University of Alberta

Regulation of Oxygen Uptake and Cardiac Function in Heart Failure:
Effects of Biventricular Pacing and High-Intensity Interval Exercise

by

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Dedication

To the participants and their families who gave so generously of their precious time for these studies.

Abstract

Cardiac resynchronization therapy (CRT) and high-intensity interval training (HIT) have been shown to be effective for left ventricular (LV) reverse remodelling and increasing aerobic capacity in patients with heart failure (HF) and reduced ejection fraction (EF). The mechanisms underlying these benefits are not well understood. Accordingly, the purpose of the first study (Chapter 2) was to investigate the effects of CRT on oxygen uptake ($\dot{V}O_2$) kinetics and exercise LV function during the transition to moderate-intensity exercise. The first study showed that *1)* CRT led to a significant speeding in $\dot{V}O_2$ kinetics, *2)* stroke volume during steady-state exercise increased due to a decrease in submaximal exercise LV ESV independent of cardiac preload, and *3)* CRT resulted in faster heart rate kinetics, suggesting that autonomic control of heart rate during exercise changed with CRT. The purpose of the second study (Chapter 3) was to examine the CRT mediated improvements in peak exercise LV function, peak $\dot{V}O_2$, and recovery from peak exercise. The second study showed that *1)* CRT increased reserve and peak cardiac output, *2)* CRT increased $\dot{V}O_2$ at peak exercise and this was related to an increase in cardiac output reserve that was secondary to an increase in LV end-systolic volume (ESV) reserve and preserved cardiac preload, *3)* CRT decreased the time to exercise recovery as measured by a speeding in gas exchange and ventilation kinetics post-exercise, and *4)* faster post-exercise $\dot{V}O_2$ kinetics were associated with greater aerobic capacity. The purpose of the third study (Chapter 4) was to assess biventricular function prior to, and immediately following acute HIT. The third study showed that biventricular ESV decreased and LV systolic annular velocity increased immediately following acute HIT. Within 30 min of exercise termination, LV EF was significantly increased compared

to pre-exercise values. Diastolic function immediately following acute HIT was also preserved secondary to increased LV recoil. Collectively, the findings of these studies show that patients with HF and reduced EF are able to increase metabolic reserve (evidenced by a speeding in $\dot{V}O_2$ kinetics) following CRT, and that interventions such as CRT and HIT are effective in reducing (chronically and acutely) LV ESV during and following exercise.

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Chapter 1

Introduction

1.1 Introduction and Purpose

Heart failure (HF) afflicts approximately 500,000 Canadians with 50,000 newly reported cases annually (1). Additionally, HF is the most frequent cause of hospitalization in those over 65 yrs of age (52, 105) and is associated with disproportionate health care spending (67). The Framingham Heart Study has shown that patients with HF may have a less than 50% 5-yr survival rate following initial diagnosis (57). Among several important prognosticators that may influence this statistic are exercise capacity and severity of ventricular remodeling. In addition to survival, HF treatments often target these important end-points in clinical trials.

Following-up on landmark pharmacologic trials (36, 56, 68, 98) for treating HF with reduced ejection fraction (EF) the past decade has yielded two important shifts in the potential for managing and rehabilitating HF patients with non-pharmacologic means. The first, cardiac resynchronization therapy (CRT) with a biventricular pacemaker has evolved to be a proven approach for improving HF symptoms, left ventricular (LV) systolic function, exercise capacity, and survival in select patients. The second, high-intensity interval training (HIT) has more recently emerged as a form of cardiac rehabilitation that may yield greater ventricular and vascular reverse remodeling and exercise capacity benefits when compared to the current standard of continuous aerobic exercise training (28, 74, 114). However, little remains known about the mechanistic basis for improvements in exercise ventricular function and exercise performance associated with CRT and HIT.

The purpose of this thesis was to *1)* study the regulation of exercise LV function and pulmonary oxygen uptake ($\dot{V}O_2$) in HF patients with CRT, and *2)* study the effects of acute HIT on post-exercise biventricular function in patients with HF. Towards this end, Chapter 1 discusses factors affecting $\dot{V}O_2$ adaptation in HF, the effects of CRT on LV function and exercise capacity in HF, and the effects of HIT on LV function in HF. Chapter 1 concludes with specific investigational hypotheses that correspond to the subsequent studies in Chapters 2, 3, and 4.

1.2 Factors Affecting $\dot{V}O_2$ in Heart Failure

Following a square-wave increase to an exercise intensity that is below the gas exchange ventilatory threshold (*i.e.*, moderate-intensity exercise), phase II $\dot{V}O_2$ measured at the mouth adapts in an exponential manner that can be characterized by a first-order mathematical model. The resultant time constant (τ) of a significant portion of the response (phase II) reflects the rate of muscle O_2 uptake throughout the exercise transient (non-steady-state period) and is a non-invasive measure of the rate of readjustment in oxidative phosphorylation to match newly required adenosine triphosphate demands in the skeletal muscle (110). Progressively slower $\dot{V}O_2$ kinetics results in a greater O_2 deficit that increases lactate production and hydrogen ions, leading to premature or exacerbated exercise fatigue. Patients with HF demonstrate a progressive slowing in $\dot{V}O_2$ kinetics at exercise onset and following exercise with worsening HF severity (14, 19, 88), and this is reflected by progressively diminished exercise capacity and increased post-exercise fatigue.

