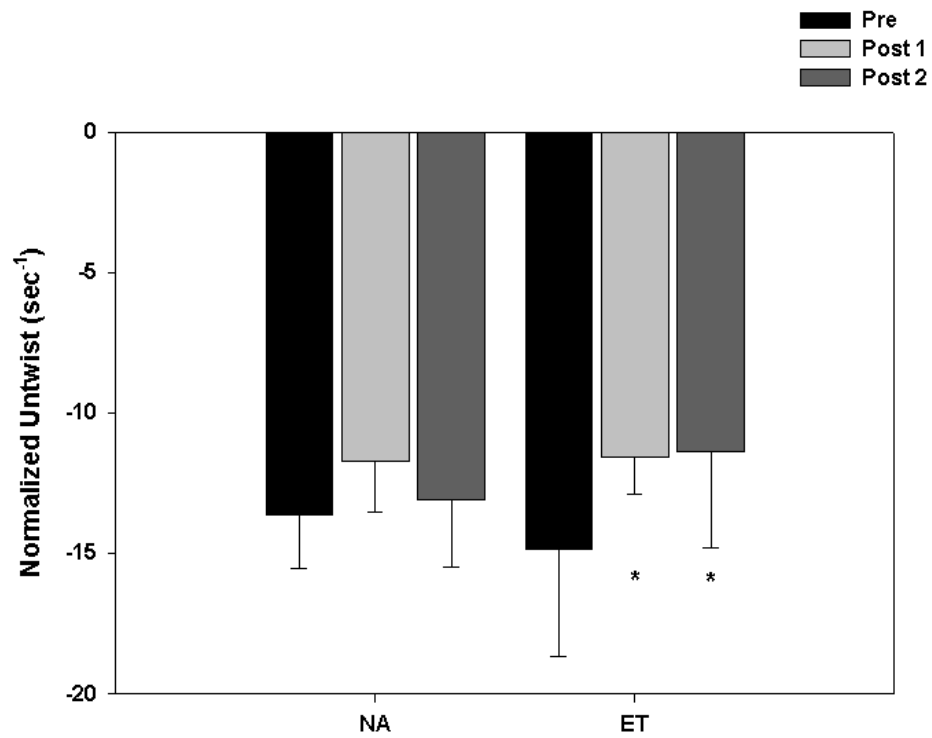
Figure 4.1 Normalized untwisting rate pre and post-exercise
NA, normally active; ET, endurance trained. * $p < 0.05$.
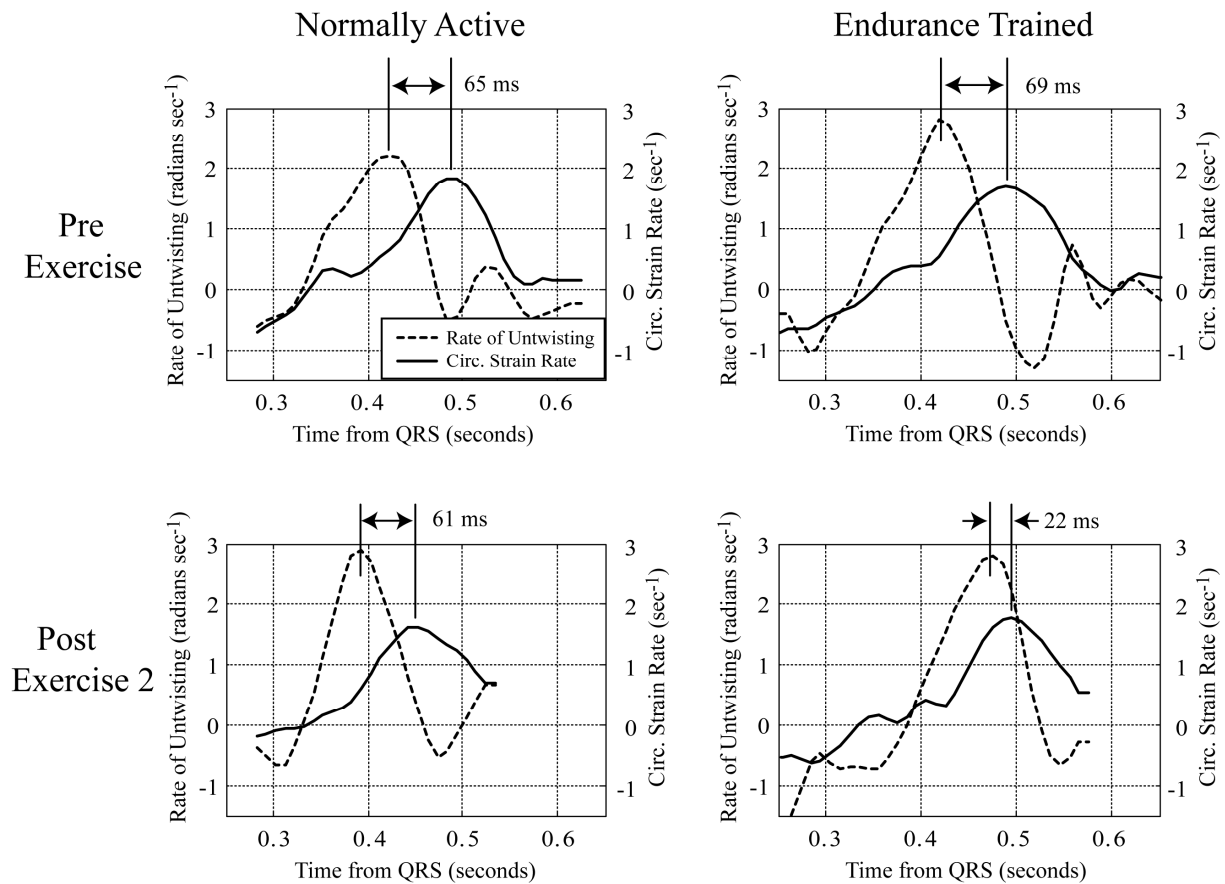
Figure 4.2 Representative tracings of peak untwisting rate and circumferential strain rate

4.4 Discussion

To our knowledge, this is the first study to examine the acute effects of brief (14 min), high intensity interval exercise on biventricular systolic and diastolic function using cMRI in ET and NA individuals. The major new findings of this investigation are: 1) high intensity exercise induces a significant reduction in global RV and LV systolic function in ET athletes; 2) regional LV systolic function is reduced post-exercise in ET athletes; 3) LV diastolic function is impaired after high intensity exercise in ET athletes; and 4) RV and LV function is not impaired following interval exercise in NA individuals.

4.4.1 Global LV and RV Function in ET Individuals

Numerous investigations have demonstrated a transient decrease in LV systolic and diastolic function in ET individuals following prolonged exercise (17, 59, 70). This study extends prior findings by demonstrating that 14 min of high intensity exercise can induce alterations in LV function similar to those that occur following prolonged exercise lasting between 5 and 30 h (59, 60). To date, only a few studies have examined the effects of acute high intensity exercise on LV function. In contrast to our findings, duManoir et al. (11), and Neilan and associates (48) reported that LV systolic function was increased immediately following one session of 6 to 8 min of high intensity rowing. The divergent post-exercise response between our results and those previously reported may be due to the duration and intensity of exercise. In our study, participants completed multiple bouts of maximal intensity exercise (Table 4.2) which could, in turn, induce alterations in ventricular function via mechanisms discussed below.

Unlike the previously described investigations, Foster and colleagues (15, 16) reported that LVEF was significantly decreased during one bout of sudden strenuous exercise (30 s cycling at 400 W). Although intriguing, it is likely that the LVEF response was altered during sudden strenuous exercise due to rapid changes in LV preload reserve secondary to abrupt changes in venous return. It is possible that our decreases in LV function were due to alterations in loading conditions (18). However, the lack of significant correlations between LV function and HR, preload and afterload in this investigation (Table 4.4) suggests that an alteration in intrinsic LV function likely occurred post-exercise in ET individuals. Furthermore, although recent studies have indicated that decreases in LV function are associated with training volume (47), and/or age (35), our data would suggest that both of these variables had little impact on LV function in the current cohort.

A depression in RV systolic function after prolonged exercise has previously been described (8, 10, 37). However, such early investigations used 2D echocardiographic quantitative assessment of RV systolic function, which is inherently difficult and often prone to error (43). More recent examinations of RV function following exercise have utilized tissue Doppler-derived strain and strain rate (48, 49, 53), methods which are purported to be a less load-dependent assessment of myocardial function (62). Of note, immediately following both prolonged (49) and brief high intensity exercise (48), Neilan et al. demonstrated a significant reduction in RV strain and strain rate at the apex. Despite these technological advancements in RV imaging, limitations continue to exist regarding tissue Doppler-derived strain and strain rate, which is even more angle-dependent than Doppler flow measures (50). Unlike previous studies, the current investigation used an accurate and reproducible method of evaluating RV function. Using

cMRI, we found that RVEF was significantly decreased post-exercise in ET individuals (Table 4.3). Similar to the LV, the lack of significant correlations between RV function and HR and RVEDV (Table 4.4) suggests that an alteration in intrinsic RV function occurred in ET individuals. The origin of RV dysfunction is unclear, but may reflect the response of the RV to increased right-sided pressures. For example, with chronic right-sided pressure-loading, the RV dilates, resulting in both systolic and diastolic dysfunction (69). Right-sided pressures have previously been shown to increase with exercise (63), and could consequently cause acute RV dilation and RV dysfunction. The potential influence of RV dilation on LV function should also be noted. The RV and LV share the interventricular septum and the pericardial sac, both of which may allow one ventricle to influence the other. The limited ability of the pericardium to stretch means that a large change in the volume of the RV may limit the volume of the LV because of a leftward shift of the interventricular septum (45). Subsequent RV dilation may cause the LV to become stiffer, thus theoretically increasing LV end-diastolic pressure, decreasing pulmonary venous return, and reducing LV stroke volume. Accordingly, exercise-induced increases in pulmonary pressures could result in impaired RV and LV function in ET athletes.