1.2.1 Evidence for Muscle Metabolic Limitations

In 1940, an experiment by Hill (43) showed in *ex vivo* frog sartorius muscle that O_2 uptake increases exponentially with electric stimulation and decreases exponentially following its removal. Hill (43) speculated in their interpretation of this observation that the (maximal) rate of muscle O_2 uptake reflected that of oxidative metabolism and that phosphocreatine (PCr) played an important role in determining this rate. Later, using *in situ* canine gastrocnemius preparations, Piiper et al. (80) demonstrated that PCr concentration ([PCr]) indeed decreased with increasing muscle O_2 uptake and O_2 deficit following square-wave muscle stimulation. Several studies since have confirmed and extended the earlier work of Hill (43) and Piiper et al. (80) in models of *in situ* rat gastrocnemius-plantaris preparations using ^{31}P-magnetic resonance spectroscopy (69), and during planter flexion (66) and knee extension exercise (90) in humans. Noteworthy is the study by Rossiter et al. (89) where simultaneous assessment of $\dot{V}O_2$ (36 ± 17 s) and [PCr] kinetics (35 ± 15 s) revealed a tight coupling between these two parameters. Thompson et al. (107) showed that PCr kinetics were delayed following nerve stimulation in a HF rat model, and this has been replicated in humans with HF (19). A reduction in skeletal muscle mass and enzyme activity, and a shift in muscle fiber type in patients with HF (25, 62, 103) may manifest as a greater and faster depletion of PCr during exercise (63, 75), subsequently prolonging $\dot{V}O_2$ kinetics. In addition, a consequence of the reduction in type I muscle fibers is an associated decline in mitochondrial density and oxidative capacity (citrate synthase) (8), which has also been linked to impaired $\dot{V}O_2$ kinetics (79, 83, 84). Cumulatively, these studies suggest that

oxidative adenosine triphosphate production and muscle O_2 uptake may be regulated, in part, by PCr.

Further supporting the impact of muscle metabolic limitations to $\dot{V}O_2$, some have shown that blood flow may not limit $\dot{V}O_2$ kinetics. This is best exemplified by the work of Grassi and colleagues (33) with their findings that muscle O_2 uptake kinetics were not affected by varying perfusion (O_2 delivery) rates during isolated *in situ* canine gastrocnemius stimulation, suggesting that muscle O_2 uptake kinetics are primarily determined by metabolic processes. However, this interpretation is restricted to a "healthy cardiovascular model" and thus may not apply to HF, as limb blood flow has been shown to be reduced in patients with HF (27, 96, 97, 104).

Using electrical stimulation and phosphorescence quenching, it has been shown in isolated rat spinotrapezius muscle (which is similar in composition and oxidative capacity to human quadricep muscle) that the microvascular partial pressure of O_2 (PO_2) (which reflects the dynamic balance between muscle O_2 delivery muscle O_2 uptake) decreases exponentially only after an approximate 20-s delay (9). This initial time delay is also observed using near-infrared spectroscopy, and indicates the presence of adequate O_2 availability for muscle O_2 uptake at least immediately following a square wave stimulus. Belardinelli et al. (11) compared $\dot{V}O_2$ and muscle oxygenation using near-infrared spectroscopy in HF patients and healthy controls and reported that the recovery kinetics for both parameters were delayed in the HF patients. This finding suggests that the regeneration of PCr and/or resaturation of venous oxyhemoglobin occurred more slowly as cardiac function worsened. The results of Belardinelli et al. (11) were confirmed in subsequent study (10) in which HF patients demonstrated slower muscle oxygenation and

$\dot{V}O_2$ kinetics compared to healthy controls following maximal and submaximal exercise. Further to these reports (10, 11), Hanada et al. (40) found that the kinetics of PCr (determined by ^{31}P-magnetic resonance spectroscopy) and oxygenated hemoglobin (determined by near-infrared spectroscopy) during calf planter flexion were slower in HF patients compared with healthy controls. In that same study however, HF patients demonstrated faster PCr kinetics relative to oxyhemoglobin kinetics, suggesting that slower oxygenated hemoglobin resaturation did not limit PCr resynthesis. Consistent with the findings of Hanada et al. (40), using isolated *in situ* dog muscle preparations, Grassi et al. (34) demonstrated that pharmacologic intervention with RSR 13, an inhibitor of O_2 hemoglobin binding that causes a rightward shift in the hemoglobin-O_2 dissociation curve, coupled with hyperoxic gas breathing (FIO_2 = 1.00) increased capillary PO_2, but did not speed $\dot{V}O_2$ kinetics. Thus, these data imply that in HF patients that O_2 utilization is a potential rate-limiting step in reaching metabolic homeostasis during exercise recovery.

Nitric oxide synthase blockade with nitro-L-arginine methyl ester has provided additional evidence (in animals and humans) suggesting that intracellular processes limit the rate of $\dot{V}O_2$ following a square-wave perturbation. In the electron transport chain, nitric oxide reversibly binds to cytochrome c oxidase, the terminal electron acceptor in the electron transport chain, thus competing with O_2 binding and subsequently mitochondrial respiration (15, 16). Importantly, if nitric oxide has a role in determining the time course of $\dot{V}O_2$, then inhibiting nitric oxide should speed $\dot{V}O_{2p}$ kinetics by favoring O_2 binding site availability (53). Supporting the notable improvements observed in animals (53), Jones et al. (51) reported a 19% speeding of $\dot{V}O_2$ kinetics in exercising

humans during nitric oxide synthase blockade. The impact of these findings are underscored as this was the first study demonstrating the ability to speed $\dot{V}O_2$ in apparently healthy young adults, as it had previously been shown that increasing O_2 availability with hyperoxic gas breathing did not favorably alter $\dot{V}O_2$ kinetics in healthy young adults (61). In the study by Funakoshi et al. (30), the authors hypothesized that diminished nitric oxide release or increased basal nitric oxide production, measured by endogenous exhaled nitric oxide, would contribute to an impaired vasodilator reserve that would subsequently reduce blood flow and prolong $\dot{V}O_2$ kinetics in HF patients. The authors found that resting and exercise exhaled nitric oxide was 61% and 55% greater, respectively, in HF patients compared to controls. Moreover, greater nitric oxide output was significantly related to slower $\dot{V}O_2$ kinetics. In light of the findings of Jones et al. (51), it is plausible that both the elevated nitric oxide in the study by Funakoshi et al. (30) and the reduced levels of cytochrome c oxidase (85) prolonged $\dot{V}O_2$ kinetics via an intracellular mechanism rather than an impaired vasodilator mechanism (42). However, this hypothesis has yet to be directly tested in HF patients.

1.2.2 Evidence for Cardiovascular Mediated Oxygen Availability Limitations

Since $\dot{V}O_2$ is the product of cardiac output and the arterial-venous O_2 content difference, it is probable that alterations in cardiac output and its determinants may impact exercising muscle O_2 uptake. Experiments studying impaired LV function or that have manipulated the time course of heart rate and muscle blood flow have provided some of the strongest evidence favoring a primary role for O_2 availability limiting $\dot{V}O_2$ in HF.

Impaired muscle blood flow may account for slower $\dot{V}O_2$ kinetics. This effect has been best demonstrated in studies controlling for the effect of perfusion pressure by comparing handgrip exercise above and below the level of the heart (46) and supine versus upright knee extension exercise (60) in healthy subjects. Consistent with a theory that muscle blood flow adaptation is rate-limiting. An impairment in endothelial function in patients with HF may also perturb blood flow and $\dot{V}O_2$ kinetics. The findings of Funakoshi et al. (30), as discussed above, attributed slower $\dot{V}O_2$ kinetics to an impaired vasodilator reserve in HF patients. Conversely however, Hepple and colleagues (42) demonstrated that impaired blood flow in HF patients was not associated with slower $\dot{V}O_2$ kinetics. An interesting study by Guazzi et al. (37) revealed that sildenafil (a phosphodiesterase-5 inhibitor) was associated with a 26% speeding in postexercise $\dot{V}O_2$ kinetics. These findings indicate that improvements in $\dot{V}O_2$ kinetics may be mediated in part by a reversal in endothelial dysfunction that enhances blood flow and O_2 availability. Supporting this line of inquiry, Patel et al. (77) found that peripheral vascular function determined by flow-mediated dilatation was reversible in non-ischemic, but not ischemic HF patients following heart transplantation. These findings were recently extended when pre-transplantation HF etiology was also shown to be associated with prolonged $\dot{V}O_2$ kinetics post-transplantation in patients with antecedent ischemic compared to non-ischemic HF (108).

Reduced beta-adrenergic sensitivity associated with HF may contribute to slower $\dot{V}O_2$ kinetics secondary to impaired chronotropy (54). In a seminal study demonstrating for the first time a direct link between heart rate and $\dot{V}O_2$ kinetics, Hughson and Morrissey (44) exercised subjects starting from rest and an elevated baseline (40% of the

ventilatory threshold) to varying target work rates. The authors reported significantly slower $\dot{V}O_2$ kinetics during a transition from 40 to 80% of the ventilatory threshold (~61 s) and slower $\dot{V}O_2$ kinetics during a transition from 40 to 120% of the ventilatory threshold (~79 s) compared with a transition from rest to 40% of the ventilatory threshold (~35 s) and rest to 80% of the ventilatory threshold (~40 s). These findings were further confirmed in later studies (45, 47) and were shown to be the result of impaired O_2 delivery as evidenced by concurrently slower heart rate kinetics. Dailey et al. (21) extended these findings and demonstrated in pacemaker dependent patients that programming slower chronotropic response patterns resulted in a markedly greater O_2 deficit. A similar effect secondary to cardiac denervation is apparent in heart transplant recipients when compared to healthy controls (78), and the impact of impaired O_2 delivery remains even when alleviating the (central) cardiac limitation associated with requiring to perfuse a large exercising muscle mass (50). In the study by Koike et al. (54), a clear slowing in heart rate kinetics in patients associated with worsening HF likely exacerbated the effects of LV dysfunction, thus impairing $\dot{V}O_2$ kinetics.