4.4.2 Myocardial Tagging in ET Individuals

Systolic rotation of the LV apex relative to the base (torsion) is a direct consequence of the innate helical fiber architecture of the LV and is a fundamental component of wall thickening and systolic ejection (27). Because torsion is defined as rotation of the LV apex relative to the base, changes in rotation at either short-axis level may adversely affect LV torsion. The rotation of the LV base during systole is minimal; thus, torsion

predominantly represents apical movement (27). Our results also indicate that basal rotation was minimally affected following exercise, whereas apical rotation rate was significantly reduced in the ET group. Furthermore, circumferential strain was decreased in the ET group post-exercise, a phenomenon we have previously reported following prolonged, low intensity exercise (60).

In healthy hearts, the torsion generated during systolic contraction is released during early diastole. This diastolic untwisting has been shown to coincide with isovolumic relaxation and is thought to result from the release of energy stored in elastic elements within the extracellular matrix during the previous systole (57). Previous reports in healthy hearts suggest that untwisting promotes LV suction (via generation of intra-ventricular pressure gradients) aiding early diastolic filling (56). Conversely, delayed untwisting despite normal or increased LV torsion or apical rotation has been observed in states associated with worsened relaxation such as chronically pressure overloaded heart (64) and aging (42). In the present study, despite a slight increase or maintenance in torsion, untwisting rates were decreased in ET athletes. Further evidence of reduced relaxation was apparent with the less load-dependent index of LV diastolic function, normalized untwisting (rate of untwisting/peak torsion). This measure is meant to remove the dependence of the untwisting rate on the amount of torsion, which has been shown to modulate untwisting (9). This index was significantly decreased post-exercise in the ET group (Figure 4.1). Moreover, the time between peak untwisting rate and peak circumferential strain rate (Figure 4.2) indicates that, as previously shown (50, 51), substantial untwisting occurs before filling in both groups pre-exercise. Post-exercise however, this time was significantly reduced in the ET group, highlighting the fact that,

in addition to substantially decreased untwisting rates, the delayed timing of untwisting post-exercise may limit diastolic suction in the ET group (51). Taken together, our results indicate that diastolic function is impaired as a result of high intensity exercise.

4.4.3 Endurance Trained and Normally Active Individuals

In contrast to Nottin et al. (52), we found no differences between torsions, rotation rates or circumferential strains in ET and NA individuals at rest. Although Nottin and associates (52) did not evaluate aerobic fitness, it is possible that athletes in their investigation were fitter than those in the present study. However, when Stuber et al. (64) evaluated torsions, rotation rates and strains using cMRI in athletes and non-athletes, their results, similar to ours, reported no differences between groups.

Several investigations have reported a post-exercise reduction in LVEF in untrained individuals following moderate intensity exercise (30, 31, 66). Indeed, Neilan et al. (47) found that changes in ventricular function following a marathon were strongly influenced by the level of preparation undertaken by amateur athletes, such that the majority of the most marked abnormalities in cardiac function were seen in those athletes training less than 35 miles/week. In contrast to these studies and to our hypothesis, we found no alterations in RV or LV function in NA individuals.

Our results raise important questions concerning why biventricular dysfunction occurs in ET athletes, but not in NA individuals following high intensity exercise. It is possible that the observed dysfunction was a result of the ET group working at a higher absolute workload. However, both groups were working at the same relative intensity (Table 4.2). Additionally, the pre- to post-exercise changes in LV and RV EF were not significantly correlated with normalized power output (Table 4.4).

Another potential mechanism contributing to the divergent response observed in ET and NA individuals is the sympathetic nervous system response to high intensity exercise. Several investigations have demonstrated that the post-exercise catecholamine concentration is significantly higher in endurance-trained than in untrained subjects, even when working at the same relative intensity (2, 39, 61). Kjaer et al. (34) suggested this may be due to a phenomenon called the 'sports adrenal medulla'; that is, a higher capacity in trained subjects to secrete catecholamines in response to exercise. In clinical populations, such as individuals with chronic heart failure, investigators have long observed that exposure of β1-receptors to increased concentrations of catecholamines results in desensitization of these receptors (3, 67). A desensitization of cardiac β1-receptors, one mechanism proposed to result in a decreased inotropic state following prolonged exercise, has recently received significant attention (13, 59, 70). Vanoverschelde et al. (66) suggested that because of the increased exposure to catecholamines during prolonged exercise, a downregulation of β1-receptor responsiveness may occur, prompting the decline in LV function. Given that ET athletes experience a significantly greater increase in catecholamines compared to NA individuals (34), it is possible that high intensity exercise may also result in a desensitization of β1-receptors in athletes. Interestingly, results from our investigation and others (47-49) demonstrating that apical function decreases more than basal function post-exercise suggest that desensitization may occur primarily at the apex. Supporting this hypothesis, Akagawa et al. (1) recently reported that strain at the apex is more sensitive and dependent on sympathetic stimulation than at the base. This initial dependence and sensitivity to sympathetic stimulation may consequently result in receptor desensitization

when apical receptors are faced with increased exposure to catecholamines during prolonged or high intensity exercise.

It is also possible that the constant training stimulus experienced by ET athletes results in a shift of sarcolemmal β1-receptors to an intracellular location. Werle et al. (71) investigated the cardiac β1-receptor adaptation to physical activity and reported a decrease in the number of cardiac β1-receptors by 26% in the maximal training group and 13% in the endurance-training group. An early investigation by Butler et al. (4) examining β1-receptor function in athletes reported that the post-training decreases in sympathetic nervous system responsiveness were related to decreases in lymphocyte β1-receptor density. Similar to inducing a receptor downregulation or desensitization, Hawkins and colleagues (23) evaluated the effects of cardio-selective β-adrenergic blockade on the ability to maintain cardiac work in average-fit and high-fit subjects during moderate- and heavy-intensity cycling exercise. They found that β-receptor blockade reduced the cardiac function, cardiac work, and cardiac efficiency of ET athletes during moderate- and heavy-intensity exercise, a phenomenon which did not occur in average-fit individuals (23). These results indicate that β-receptor desensitization or downregulation could, in fact, account for the decreases in cardiovascular function in the ET group observed in the current investigation.

An additional mechanism that could contribute to the observed differences between ET and NA individuals involves free fatty acid (FFA) metabolism. Coggan et al. (7) evaluated the effects of exercise on fat metabolism and found that plasma FFA concentration and FFA oxidation were significantly higher in trained versus untrained men during intense exercise performed at the same relative intensity. Given that Kaijser

and colleagues (28) demonstrated coronary sinus FFA concentration was only slightly less than arterial FFA concentration during exercise, it is possible that ET males may have greater myocardial FFA oxidation than NA males. Interestingly, high levels of FFA have been shown to significantly depress regional and global mechanical LV function in swine hearts (41). These findings were hypothesized to be due to the uncoupling of the electron transport chain, ultimately reducing mitochondrial respiration (41). Taken together, a higher myocardial FFA metabolism could account for the decreased RV and LV function observed in ET individuals versus NA individuals in the present investigation. To the best of our knowledge this hypothesis has never been directly tested, and future investigations should examine if inhibition of FFA oxidation could improve ventricular performance in ET individuals.

4.4.4 Functional Implications

The decrease in RV and LV function post-exercise in ET athletes may reflect a physiological adaptation resulting from recurring episodes of cardiac volume and pressure overload – a process analogous to the well documented response to training in skeletal muscle (6). Future investigations should examine if, similar to skeletal muscle, there is a subsequent "super compensation" in the heart several days following the acute bout of exercise. Alternatively, the aforementioned desensitization or downregulation of β1-receptors as a result of endurance training could be a protective mechanism against the chronic exposure to high concentrations of catecholamines. Although the observed impairment in RV and LV function may be an adaptive or protective mechanism, there is also the potential for clinical consequences. Generation of scar tissue may have serious long term sequelae including a predisposition to ventricular arrhythmias (73). Indeed,

following intense exercise in animal models there is histological data demonstrating reactive scar tissue formation (5, 32). Evidence in humans is scarce, although at least one case report describes multiple unexplained foci of fibrosis in an elite marathon runner at necropsy following sudden cardiac death (58).

4.5 Limitations

This study must be examined in light of several potential limitations. First, although we did not assess catecholamines or metabolic substrates, several other investigations have reported the catecholamine and FFA response to high intensity exercise in trained and normally active individuals (7, 39, 61). Second, we did not assess cardiovascular function during exercise and are therefore unable to determine if the observed changes only occur post-exercise. Although previous investigations (14, 15, 18) have examined ventricular function during exercise, they have produced conflicting results. Subsequent research should consider assessment of ventricular function during high intensity exercise. Third, because the current study included only men, our findings cannot be generalized to women. Prior studies have demonstrated gender differences in the cardiovascular response during cycle exercise (24, 46), and future investigations should explore the consequences of acute, high intensity exercise in women. Finally, we do not have follow-up data on participants to determine the chronology of these changes on recovery.

4.6 Conclusions

Biventricular systolic and diastolic dysfunction occurs following 14 min of high intensity exercise in ET athletes, a phenomenon which is not observed in NA individuals. Although further research is required to elucidate the mechanisms contributing to the

observed differences, our findings suggest that the myocardial response of ET individuals

to high intensity exercise is altered as a consequence of chronic exercise training.