Left ventricular function has also been implicated as a mediating factor for $\dot{V}O_2$. In the normal functioning heart, the delay between the atria and ventricles shortens with an increasing heart rate (22). Two studies (87, 109) found that $\dot{V}O_2$ kinetics were ~15% slower during dyssynchronous compared with synchronous atrioventricular pacing, which effectively mimics functional mitral regurgitation that is typical in HF patients. In the latter study (109), stroke volume was consistently lower throughout exercise and was negatively correlated with $\dot{V}O_2$ kinetics. Taniguchi and colleagues (106) showed that the favorable effects of β-blocker therapy on cardiac index and stroke index (4) in HF

patients following 6-mo of therapy was associated with a 31% improvement in $\dot{V}O_2$ kinetics and an absolute 14% improvement in LV EF. In a well designed cross-sectional investigation, Matsumoto and colleagues (64) demonstrated in HF patients with a lower peak $\dot{V}O_2$ (< 18 ml/kg/min) that cardiac output and $\dot{V}O_2$ kinetics were 54% and 38% slower, respectively, compared to patients with a higher peak exercise $\dot{V}O_2$ (≥ 18 ml/kg/min). Notably, the slower cardiac output kinetics were significantly related to prolonged $\dot{V}O_2$ kinetics ($r = 0.85$, $P < 0.05$). In that same study (64), the kinetics of the arterial-venous O_2 content difference were similar between the lower (34 ± 10 s) compared to higher peak $\dot{V}O_2$ group (39 ± 20 s). This latter finding confirmed that O_2 availability and not O_2 extraction ability was the rate-limiting step for $\dot{V}O_2$ kinetics in that HF cohort. Koike et al. (54) also demonstrated that both cardiac output and $\dot{V}O_2$ kinetics were 21% slower in patients with a lower (30 ± 3%) compared to those with higher (40 ± 5%) LV EF, suggesting a predictive effect of LV function on potential muscle O_2 uptake impairments. Notably, slower $\dot{V}O_2$ kinetics ($r = –0.51$, $P < 0.05$) and slower cardiac output kinetics ($r = –0.33$, $P = 0.02$) were associated with a lower LV EF.

Finally, a pivotal study by Richardson et al. (86) examined the potential mechanism by which O_2 availability impairs $\dot{V}O_2$ kinetics in HF. In their study (86), coronary ligation was used to induce ischemic HF in rats. The main findings demonstrated that the speed of red blood cell flux was 83% slower in spinotrapezius muscles compared to a control condition following square-wave muscle stimulation. A consequence of the reduction in red blood cell flux is a faster decline in microvascular PO_2 (with a shorter time delay), which is expressed as a widening of the arterial-venous O_2 content difference and is indicative of slower microvascular O_2 delivery (9). When

extended to human HF, these findings suggest that impaired cardiac output and blood flow may slow capillary hemodynamics to the degree that the pressure gradient for blood-myocyte diffusion is lowered, thereby prolonging muscle O_2 uptake.

1.3 Effects of CRT in Heart Failure

CRT has proven to be safe and tolerable in those with HF and the survival impact associated with CRT is evident. A meta-analysis (65) of major CRT trials reported a 21% reduction in all-cause mortality in 3216 patients, due primarily to reductions in death from progressive heart failure. A more recent meta-analysis of 7538 patients, including those with New York Heart Association class I and II HF, also demonstrated similar survival benefit with CRT (112). These analyses show that the progressive nature of HF is mitigated to a greater degree with CRT than with standard pharmacotherapy alone.

A number of cardiac and functional outcome changes have been attributed to CRT. Clinical trials have demonstrated that patients undergoing CRT may experience improvements in NYHA functional class (2, 6, 32, 59), improved quality of life scores (6, 18, 32, 58, 59), and reduced hospitalization (2, 18). Cardiac changes reflecting reverse cardiac remodeling include an increased LV EF (2, 32, 59, 99, 101), decreased left atrial volume (92), decreased LV end-systolic dimension (26, 92, 101), decreased LV end-diastolic dimension (26, 32, 92, 99, 101), reduced LV end-systolic volume (ESV) (92, 99, 101), reduced LV end-diastolic volume (EDV) (101), and reduced LV mass (99). CRT has also been shown to decrease interventricular mechanical delay (32), reduce mitral regurgitation (32, 59, 99), and increase LV filling time (32). These established changes in resting cardiac function appear to contribute, in part, to an enhanced exercise ability that is evidenced by an increased distance covered in walk testing (2, 5, 6, 18, 26, 32, 59),

increased treadmill exercise duration (2), increased $\dot{V}O_2$ at the ventilatory threshold (6), and increased peak $\dot{V}O_2$ (5, 6, 18, 26, 59).