4.7 Chapter Four References

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[1]CHAPTER FIVE: Cardiovascular Responses to Incremental and Sustained Sub-maximal Exercise in Heart Transplant Recipients

5.1 Introduction

Heart transplantation is a life-saving intervention for select individuals with end-stage refractory heart failure. Despite normal left ventricular (LV) systolic function after surgery, heart transplant recipients (HTR) peak oxygen consumption remains 40–60% lower than age-matched healthy individuals (7, 9, 21, 23). A limitation of previous investigations examining exercise performance in HTR is the primary focus on incremental to peak aerobic exercise responses (20, 21). Although these protocols provide important information regarding the maximal capacity of cardiac and vascular function, they are neither directly applicable to the typical sub-maximal sustained activities of everyday living, nor do they take into account the fact that the overall

duration of exercise incorporated in most cardiac rehabilitation programs is approximately 1 h (22). Given that few HTR exercise at maximal intensities, it is particularly important to expand the understanding of preload, heart rate, and vascular responses to sustained sub-maximal exercise in this population. An additional limitation of previous studies is that cardiovascular performance has only been compared between HTR and healthy individuals matched to the recipient age (1, 4, 21, 32, 33). Given that the mean donor age is nearly two decades lower than the recipient age (45), the interaction of the heart with the systemic vasculature (ventricular-vascular coupling) may be a significant determinant of cardiovascular exercise performance. Furthermore, although abnormalities in ventricular-vascular coupling are well documented in HTR at rest (1, 32, 33), no investigation to our knowledge has compared the effects of exercise on ventricular-vascular coupling in HTR. In particular, by contrasting the exercise responses of HTR with those of donor age-matched individuals, insight into the limitations of coupling a younger, transplanted cardiac allograft with an older, foreign circulation in HTR can be obtained (30, 31, 43). The primary aim of this investigation was to compare the cardiovascular responses to incremental exercise and sustained sub-maximal aerobic exercise (1 h) in HTR and healthy individuals matched to the age of the recipient and the age of the donor heart. Our primary hypothesis was that HTR would have impaired preload, heart rate, and vasodilator reserve during incremental and sustained sub-maximal exercise compared to the recipient-matched group, and that the magnitude of these differences would be markedly greater compared to the donor-matched group.

5.2 Methods

5.2.1 Participants

The participants for this study included nine clinically stable male HTR (63 ± 10 years) and eleven controls (six male recipient age-matched healthy controls [RM], and five male donor age-matched healthy controls [DM]). Heart transplant recipients were recruited from the University of Alberta Heart Transplant Clinic, and controls were recruited from the surrounding area. This investigation received approval from the University of Alberta Health Research Ethics Board and informed consent was obtained prior to study participation.

5.2.2 General Protocol

Participants reported to the Alberta Cardiovascular and Stroke Research Centre exercise stress laboratory at the Mazankowski Alberta Heart Institute on two separate occasions to perform: 1) an incremental exercise test, and 2) 1 h of sustained sub-maximal exercise.

5.2.3 Incremental Exercise Test

On the first day, an incremental exercise test was performed on a semi-recumbent cycle ergometer. After a brief rest period, the workload increased by 20 W every two minutes until reaching the ventilatory threshold (49), thereafter power output increased by 20 W each minute until exhaustion. Heart rate (12 lead ECG), blood pressure (cuff sphygmomanometer), expired gas analysis (Parvomedics, Salt Lake City, UT), and ventricular volumes (2-D echocardiography, Vivid-*i*, GE Healthcare) were obtained at rest and during exercise to determine VO_2, heart rate (HR), end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), cardiac output, and ejection fraction

(EF). All images were obtained by a single, experienced sonographer in accordance with the American Society of Echocardiography guidelines (27) at rest and during the last 30 sec of each workload. Images were analyzed off-line by a single experienced technician. A minimum of three consecutive cardiac cycles were measured and averaged.

5.2.4 Sustained Sub-maximal Exercise

On the second day, participants performed 1 h of sustained sub-maximal exercise on a semi-recumbent cycle at 80% to 90% of the ventilation threshold determined from the incremental exercise test (day 1) (49). All of the ventilatory and ventricular measures were taken prior to, and at 30 and 60 minutes of exercise. Images were obtained and analyzed as previously stated. Participants were encouraged to consume fluid *ad libitum* during exercise, and body mass was measured before and after the exercise session to estimate fluid loss.

5.2.5 Calculations

End-systolic pressure (ESP) was calculated as 0.9 x brachial systolic blood pressure (SBP), a noninvasive estimate that accurately predicts LV pressure-volume loop measurements of ESP (25). Left ventricular volumes were determined using Teichholz method (46), and were normalized to body surface area (BSA) (13) to calculate ESV index (ESVI), EDV index (EDVI), SV index (SVI), and cardiac output index (CI). End-systolic elastance index (EesI) was calculated as EesI = ESP/ESVI, effective arterial index (EaI) was calculated as EaI = ESP/SVI, and ventricular-vascular coupling was determined as EaI/EesI (25). Systemic vascular resistance index (SVRI) was calculated as mean arterial pressure/CI x 80. Reserve function was defined as the difference in these variables between rest and peak exercise for incremental exercise, and sub-maximal

reserve was defined as the difference in these variables between rest and 60 minutes for sustained sub-maximal exercise.

5.2.6 Statistical Analysis

Repeated measures ANOVA (analysis of variance) was initially used to compare means between groups. Due to the small sample size and large amount of variability in the data, non-parametric tests were then carried out at each level of intensity and at each time of measurement. Comparisons among groups were performed using the Kruskal-Wallis test. When significant, pairwise comparisons were made using the Mann-Whitney method and Bonferroni-adjusted significant level was applied. Associations between oxygen consumption and ventricular-vascular coupling were examined using Pearson's correlation coefficient. Data are presented as means ± SD and the significant level is set at 0.05. A corrected p value of < 0.017 was considered statistically significant for Bonferroni-adjusted pairwise comparisons.

5.3 Results

Participant characteristics are shown in Table 5.1. There were no statistical group differences in height, mass, BSA, LV mass, or self-reported physical activity levels (HTR: 201 ± 174 min/week; RM: 210 ± 166 min/week; DM: 240 ± 228 min/week). By study design, HTR and RM were significantly older than DM. Peak VO_2 was lower in HTR versus RM and DM by 33% and 53%, respectfully (Table 5.1).

	HTR (n=9)	RM (n=6)	DM (n=5)
Age (years)	63 ± 10#	60 ± 12#	35 ± 8
Height (cm)	174 ± 7	174 ± 10	177 ± 11
Weight (kg)	79 ± 11	79 ± 7	78 ± 4
Body surface area (m^2)	1.9 ± 0.2	1.9 ± 0.1	1.9 ± 0.1
VO_2 (ml/kg/min)	24.2 ± 10.9#	36.3 ± 10.7	51.1 ± 10.4
Left ventricular mass (g)	182 ± 43	172 ± 27	204 ± 60
Left ventricular mass index (g/m^2)	95.6 ± 21.6	88.1 ± 9.7	105.9 ± 34.9
Years post transplant	8 ± 6	---	---
Medications			
Corticosteroid	1	---	---
Antiproliferative agent	7	---	---
Calcineurin inhibitor	8	---	---
TOR inhibitor	2	---	---
Beta-blocker	1	---	---
Calcium channel blocker	4	---	---
ACE inhibitor	5	1	---
Diuretic	3	1	---
Aspirin	7	1	---
Lipid lowering agent	8	1	---

Table 5.1 Participant characteristics

HTR, heart transplant recipient; RM, recipient age-matched control; DM, donor age-matched control; TOR, target of rapamycin; ACE, angiotensin converting enzyme (Data are means ± SD or n).

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5.3.1 Incremental Exercise Test

Resting and exercise cardiovascular responses during incremental exercise are summarized in Table 5.2. Resting HR, EaI and EaI/EesI were significantly higher in HTR compared to RM and DM. No significant difference was found between groups for any other resting parameter. In all groups, HR, EDVI, EesI, SVI, and EF increased, while ESVI, SVRI, and EaI/EesI decreased throughout the incremental exercise. Peak exercise HR, SVI and CI were significantly lower and SVRI significantly higher in HTR compared to DM, while EDVI was lower in HTR compared to both RM and DM. There was no significant difference in peak HR between HTR and RM. Furthermore, no significant difference was found between groups for peak ESVI or EF. The reserve HR, SVI, and CI were significantly lower in HTR compared to DM, while EDVI reserve was lower in HTR compared to RM and DM (Figure 5.1). Arterial elastance index increased throughout incremental exercise in RM and DM, whereas it decreased in HTR, resulting in a significantly lower EaI reserve in HTR (Figure 5.2). There were no differences between groups in EesI or EaI/EesI reserve (Figure 5.2). In HTR, reserve heart rate was associated with time post transplant and VO_{2peak} (Figure 5.3).

	HTR (n=9)	RM (n=6)	DM (n=5)
Heart rate (beats/min)			
Rest	90 ± 7 *#	68 ± 16	69 ± 16
50%	119 ± 14	117 ± 21	138 ± 19
75%	139 ± 16 #	136 ± 20	161 ± 15
100%	151 ± 19 #	152 ± 19 #	183 ± 6
End systolic pressure (mmHg)			
Rest	107 ± 15	106 ± 11	101 ± 8
50%	138 ± 19	154 ± 19	146 ± 20
75%	150 ± 18	172 ± 23	168 ± 10
100%	159 ± 24 #	193 ± 23	190 ± 8
Ejection Fraction (%)			
Rest	61.0 ± 4.2	69.6 ± 4.7	67.9 ± 6.0
50%	71.6 ± 8.5	76.6 ± 5.4	77.0 ± 6.6
75%	77.7 ± 7.1	80.7 ± 5.6	82.4 ± 4.9
100%	80.0 ± 7.4	83.3 ± 5.9	84.6 ± 4.8
End diastolic volume index (ml/m^2)			
Rest	45.5 ± 11.6	51.9 ± 4.3	56.9 ± 10.8
50%	51.7 ± 13.1	59.0 ± 7.1	65.7 ± 12.3
75%	53.0 ± 13.5 #	64.7 ± 7.3	72.8 ± 11.0
100%	54.1 ± 13.2 *#	68.6 ± 5.7	75.7 ± 11.4
End systolic volume index (ml/m^2)			
Rest	18.5 ± 3.0	15.9 ± 3.8	18.6 ± 6.8
50%	14.3 ± 4.4	13.8 ± 3.7	15.2 ± 5.9
75%	11.6 ± 4.2	12.6 ± 4.5	13.0 ± 5.1
100%	10.7 ± 4.4	11.7 ± 4.7	11.9 ± 5.1
Stroke volume index (ml/m^2)			
Rest	27.2 ± 9.1	36.0 ± 1.3	38.3 ± 5.0
50%	37.4 ± 11.9	45.2 ± 5.8	50.5 ± 9.8
75%	41.4 ± 11.6 #	52.1 ± 5.0	59.8 ± 8.2
100%	43.4 ± 11.6 #	56.9 ± 3.7	63.8 ± 8.3
Cardiac output index (L/min/m^2)			
Rest	2.5 ± 1.0	2.4 ± 0.6	2.6 ± 0.5
50%	4.6 ± 2.0	5.3 ± 1.1	6.9 ± 1.3
75%	5.8 ± 2.1 #	7.1 ± 1.3 #	9.5 ± 1.0
100%	6.7 ± 2.4 #	8.7 ± 1.3 #	11.6 ± 1.4
Effective arterial elastance index, EaI (mmHg/ml/m^2)			
Rest	4.21 ± 1.14 *#	2.92 ± 0.30	2.66 ± 0.33
50%	3.91 ± 0.92	3.50 ± 0.70	2.99 ± 0.81
75%	3.84 ± 1.04	3.33 ± 0.53	2.87 ± 0.54
100%	3.88 ± 1.03	3.40 ± 0.41	3.09 ± 0.50