As noted, chronic CRT decreases LV EDV and LV ESV (92), and these are the commonly reported primary indices of reverse remodeling. In their investigation, St. John Sutton and colleagues (99) enrolled 323 patients implanted with a biventricular pacemaker. Patients were randomized a CRT "on" arm (n = 172) or CRT "off" arm (n = 151) in double blind fashion. Following a 6-mo intervention, the main findings indicated that CRT was associated with a 9% reduction in LV EDV and an 11% reduction in LV ESV, which is consistent with an approximate 10% reduction in LV EDV and LV ESV observed in the study by Saxon et al. (92), but is less than a reported 18% reduction in LV EDV and 25% reduction in LV ESV in the study by Yu et al. (117). The study by Yu et al. (117) also confirmed that reverse remodeling associated with CRT is secondary to favorable changes in LV function because of chronic, and not just acute, CRT effects. Following 3 mo of CRT, pacing was terminated and LV function assessed. The main findings indicated that following CRT cessation, maximal dP/dt decreased ~60% whereas LV EDV and ESV did not change, which is consistent with the hypothesis that improvements in HF symptoms and exercise capacity are due in part to the chronic effects (reverse remodeling) of CRT. However, in that same study (117), LV remodeling (increased LV EDV and LV ESV) occurred following 1-wk of CRT restriction, further supporting the efficacy of CRT to reverse remodel the heart. Interestingly, the decline in 6-min walk distance was marginal even after four weeks of CRT restriction, suggesting that favorable chronic skeletal muscle changes may have occurred with increased physical activity during the CRT treatment period.

Chronic CRT also improves LV function during simulated exercise with increased pacing rates. Steendijk et al. (100) investigated the effects of CRT on LV function at baseline (prior to CRT) during right atrial pacing at 80, 100, 120, and 140 beats/min and at the same rates during biventricular pacing following 6 mo of CRT. Detailed hemodynamic measurements were obtained in 22 patients using right and left heart catheterization. Following 6 mo of CRT, right atrial-biventricular pacing at 80 beats/min increased LV EF from 29 ± 10% to 40 ± 13%, increased cardiac output from 4.36 ± 0.70 L/min to 4.98 ± 0.86 L/min, decreased end-diastolic pressure from 18 ± 8 mmHg to 13 ± 06 mmHg, and decreased LV EDV from 257 ± 67 ml to 205 ± 54 ml. Improved systolic function was evidenced by an increase in the maximum dP/dt from 807 ± 264 mmHg/s to 953 ± 287 mmHg/s. During right atrial stimulated increases in pacing rate, cardiac output increased at 100 beats/min and remained stable at follow-up compared to a reduction in cardiac output at 140 beats/min at baseline. At follow-up, LV EF reduced more gradually and to a lesser degree compared to baseline with increasing pacing rate. Additionally, LV ESV remained unchanged and LV EDV lowered to a lesser degree at 140 beats/min compared to baseline. While there was no effective increase in maximal dP/dt throughout incremental at baseline, maximal dP/dt progressively increased with incrementing pacing rates at follow-up. The changes in LV reverse remodeling culminated in a leftward shift in the LV pressure-volume loop at each pacing rate. Although stroke volume was comparable at 80 beats/min, right atrial pacing at baseline (~62 ml) compared to follow-up (~68 ml), stroke volume was well preserved throughout the increases in pacing rate at follow-up, while at baseline stroke volume declined ~50% at the highest pacing rate (140 beats/min).

In addition to improving LV function at rest and during simulated exercise, CRT causes a reduction in sympathoexcitation, which may increase exercising muscle O_2 uptake. Hamdan et al. (39) examined muscle sympathetic nerve activity with microneurography in HF patients during right atrial-right ventricular pacing, right atrial-LV pacing, and right atrial-biventricular pacing (*i.e.*, CRT). Acute CRT and right atrial-LV pacing were found to increase blood pressure and decreased sympathetic nerve activity. Adamson et al. (3) reported that heart rate variability (a surrogate of autonomic function) significantly improved following 3 mo of CRT in favor of increased parasympathetic activity and a reduction in sympathetic activity. Similarly, Grassi et al. (35) found that 2 mo of CRT was associated with an improvement in blood pressure and a reduction in sympathetic excitation. Reductions in the maximal dP/dt associated with HF causes a decline in cardiac output and blood pressure, which subsequently diminishes the inhibitory effect of the baroreceptors on sympathetic activity. This can lead to a chronic compensatory sympathoexcitation. Therefore, favorable blood pressure changes secondary to an enhanced dP/dt and cardiac output may be the mechanism explaining the reduction in sympathoinhibitory effect previously reported with CRT (70). A consequence of chronically heightened sympathetic activation associated with HF includes a decline peripheral vascular blood flow, arteriolar dilatation, and capillary recruitment. Based on previous reports, the peripheral effects of sympathoexcitation may subsequently manifest as a major reduction in microvascular *P*O2, which may be exacerbated during physiologic stress. Accordingly, this would cause a decline in the O_2 diffusion pressure gradient into the skeletal myocyte, thus prolonging muscle O_2 uptake during exercise (86). This effect may potentially be reversed with increased blood flow

secondary to an increase in sympathoinhibition. Alternatively, the reduction in chronically elevated sympathetic activity associated with long-term CRT may reverse the skeletal muscle myopathy associated with HF, which is distinguished by a shift from oxidative to glycolytic muscle fibers and a reduction in oxidative enzymes and mitochondrial density (25, 62, 103) that is secondary to chronic underperfusion (111). Subsequently, a reversal in the skeletal muscle oxidative capacity may then favor an enhanced O_2 utilization ability profile.

1.4 Effects of HIT in Heart Failure

Cardiac rehabilitation programming for patients with HF is currently predominated by a continuous aerobic exercise training model that includes performing moderate intensity exercise (approximating 50 to 80% of peak capacity) (48, 81, 102, 115). Previous reports have shown some improvement in aerobic capacity and varying effects on LV function with this type of training. For example, Belardinelli et al. (12) found that continuous aerobic exercise training 3 days/wk at 60% of peak $\dot{V}O_2$ increased peak $\dot{V}O_2$ and did significantly increase LV EF. Another study by Belardinelli et al. (13) also found that exercise training 3 days/wk at 60% of peak $\dot{V}O_2$ increased peak $\dot{V}O_2$ (15%) with only slightly greater increases (1% absolute) in LV EF. The studies by Hambrecht et al. (38), Myers et al. (71), Passino et al. (76) and Gianuzzi et al. (31) reported absolute increases in LV EF ranging from 3 to 5% following continuous aerobic exercise training. A meta-analysis that included these and other studies showed that continuous aerobic exercise training decreased LV EDV ~12 ml and LV ESV ~13 ml in 371 patients, and increased LV EF an absolute 2.6% in 538 patients with HF (41). These modest changes in LV function are mirrored in the recent prospective multicenter Heart

Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study that reported minimal improvements in self-reported health and survival with this type of training (28, 74).

In contrast to continuous aerobic exercise training, HIT is typically associated with performing a number of relatively short duration (~1 min to 4 min), high-intensity bouts (near or above ~90% peak $\dot{V}O_2$, or above 90% of peak heart rate) that are separated by brief periods of rest or low-intensity active recovery. Subsequently, total exercise volume over the course of a training program is substantially lower with HIT compared to continuous aerobic exercise training (17). However, given a number of previous study findings in healthy subjects, some of which are conflicting, caution may be warranted with this type of training for individuals with LV dysfunction. For example, healthy fit subjects have been shown to have a reduction in LV EF (94) or no change in LV EF (72, 82) immediately following acute HIT, whereas normally active healthy subjects have no, or minimal, change in the immediate post-exercise LV EF (94). Specifically, Scott et al. (94) found that 14 1-min cycling intervals at 99 ± 6% of peak power output in endurance trained individuals caused a 2% and 3% absolute reduction in the immediate post-exercise right ventricular EF and LV EF, respectively. In contrast, there was no change in right ventricular EF and LV EF for normally active subjects who performed the same protocol at 97 ± 11% of peak power output. During acute incremental exercise, patients with HF increase or have no change in LV ESV in part because of increased afterload and decreased contractile reserve (91, 104). Additionally, LV EDV has also been shown to not change or decrease during exercise (55, 91), thus impairing the use of an enhanced Frank-Starling effect. Thus, the reductions in LV ESV and LV EDV contribute to global

LV dysfunction that is often measured by a decrease in LV EF. More recently, it has also been shown that patients with HF have a reduction in systolic twist and subsequently LV untwisting (29). Given that a significant portion of LV untwisting occurs prior to mitral valve opening, LV untwisting is an important factor that aids in the generation of low LV pressure that further contributes to the transmitral pressure gradient that drives early LV filling (20, 49). The importance of this was demonstrated by Notomi et al. (73) in patients with hypertrophic cardiomyopathy whereby, during exercise, 1) untwisting rate did not significantly increase, 2) peak untwisting rate occurred about the time of peak early filling after mitral valve opening, and 3) the peak intraventricular pressure gradient subsequently increased only marginally from rest, and thus filling rate was likely dominated by a high left atrial pressure. Therefore, the failure to augment untwisting during incrementally higher intensity exercise protocols may further impair diastolic filling in patients with HF.

Chronically, HIT does appear to confer substantial aerobic benefit in healthy subjects and those with HF, and this may be secondary in part to an increase in mitochondrial function (17, 114). Less is know, however, about the cardiovascular benefits associated with HIT in HF. Wisløff et al. (113) did show in a HF rat model that contractile function increased following HIT, which is similar to previous animal studies (118). The more recent investigation by Wisløff et al. (114) is the only study to date that has assessed the effects of chronic HIT on cardiovascular function in patients with HF. Among other findings, Wisløff et al. (114) reported a 10% absolute increase in a baseline LV EF of 28.0 ± 7.3% following chronic HIT (3 times/wk for 12 wks) in older subjects (76 ± 11 yrs) with ischemic HF. This contrasted a 0.7% absolute increase in LV EF in

similar subjects who completed continuous aerobic exercise at 70 – 75% of peak heart rate for the same duration, and effectively no change in LV EF in control subjects. The same study reported volumetric changes in LV chamber size consistent with reverse remodeling (45 ml reduction in LV EDV and 44 ml reduction in LV ESV). Likely contributing the reported improvement in peak $\dot{V}O_2$ associated with HIT was a significant increase brachial artery flow-mediated dilation.