	HTR (n=9)	RM (n=6)	DM (n=5)
End-systolic elastance index, EesI (mmHg/ml/m^2)			
Rest	6.02 ± 1.17	6.98 ± 1.79	5.88 ± 1.78
50%	10.69 ± 4.38	12.08 ± 4.69	10.90 ± 4.44
75%	15.25 ± 8.71	15.58 ± 7.20	14.45 ± 5.02
100%	18.41 ± 10.52	19.94 ± 10.51	18.13 ± 6.57
EaI/EesI			
Rest	0.72 ± 0.14 *#	0.44 ± 0.10	0.48 ± 0.13
50%	0.41 ± 0.17	0.31 ± 0.10	0.31 ± 0.11
75%	0.27 ± 0.10	0.24 ± 0.09	0.22 ± 0.07
100%	0.26 ± 0.11	0.21 ± 0.09	0.19 ± 0.07
Systemic vascular resistance index (dyne/sec/cm^5/m^2)			
Rest	3345 ± 909	3154 ± 648	2912 ± 526
50%	2108 ± 626 #	1703 ± 434	1250 ± 185
75%	1691 ± 529`#	1334 ± 252	965 ± 106
100%	1541 ± 506 #	1148 ± 198 #	855 ± 99

Table 5.2 Cardiovascular responses at rest and during incremental exercise

HTR, heart transplant recipient; RM, recipient age-matched control; DM, donor age-matched control. * $p<0.017$ vs. RM. # $p < 0.017$ vs. DM (Data are means ± SD).
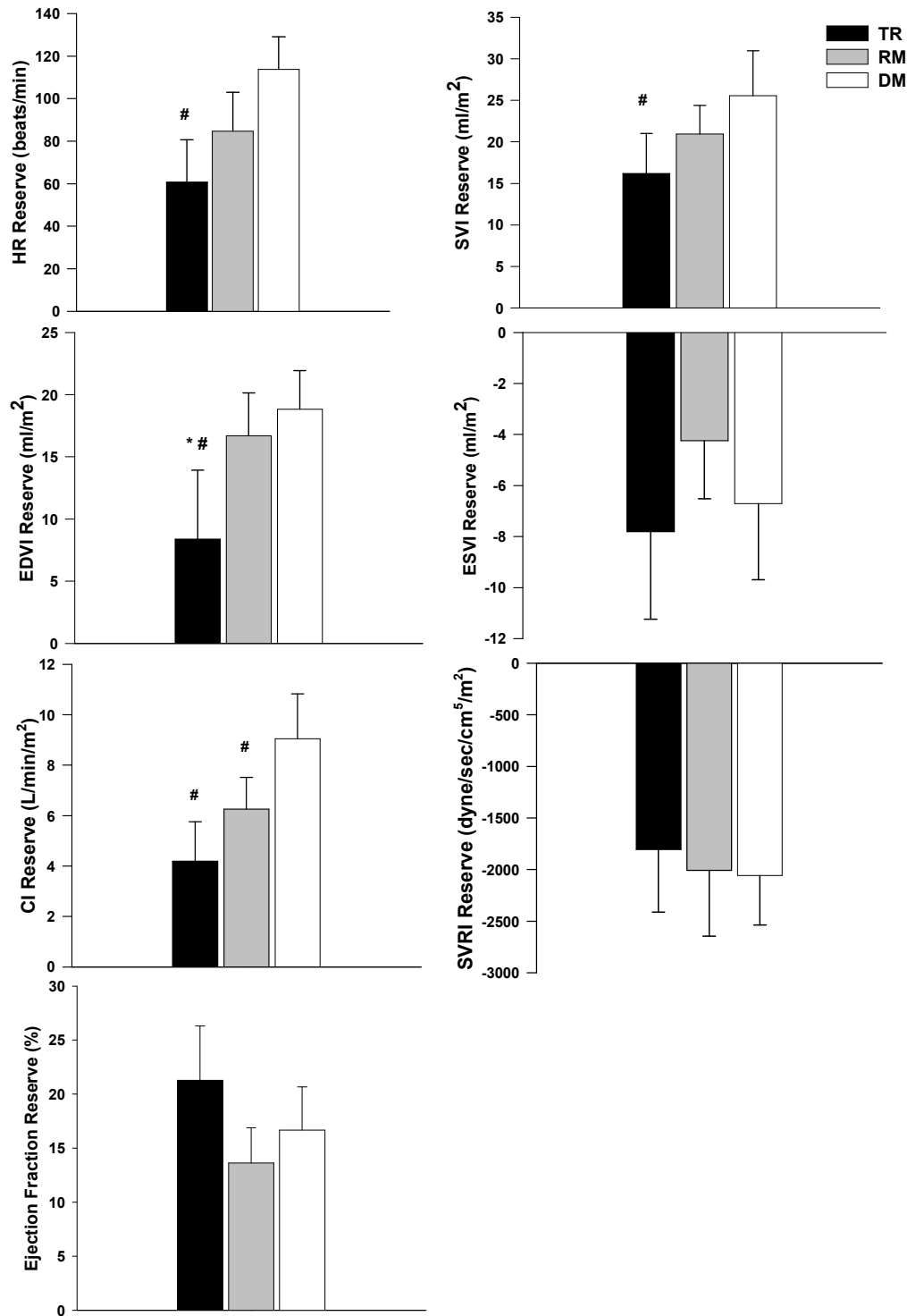
Figure 5.1 Cardiovascular function and reserve during incremental exercise
HR, heart rate; ESVI, end systolic volume index; EDVI, end diastolic volume index;
SVI, stroke volume index; CI, cardiac index; SVRI, systemic vascular resistance index;
EF, ejection fraction. * p<0.017 vs. RM. # p < 0.017 vs. DM (Data expressed as mean ±
SD).
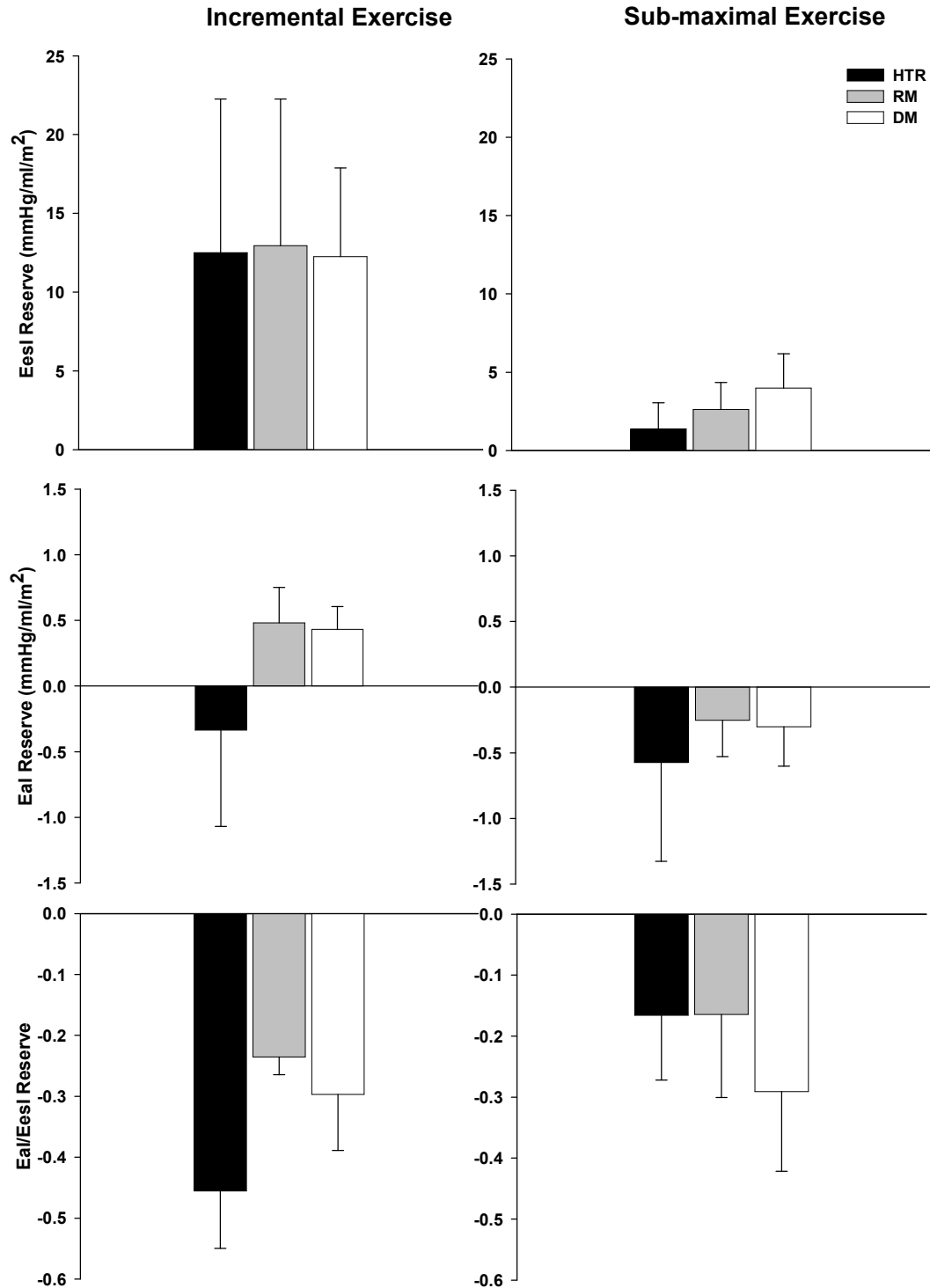
Figure 5.2 Ventricular-vascular coupling reserves during incremental and sustained sub-maximal exercise

EaI, arterial elastance index; EesI, ventricular elastance index; EaI/EesI, ventricular-vascular coupling ratio. * $p<0.017$ vs. RM. # $p < 0.017$ vs. DM (Data expressed as mean $\pm$ SD).

113
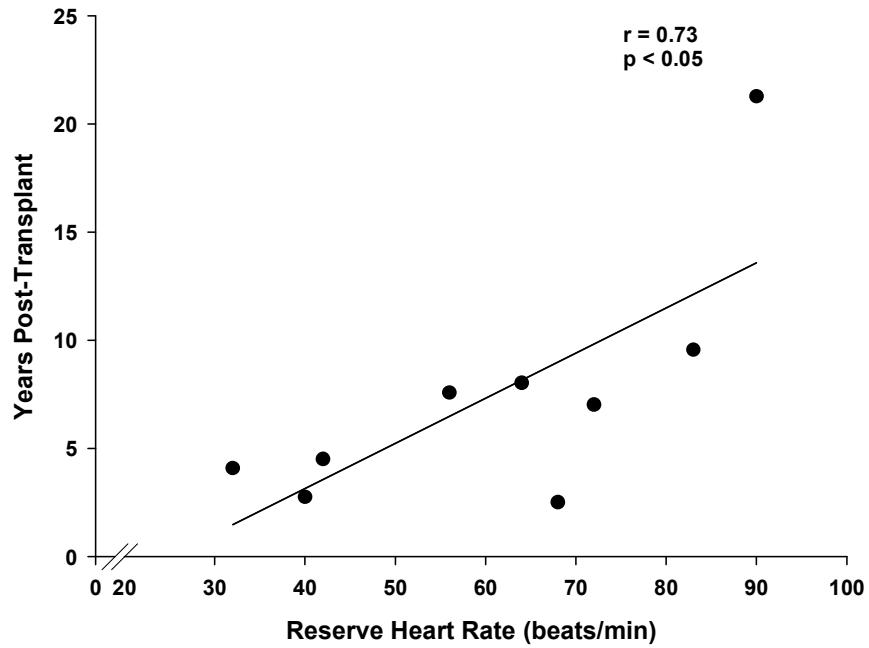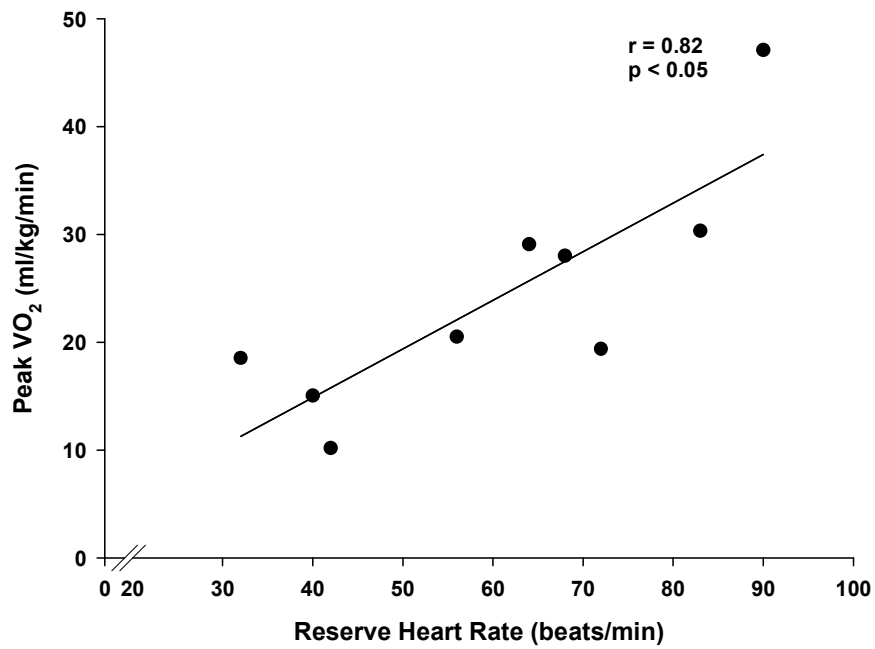
Figure 5.3 Heart rate reserve correlations in HTR
Relationship between heart rate reserve and years post-transplant (A); and heart rate reserve and peak VO_2 (B).
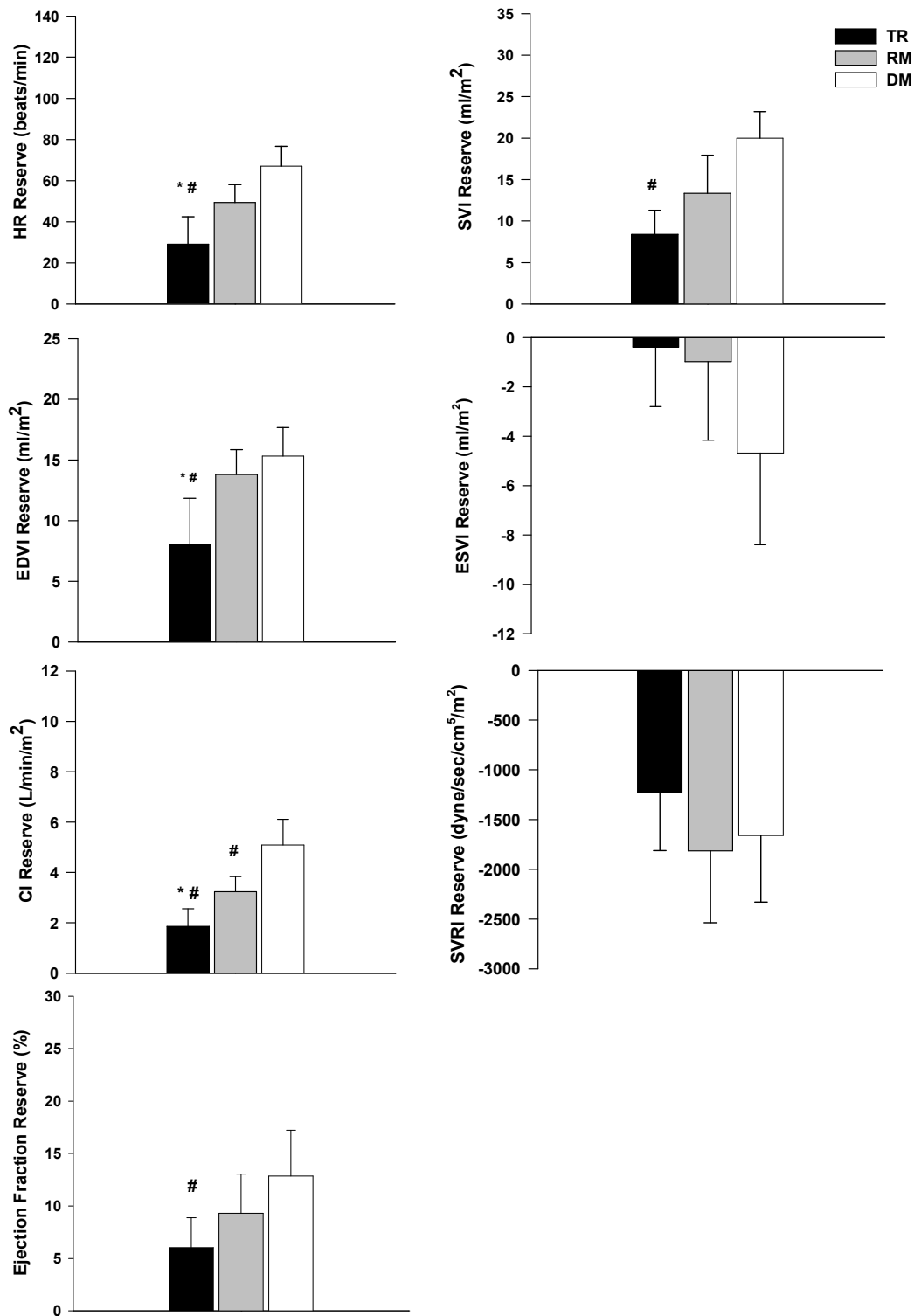
5.3.2 Sustained Sub-maximal Exercise

All participants successfully completed 1 h of sub-maximal exercise. Mean exercise VO_2 at 60 minutes corresponded to $85 \pm 8\%$ of ventilation threshold for all groups (HTR: $88 \pm 8\%$; RM: $82 \pm 7\%$; DM: $80 \pm 8\%$), and $60 \pm 9\%$ of VO_{2peak} (HTR: $65 \pm 8\%$; RM: $59 \pm 8\%$; DM: $53 \pm 7\%$). Cardiovascular function at rest and during sustained sub-maximal exercise is shown in Table 5.3. Resting values were not different from day 1 (incremental exercise). In each group, all variables were significantly higher at 30 and 60 minutes compared to rest except EaI, EaI/EesI, and SVRI, which were significantly lower. At 1 h of sustained exercise, SVI, CI and EF were lower and SVRI was significantly higher in HTR versus DM (Table 5.3). There were no significant differences between groups in sub-maximal reserve EaI, EesI, or EaI/EesI (Figure 5.2). Sub-maximal reserve HR, EDVI, and CI were significantly lower in HTR compared to RM and DM, while SVI and EF reserve were lower in HTR compared to DM (Figure 5.4). There were no significant changes in mass post-exercise in any group.