1.5 Hypotheses

The first study of this thesis examined $\dot{V}O_2$ kinetics during the transition to moderate-intensity exercise in patients with HF and CRT. The study was based on the premise that CRT may improve exercise LV function during moderate-intensity exercise (100) and that this improvement in LV function may further confer a speeding in the rate of muscle O_2 uptake adaptation by increasing O_2 transport throughout the exercise transient. As well, the study was also based on findings that patients with HF maintain a certain degree of metabolic reserve (27), and therefore the potential for increasing metabolic rate exists. Thus, the hypotheses tested in Chapter 2 were that *1)* chronic (6 mo) CRT would speed phase II $\dot{V}O_2$ kinetics in patients with HF, and that this would be due to an increase in exercise stroke volume, *2)* the increase in exercise stroke volume would be attributable to a further reduction in LV ESV from rest to exercise, and 3) that resting and exercise heart rate would be lower following CRT, secondary to an increase in stroke volume.

In the same cohort of subjects reported in Chapter 2, the second study of this thesis investigated the CRT mediated changes in peak exercise LV function. The primary motivation for the study was the lack of simultaneous assessment of $\dot{V}O_2$ and LV

function at peak exercise during physiologic conditions (*i.e.*, whole-body exercise), and thus a mechanistic explanation for reported improvements in peak $\dot{V}O_2$ following CRT was needed (2, 7, 26, 59, 116). Additionally, whether the increase in aerobic capacity associated with CRT would confer a speeding in the recovery of previously reported sluggish $\dot{V}O_2$ kinetics following peak exercise was unknown (19, 23). Therefore, the hypotheses tested in Chapter 3 were that 1) CRT would increase reserve and peak cardiac output, 2) the increase in $\dot{V}O_2$ at peak exercise would be related to an increase in cardiac output reserve, 3) CRT would decreased the time to exercise recovery as measured by a speeding in gas exchange and ventilation kinetics, and 4) faster post-exercise $\dot{V}O_2$ kinetics would be associated with greater aerobic capacity.

The third study of this thesis investigated the acute effects of HIT on post-exercise biventricular function in patients with non-ischemic mild HF. The study was founded in contrasting reports of varying magnitude effects in LV reverse remodeling associated with continuous aerobic exercise training (41) versus HIT (114). Acutely, the effects of HIT on post-exercise LV function were unknown in patients with HF. Given the limited ability of the failing LV to augment cardiac output during exercise and the varying effects of HIT on LV function in health subjects (20, 24, 49, 55, 72, 73, 82, 91, 93-95), the acute effects of HIT on post-exercise cardiac function was warranted. Therefore, the hypotheses tested in Chapter 4 were that *1)* immediately following acute HIT, HF patients would have a reduction in biventricular EF as the result of an increase or no change in LV ESV and a decrease in LV EDV, and *2)* HF patients would have reduced diastolic function, comprising of reductions in filling rate, mitral annular tissue velocity, and LV peak untwisting rate immediately following acute HIT.

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Chapter 2

Effects of Cardiac Resynchronization Therapy on Oxygen Uptake Kinetics and Left Ventricular Function during Moderate-Intensity Exercise

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2.1 Introduction

Pulmonary oxygen uptake ($\dot{V}O_2$) kinetics at exercise onset are slower in patients with heart failure (HF) and reduced ejection fraction (EF) compared to healthy individuals (18, 20, 34), and progressively worsening HF is associated with a concomitant slowing of $\dot{V}O_2$ kinetics (5). A slowing of $\dot{V}O_2$ kinetics in patients with HF may potentially be explained by an impairment of metabolic processes within the exercising muscle (41) or by a reduction in the availability of O_2 for the exercising muscle (9), or a combination of both. Given that HF with reduced EF is characterized in part by significant left ventricular (LV) systolic dysfunction, impaired exercise cardiac function may explain an important mediating factor accounting for the delayed $\dot{V}O_2$ kinetic response to exercise (18, 20, 25). However, whether improving exercise systolic function can reverse the impaired $\dot{V}O_2$ kinetics in patients with HF has not been studied.

Cardiac resynchronization therapy (CRT) with a biventricular pacemaker improves several aspects of resting cardiovascular function in patients HF. These changes include a reduction in both LV end-diastolic volume (EDV) and LV end-systolic volume (ESV) with a net benefit of increasing LV EF and stroke volume, thus accounting for the typically reported greater decrease in LV ESV than LV EDV (1, 12, 23, 38, 40). Given that CRT increases functional capacity such as $\dot{V}O_2$ at peak exercise, it is plausible that CRT also improves exercise systolic performance; though the literature is limited in this regard (39). The potential for CRT to improve exercise systolic function during the

transition to moderate-intensity exercise (*i.e.*, exercise below the ventilatory threshold) may further confer a speeding in the rate of muscle O_2 uptake adaptation in patients with HF by increasing O_2 transport throughout the exercise transient.