	HTR (n=9)	RM (n=6)	DM (n=5)
Heart rate (beats/min)			
Rest	91 ± 9.9 *#	67 ± 13.1	65 ± 10.1
30 min	120 ± 8.4	115 ± 8.4	128 ± 10.0
60 min	120 ± 8.6	118 ± 7.8	132 ± 8.8
Ejection Fraction (%)			
Rest	62.3 ± 5.3	67.4 ± 5.9	65.2 ± 4.6
30 min	69.9 ± 7.2	76.3 ± 3.9	76.8 ± 4.1
60 min	69.3 ± 6.1 #	75.5 ± 5.7	78.0 ± 3.0
End diastolic volume index (ml/m^2)			
Rest	45.5 ± 12.3	49.0 ± 3.5	57.0 ± 13.1
30 min	54.8 ± 15.0	62.5 ± 5.8	71.0 ± 15.6
60 min	53.5 ± 13.8 #	62.8 ± 3.5	70.4 ± 8.7
End systolic volume index (ml/m^2)			
Rest	16.8 ± 3.8	16.5 ± 3.4	20.7 ± 7.0
30 min	16.4 ± 6.4	14.9 ± 3.5	16.7 ± 5.7
60 min	16.4 ± 5.4	15.5 ± 4.4	16.1 ± 4.6
Stroke volume index (ml/m^2)			
Rest	28.7 ± 9.7	34.0 ± 3.9	36.3 ± 7.4
30 min	38.4 ± 11.2	47.6 ± 3.5	54.3 ± 10.7
60 min	37.1 ± 10.1 #	47.3 ± 2.0	56.3 ± 9.0
Cardiac output index (L/min/m^2)			
Rest	2.6 ± 1.1	2.3 ± 0.5	2.3 ± 0.4
30 min	4.6 ± 1.6	5.5 ± 0.7	6.9 ± 1.2
60 min	4.5 ± 1.5 #	5.5 ± 0.4 #	7.4 ± 1.1
Effective arterial elastance index, EaI (mmHg/ml/m^2)			
Rest	4.06 ± 1.28 *#	3.11 ± 0.26	2.81 ± 0.60
30 min	3.31 ± 0.87	2.77 ± 0.27	2.63 ± 0.54
60 min	3.26 ± 0.90	2.85 ± 0.23	2.51 ± 0.46
End-systolic elastance index, EesI (mmHg/ml/m^2)			
Rest	6.35 ± 1.72	6.59 ± 1.51	5.13 ± 1.43
30 min	8.15 ± 2.97	9.22 ± 2.41	8.96 ± 2.64
60 min	7.73 ± 2.84	9.22 ± 2.33	9.12 ± 2.40
EaI/EesI			
Rest	0.62 ± 0.16 *#	0.49 ± 0.14	0.51 ± 0.11
30 min	0.44 ± 0.15	0.31 ± 0.07	0.31 ± 0.07
60 min	0.45 ± 0.13	0.33 ± 0.10	0.28 ± 0.05
Systemic vascular resistance index (dyne/sec/cm^5/m^2)			
Rest	3045 ± 1018	3227 ± 667	2622 ± 903
30 min	1824 ± 537 #	1453 ± 184 #	1059 ± 330
60 min	1821 ± 535 #	1412 ± 161 #	964 ± 277

Table 5.3 Cardiovascular responses at rest and during sustained exercise

HTR, heart transplant recipient; RM, recipient age-matched control; DM, donor age-matched control. * p<0.017 vs. RM. # p < 0.017 vs. DM (Data are means ± SD).

Figure 5.4 Cardiovascular Function and Reserve during Sustained Sub-maximal Exercise

HR, heart rate; ESVI, end systolic volume index; EDVI, end diastolic volume index; SVI, stroke volume index; CI, cardiac index; SVRI, systemic vascular resistance index; EF, ejection fraction. * p<0.017 vs. RM. # p < 0.017 vs. DM (Data expressed as mean ± SD).

117

5.3.3 Ventricular-vascular Coupling and Oxygen Consumption

In all groups, a significant inverse linear relationship between EaI/EesI and VO_2 was observed (Figure 5.5).
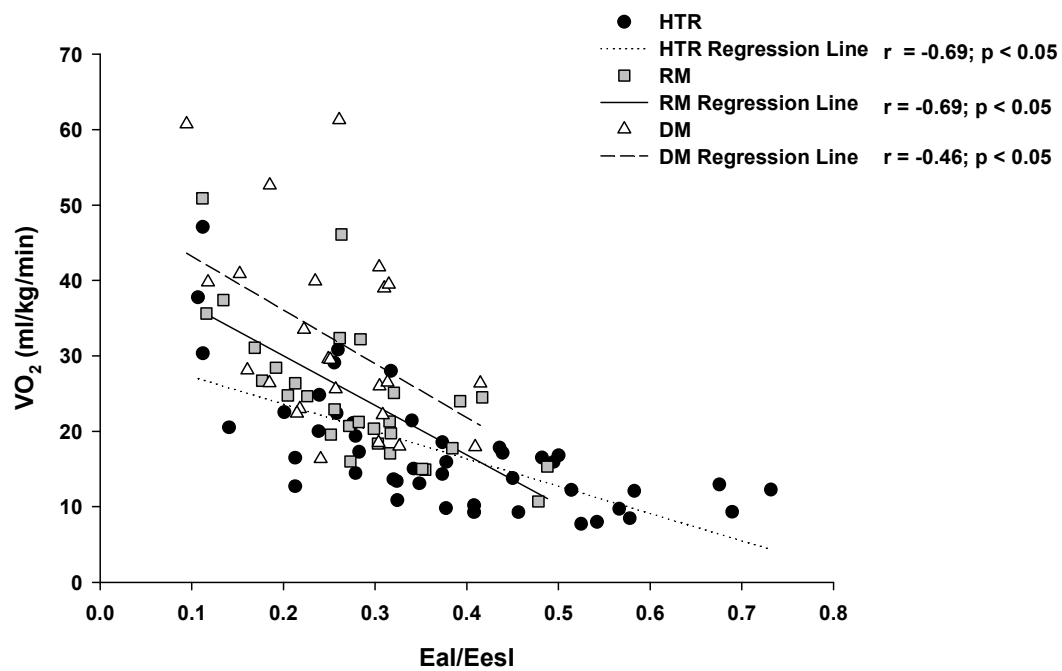
Figure 5.5 Relationship between VO$_2$ and Ventricular-Vascular Coupling

5.4 Discussion

To our knowledge, this study is the first to examine the cardiovascular responses to incremental and prolonged sustained exercise in HTR in comparison to DM and RM controls. The major new findings of this investigation are: 1) during incremental exercise, the lower peak and reserve CI observed in HTR compared to DM is due to a lower peak and reserve HR and EDVI, and higher peak SVRI; in contrast, the decreased peak and reserve CI in HTR versus RM is primarily due to a reduced peak and reserve EDVI; 2) in HTR, the contribution of preload, systolic volume reserve and vascular reserve was limited during sustained sub-maximal exercise; 3) the abnormal peak VO_2 found in HTR is due, in part, to impaired ventricular-vascular coupling.

5.4.1 Cardiovascular Responses to Incremental Exercise in HTR

Kao and colleagues (20, 21), using invasive hemodynamic, radionuclide angiography and expired gas analysis, demonstrated that the reduced peak VO_2 in HTR compared with age-matched controls was primarily due to a lower peak CI. In turn, the blunted peak CI was the result of a lower peak HR and EDVI, as EF was similar between HTR and controls. Our data confirm and extend these findings by demonstrating that despite preserved peak and reserve EF, the peak VO_2 of HTR remains 33% and 53% lower than RM and DM, respectively. When compared to DM subjects, the reduced peak CI in HTR was secondary to a blunted peak and reserve HR and EDVI. However, in contrast to Kao et al. (20, 21), we found that the lower CI in HTR versus RM ($p > 0.017$), was primarily due to a lower peak and reserve EDVI and not a consequence of a blunted HR response (which was similar in these groups).

The divergent exercise HR response we found compared to others (14, 20, 21, 23) may

be due to the length of time post-transplant and subsequent partial cardiac reinnervation,

or to differences in fitness levels of study participants. In our study, the average time

post-transplant was 8 ± 6 years compared to 29.4 ± 24.4 weeks (23), 9 ± 4 months (21),

and 41 ± 8 months (14) for HTR in other studies. A number of studies have reported

partial and non-uniform sympathetic reinnervation of the allograft one to eight years after

transplantation (2, 12, 50). Given that 8 out of 9 of our HTR demonstrated functional

evidence of cardiac reinnervation (i.e. >36 beats/min increase in exercise HR, Figure 5.3

A) (38, 48), this may account for the similar peak HR between HTR and RM groups.

Also, the fact that HTR may only have partial and non-uniform reinnervation (2) could

explain why HTR have a significantly lower peak HR compared to the DM group.

A second contributing factor related to HR responsiveness may be underlying

differences in fitness of HTR between studies. Pokan et al. (38) examined the effects of

high volume and intensity endurance training in HTR, and, similar to our findings,

reported that the peak HR of trained reinnervated HTR was not significantly different

than healthy controls. Notably, they also demonstrated that the peak HR of sedentary

reinnervated HTR was significantly lower than that of healthy age-matched controls (142

± 10 vs. 164 ± 17 beats/min) (38). The HTR in our study were more aerobically fit than

those in the Kao et al. study (21) (peak VO_2: 24.2 ± 10.9 vs. 12.3 ± 3.5 mL/kg/min

respectively), and in fact, were as fit as the previous study's healthy age-matched

controls (22.9 ± 4.0 mL/kg/min). We additionally found that HR reserve was correlated

with peak VO_2 in HTR (Figure 5.3 B; $p < 0.05$). Taken together, these results suggest

that time post-transplant and exercise training could be major factors contributing to reinnervation, and consequently improvements in cardiovascular performance.

A second main finding of this study was that the reduced CI during incremental or sustained sub-maximal exercise, in HTR versus RM and DM controls, was due to impaired peak and reserve EDVI (Table 5.2; Figure 5.3). Previous investigators have demonstrated that cardiac allograft diastolic dysfunction is not associated with the number of rejection episodes, immunosuppressive medication or the interval post-transplant (15, 18, 44). We also found that EDVI reserve was not related to time post-transplant (r = -0.15, p > 0.05), suggesting that other mechanisms may contribute to diastolic impairments. As previously mentioned, it appears that the majority of our HTR were functionally reinnervated. Thus, if sympathetic reinnervation is regionally heterogeneous (2, 3), adrenergic stimulation of the left ventricle through neural release of catecholamines may also be non-uniform. This non-uniformity has been shown to slow left ventricular relaxation, as select infusion of isoproterenol in the mid-left anterior descending coronary artery increased the time constant of isovolumic left ventricular pressure fall (28). Limited reinnervation could also result in alterations in cardiac calcium homeostasis. Paulus et al. (37) observed a slow relaxation with downward convexity of the dP/dt signal in the cardiac allograft after postextrasystolic potentiation with nitroprusside infusion, which could be due to delayed sarcoplasmic reticulum calcium reuptake (29), alterations in myocardial calcium sensitivity (11), or decreased SERCA2a expression (42). In order to understand why diastolic volume is so impaired during exercise in HTR compared to both RM and DM groups, future investigations should address the issue of heterogeneous reinnervation and abnormal lucitropy in HTR.

The blunted peak exercise and reserve CI in HTR could also be due to an increased

afterload associated with pre- and post-transplant vascular dysfunction. Indeed, Scherrer

et al. (39) demonstrated that cyclosporine therapy is associated with sympathetic neural

activation, and plays a key role in the damage of microvasculature leading to

hypertension. Milani et al. (33) also reported that compared to patients with

uncomplicated hypertension and normal controls at rest, HTR demonstrated significantly

elevated Ea and Ea/Ees. Consistent with this, we found that HTR had significantly higher

EaI compared to RM and DM groups at rest (+44% and +58% respectively, $p<0.017$),

resulting in significantly elevated EaI/EesI (+27% vs. RM and +41% vs. DM, $p<0.017$).

These vascular abnormalities apparent at rest are also present during exercise. Supporting

previous findings (20, 21), we found that peak SVRI was higher (34% vs. RM; $p>0.017$,

and 80% vs. DM, $p<0.017$) and reserve SVRI was lower (10% and 12%, $p>0.017$) in

HTR compared to RM and DM groups respectively. Additionally, whereas RM and DM

groups increased EaI in a typical response during incremental exercise (10), HTR had an

abnormal response and decreased EaI (Table 5.2). Given that HTR and the RM group

achieved the same maximal HR, the decrease in EaI in HTR was not due to chronotropic

incompetence. Previous investigations have demonstrated impaired blood pressure

responses to maximal exercise in HTR (6, 20, 21), and it is likely that the observed

decrease in EaI was due to a disproportionate increase in SVI versus ESP. This is

supported by the fact that EaI also decreased during sustained sub-maximal exercise in

all three groups when blood pressures were lower (Figure 5.2). Taken together, these

findings suggest that the lower peak VO_2 in HTR may be secondary to an impaired CI

and vascular abnormalities, resulting in a reduction of oxygen delivery to exercising muscles.

5.4.2 Cardiovascular Responses to Sustained Sub-maximal Exercise in HTR

The cardiovascular responses noted above are also limiting during sustained sub-maximal exercise in HTR. However, in sharp contrast to incremental exercise, HTR demonstrated diverse LV volume and EF responses during sustained sub-maximal exercise compared to DM and RM controls. Of note, HTR reached the same EDVI and sub-maximal reserve found at peak exercise when exercising at 80% of ventilatory threshold, a response that was not fully compensated for by changes in ESVI, HR, or EF. Several reasons could account for the differential responses between exercise protocols. First, HTR were working at a lower absolute workload compared to DM and RM controls. However, HTR were able to decrease ESVI and increase EF during incremental exercise despite reaching a lower absolute workload. Furthermore, because all groups exercised at an identical percent of their ventilatory threshold by study design, the blunted HR, ESVI and EF response in HTR is not explicable by a lesser relative effort. Second, it is possible that HTR rely on relatively greater increases in plasma catecholamines in order to decrease ESVI and augment EF and HR during sustained sub-maximal exercise. Previous investigations (5, 6) have reported that plasma norepinepherine levels were not different between HTR and controls at 40% of peak power output, but were significantly higher in HTR during exercise at 70% of peak power output and at peak exercise. Our participants were exercising at approximately 40% of peak power output throughout sustained sub-maximal exercise, and HTR may consequently not have achieved the "critical point" in catecholamine concentration

necessary to decrease ESVI and increase EF and HR. Finally, an increased vascular load could also contribute to lower systolic function in HTR during sub-maximal exercise. Exercise SVRI was higher in HTR compared to RM ($p>0.017$) and DM ($p<0.017$) groups during sustained exercise, which would increase ESVI and decrease SVI. Taken together, these results suggest that HTR were reliant on the Frank-Starling mechanism to enhance exercise cardiac performance during sustained sub-maximal exercise.

5.4.3 Ventricular-vascular coupling and oxygen uptake in HTR

Although the importance of central and peripheral limitations to peak VO_2 has been described in detail (19-21), few studies have examined the impact of ventricular-vascular coupling on exercise capacity. Najjar et al. (35) examined the association between VO_2 and ventricular-vascular coupling in men and women and found no significant associations between peak VO_2 and EaI, EesI, and EaI/EesI. In contrast, given our findings of an inverse linear relationship between VO_2 and EaI/EesI in all groups ($p < 0.05$), our results suggest that coupling of ventricular and vascular properties may be an important aspect in exercise tolerance.

5.4.4 Clinical Implications

Our investigation demonstrated that HTR have decreased ESVI reserve and vascular reserve during sustained sub-maximal exercise compared to incremental to peak exercise. Considering that the overall duration of aerobic exercise incorporated in most cardiac rehabilitation programs is approximately 1 h at sub-maximal intensities (22), alternate exercise therapies may be of significant benefit for improving functional capacity in HTR. High intensity interval exercise training has recently been shown to significantly improve exercise performance in HTR to levels comparable to, or even exceeding, values

of sedentary or moderately trained healthy subjects (38). Thus, high intensity exercise may be essential for achieving the critical concentration of catecholamines (5, 6) necessary to augment HR, EesI and EF. Additionally, given the impaired resting and exercise EaI and SVRI found in HTR, therapies which target the vasculature such as minor muscle mass training and/or interval training would allow for close to maximal skeletal muscle work with beneficial peripheral adaptations (47). Taken together, these forms of exercise training could improve ventricular-vascular coupling in HTR, a limitation to exercise tolerance confirmed in the present study.

5.5 Limitations

This study must be examined in the light of several potential limitations. First, although we did not assess catecholamines, several other investigations have reported the catecholamine response to sub-maximal and peak exercise in HTR (5, 6). Second, because the current study included only men, our findings cannot be generalized to women. Prior studies have demonstrated gender differences in the cardiovascular response during cycle exercise (17, 35). Third, using 2-D ultrasound to quantify ventricular volumes has its limitations; however, it has previously been used for volume measurement during sub-maximal and maximal exercise in numerous populations (16, 36, 41). This technique was additionally applied across all groups, making any errors systematic in nature. Finally, we used the functional consequences of reinnervation (HR response to exercise) to infer reinnervation. This technique assesses sympathetic reinnervation only, and autonomic regulation involving both parasympathetic and sympathetic innervation may be more accurately inferred from dobutamine stress testing with atropine (26). Additionally, there is direct evidence that reinnervation of the heart

occurs after transplantation in animals (34), and there is growing evidence from clinical (40), physiological (3, 8), and biochemical (2, 24) studies in humans that partial reinnervation may occur at least one year after transplantation.

5.6 Conclusions

Heart transplant recipients have a severe and marked reduction in peak VO_2 and peak CI when compared to DM controls, which is primarily due to blunted HR and EDVI. In contrast, when comparing fitness matched HTR and RM controls, CI is not limited by peak HR, but is primarily reduced due to blunted EDVI. Further, unlike during incremental exercise where HTR were able to increase SVI and EF by catecholamine induced increases in systolic function (6), during sustained sub-maximal exercise HTR exhausted their preload reserve and did not compensate with changes in ESVI, HR or EF. Finally, the coupling of ventricular and vascular properties is an important aspect in determining aerobic performance in HTR.

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CHAPTER SIX: General Summary and Conclusions

A growing body of evidence suggests that acute exercise may induce a transient reduction in ventricular function (13). As was noted in Chapter Two, recent scientific and media interest in this issue has led to an increased awareness and heightened concern in endurance athletes, coaches, scientists and clinicians alike. Consequently, the focus of this manuscript was to examine ventricular function during and following acute exercise in a variety of subjects. Specifically, this series of studies comprehensively investigated the cardiovascular consequences of acute exercise in ET and NA individuals, as well as HTR.

As discussed in Chapter Three, the increasing popularity of extreme endurance exercise highlights the need for a clear understanding of the cardiovascular consequences associated with such races. The studies which have previously examined cardiovascular function following ultra-endurance events (16, 17) were conducted over 20 years ago and utilised only global measures of LV function. Newer techniques such as speckle tracking assessment of tissue strain and strain rates provide a much more sensitive and accurate assessment of both regional and global LV function. Accordingly, the cardiovascular consequences of ultra-endurance exercise (25.5 ± 3.2 hours) were examined using traditional echocardiography, speckle tracking imaging, cardiac biomarkers and HRV. Confirming previous investigations (16, 17), the results presented in Chapter Three reveal a significant reduction in both LV systolic and diastolic function post-race using standard two dimensional echocardiography measures. Relatively few athletes demonstrated increases in cTnT following the race but there was a significant increase in plasma NT-pro-BNP in all athletes. Finally, in contrast with several recent studies (10,

15) the echocardiographic evidence of decreases in LV function were neither associated with alterations in cardiac biomarkers, nor with cardiac autonomic regulation. These results suggest that extraordinarily prolonged duration may be pivotal in the development of decreases in LV function. However, the importance of exercise intensity on the development of decreases in ventricular function requires further research.

The investigation presented in Chapter Four addresses the aforementioned issue of exercise intensity on the development of cardiac fatigue in ET and NA individuals. This investigation was the first study to examine the acute effects of brief (14 min), high intensity interval exercise on biventricular systolic and diastolic function using cMRI in ET and NA individuals. Results from this study revealed that biventricular systolic and diastolic dysfunction occur following 14 min of high intensity exercise in ET athletes, a phenomenon which is not observed in NA individuals. While further research is required to elucidate the mechanisms contributing to the observed differences, these findings suggest that the myocardial response of ET individuals to high intensity exercise is altered as a consequence of chronic exercise training.

Although Chapters Three and Four clarify the significance of exercise duration and intensity on the development of cardiac fatigue, little information exists regarding the consequences of acute exercise in clinical populations. Heart transplantation is a life-saving intervention for select individuals with end-stage refractory heart failure. Despite normal LV systolic function after surgery, HTR peak oxygen consumption remains 40 – 60% lower than age-matched healthy individuals (3, 4, 7, 9). A limitation of previous investigations examining exercise performance in HTR is the primary focus on incremental to peak aerobic exercise responses (6, 7). Although incremental exercise

tests provide important information regarding the maximal capacity of cardiac and vascular function, they are neither directly applicable to the typical sub-maximal sustained activities of everyday living, nor do they take into account the fact that the overall duration of exercise incorporated in most cardiac rehabilitation programs is approximately 1 h (8). Given that few HTR exercise at maximal intensities, it is particularly important to expand the understanding of preload, heart rate, and vascular responses to sustained sub-maximal exercise in this population. An additional limitation is that cardiovascular performance has only been compared between HTR and healthy individuals matched to the recipient age (1, 2, 7, 12, 14). Since the mean donor age is nearly two decades lower than the recipient age (18), the interaction of the heart with the systemic vasculature (ventricular-vascular coupling) may be a significant determinant of cardiovascular exercise performance. Results presented in Chapter Five demonstrate that HTR are limited by impaired preload reserve, heart rate reserve and impaired vascular reserve during exercise conditions. These findings suggest that although the overall duration of aerobic exercise incorporated in most cardiac rehabilitation programs is approximately 1 h at sub-maximal intensities (22), alternate exercise therapies may be of significant benefit for improving functional capacity in HTR. Indeed, as illustrated in Chapter Four, given that high intensity exercise does not cause alterations in NA individuals, this type of activity may be beneficial for HTR. High intensity interval exercise training has recently been shown to significantly improve exercise performance in HTR to levels comparable to, or even exceeding, values of sedentary or moderately trained healthy subjects (38). Thus, high intensity exercise may be essential for achieving the critical concentration of catecholamines (5, 6) necessary to augment heart rate and

ejection fraction. Additionally, therapies which target the vasculature such as minor muscle mass training and/or interval training would allow for close to maximal skeletal muscle work with beneficial peripheral adaptations (47). Taken together, these forms of exercise training could improve ventricular-vascular coupling in HTR, a limitation to exercise tolerance confirmed by the results presented in Chapter Five.

6.1 Future Research

There is significant scope for future research in the area of cardiovascular responses to acute exercise. For example, there has been no structured approach to the assessment of the impact of exercise mode on cardiac fatigue. Given the fact that different exercise modes may place different hemodynamic loads upon the RV and LV, further research is warranted in this area. As illustrated in Chapter Four, an acute bout of interval exercise does not result in decreases in ventricular function in normally active individuals. However, the impact of prolonged exercise in normally active individuals is far from clear. The study of mechanisms underlying cardiac fatigue is the least explored area, and future research in this area will likely have a significant impact on our understanding of the clinical significance of cardiac fatigue. A particularly intriguing topic to pursue is the possibility of alterations in myocardial metabolism during exercise. There is also scope for broadening research interests to include topics such as elevated free radicals (19) and potassium (11) concentrations and their impact on ventricular function. Finally, the clinical impact of these reductions in ventricular function requires greater analysis. The consequences of repeated exposure to high intensity or prolonged endurance activities over many years are as yet undetermined, and may result in myocardial scarring (5). In order to expand the knowledge base of cardiovascular responses to exercise, and to

further understand the mechanisms of cardiac fatigue, additional study of this area is

clearly warranted.

6.2 Chapter Six References

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Appendix A: Ethics Certificate of Approval

The University of British Columbia
Office of Research Services
Clinical Research Ethics Board – Room
210, 828 West 10th Avenue, Vancouver,
BC V5Z 1L8

ETHICS CERTIFICATE OF EXPEDITED APPROVAL: RENEWAL

PRINCIPAL INVESTIGATOR:	DEPARTMENT:	UBC CREB NUMBER:
Darren Warburton	UBC/Education/Human Kinetics	H08-00607

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:	
Institution	Site
UBC	Vancouver (excludes UBC Hospital)
N/A	N/A

Other locations where the research will be conducted:
The data will be collected in Squaw Valley, California, and analyzed at the University of British Columbia.

CO-INVESTIGATOR(S):
N/A

SPONSORING AGENCIES:
- UBC Faculty of Education - "Jessica Scott: The effects of prolonged exercise on cardiovascular function in masters athletes"

PROJECT TITLE:
The effects of prolonged exercise on cardiovascular function in masters athletes: Can an old heart cope?

EXPIRY DATE OF THIS APPROVAL: April 17, 2010

APPROVAL DATE: April 17, 2009

CERTIFICATION:

In respect of clinical trials:
1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.
2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.
3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

The Chair of the UBC Clinical Research Ethics Board has reviewed the documentation for the above

named project. The research study, as presented in the documentation, was found to be acceptable on

ethical grounds for research involving human subjects and was approved for renewal by the UBC Clinical
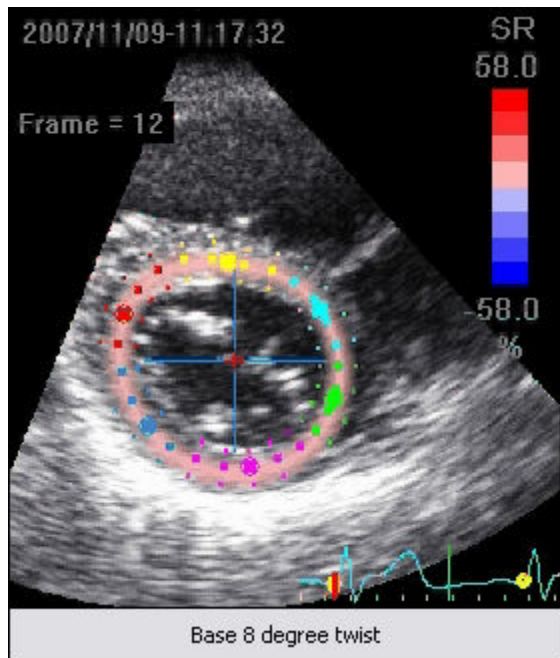
Research Ethics Board.

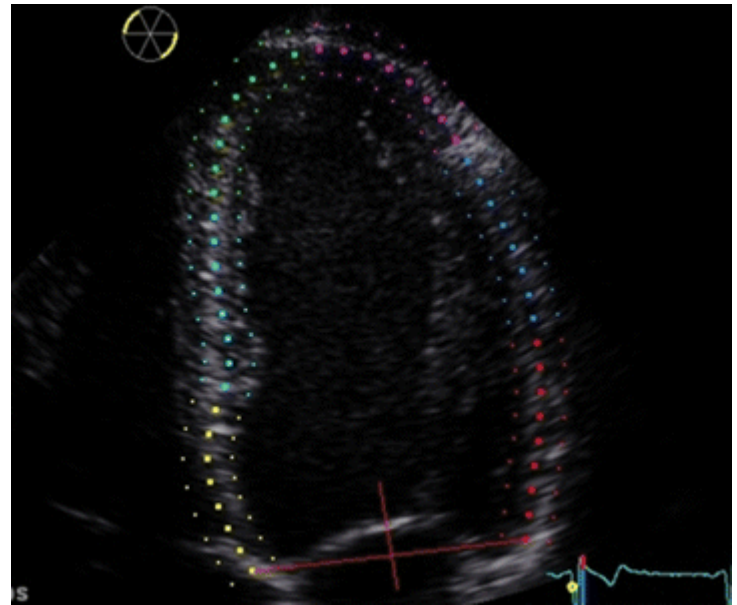*Approval of the Clinical Research Ethics Board by :*

**Dr. Stephen
Hoption Cann ,
Associate Chair**

**Appendix B: Speckle Tracking Imaging**

A.

B.

Figure B.1 Measurement of ventricular strain by speckle tracking imaging
A) Radial and circumferential strain data were derived from a parasternal short axis view
imaged at the basal level; B) Longitudinal strain was derived from an apical view. The
focal point was positioned at the level of the mitral valve. In both orientations frame rates
were maximised (>40 and <90 frames per second).

Appendix C: Cardiac Magnetic Resonance Imaging

A.

B.
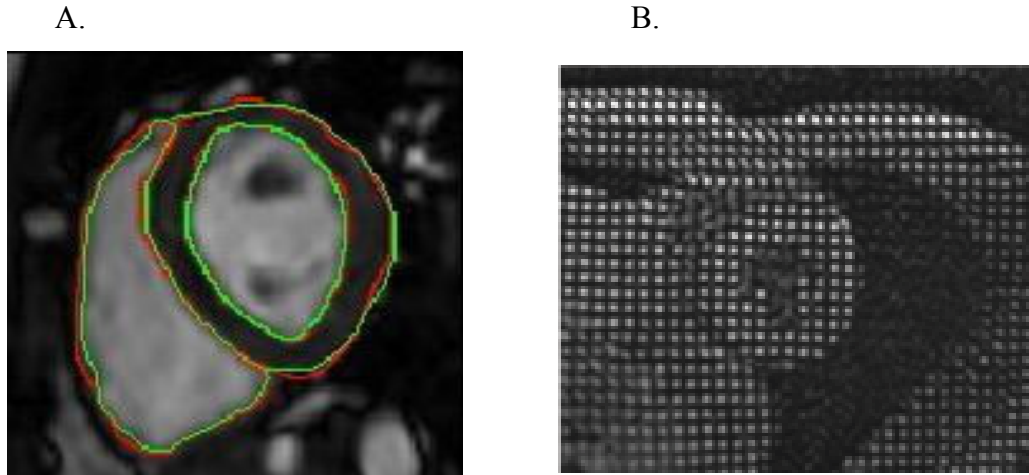
Figure C.1 Measurement of ventricular volumes and strains by cMRI
A) Assessment of LV and RV volumes was performed by manual segmentation of short-axis cine images at end diastole and end systole; B) Assessment of rotation, torsion and circumferential strain was performed using a custom designed software package.