The purpose of this study was to investigate the effects of 6 mo of CRT on $\dot{V}O_2$ kinetics and exercise LV function in patients with HF and reduced EF. Using a prospective designed study, we tested the main hypothesis that chronic (6 mo) biventricular pacing with a CRT device would speed phase II $\dot{V}O_2$ kinetics in patients with HF and reduced EF, and that this would be due to an increase in exercise stroke volume. A secondary hypothesis was that the increase in exercise stroke volume would be attributable to a further reduction in LV ESV from rest to exercise. Lastly, we hypothesized that resting and exercise heart rate would be lower following CRT, secondary to an increase in stroke volume.

2.2 Methods

2.2.1 Subjects

Twenty-one subjects provided written and informed consent to participate in this investigation that was approved by the University of Alberta Hospital Research Ethics Board (Appendix A). Subjects met our hospital criteria for a CRT biventricular pacemaker, which included a diagnosis of New York Heart Association functional class III or IV HF with persistent symptoms despite stable and optimal medical therapy, a LV EF ≤ 35%, and a QRS duration > 120 ms consistent with interventricular conduction delay. Subjects further met our study criteria if they had a normal sinus rhythm and did not require atrial pacing, if their medications and HF symptoms had not changed in the previous 3 months, if they reported being able to perform stationary bicycle exercise, and

had no change in medications while enrolled in our study. Subjects were excluded if they did not have a normal intrinsic sinus rhythm, the CRT device/lead wire implantation was not successful, or if HF symptoms/condition or comorbidities precluded exercise testing. Medications were not discontinued for testing.

2.2.2 Peak Exercise Protocol

Subjects underwent 2 days of testing. On the first day, a peak exercise test to volitional fatigue was completed on a customized semi-recumbent (112º seat angle) electronically braked cycle ergometer (Corival, Lode, Groningen, The Netherlands). The test began at 15 W for 1 min followed by 10 W/min increments and subjects were provided standardized encouragement during the protocol. A 12-lead electrocardiogram (CASE® 8000, GE Healthcare, Freiburg, DE), manual brachial cuff blood pressure (BP), and pulse oximetry were monitored every 2 min. Breath-by-breath gas exchange and ventilation parameters were also measured. Data from this test was used to develop individualized work rates approximating 90% of the ventilatory threshold for subsequent square-wave moderate-intensity exercise testing. The ventilatory threshold was identified as the point of change in the $\dot{V}CO_2$ and $\dot{V}O_2$ slope as this method has been shown to be determined more reliably between raters than previous gas exchange techniques (4). Following a resting period after the peak exercise test, subjects were familiarized with the square-wave exercise protocol and specifically trained on obtaining and strictly maintaining a constant target pedaling rate from quiet rest within 1–2 revolutions upon verbal command.

2.2.3 Square-Wave Exercise Protocol

Subjects completed 4 square-wave exercise tests 1 wk following the peak exercise test. The square-wave protocol was completed at the same time of day as the peak test. Although it has previously been shown that prior moderate-intensity exercise does not influence the kinetics of $\dot{V}O_2$ during subsequent moderate-intensity exercise in healthy young subjects (11), we separated each square-wave test by a 30-min rest period to ensure subjects were fully rested and able to perform the 4 square-wave repetitions. The protocol entailed a 5-min resting baseline followed by an abrupt commencement of exercise to a predetermined work rate approximating the $\dot{V}O_2$ at 90% of the estimated gas exchange ventilatory threshold. The duration of exercise was 5 min. A target pedal rate of 50 revolutions/min was obtained within 1–2 revolutions from rest. Subjects had visual feedback of their pedal rate on a display for the test duration. Because a low $\dot{V}O_2$ amplitude response negatively impacts the confidence estimate of the $\dot{V}O_2$ time constant (22), and because we expected relatively very low moderate-intensity work rates from our study group, we elected to have subjects begin exercise from a resting baseline to further enhance our estimation of time-course changes in $\dot{V}O_2$.

2.2.4 Pulmonary Gas Exchange

Breath-by-breath pulmonary gas exchange was measured at 125 samples/s using a commercial system (SensorMedics® Vmax 229; VIASYS™ Healthcare Respiratory Technologies, Yorba Linda, CA, US). Prior to both the peak exercise and square-wave exercise protocol, the low resistance, low deadspace (90 ml), bi-directional mass flow sensor was calibrated with a 3.0 L syringe across expected breathing frequencies. The paramagnetic O_2 analyzer and non-dispersive infrared CO_2 analyzer were calibrated using

a 2-point calibration with known gas concentrations. The gas analyzers were also calibrated between each square-wave transition and a second mass flow sensor calibration was completed following 2 square-wave bouts.

2.2.5 Contrast-Enhanced Echocardiography

Resting and exercise 2-dimensional echocardiograms (Vivid-*i*® or Vivid 7®; GE Medical Systems, Milwaukee, Wisconsin, US) were performed with subjects sitting on the semi-recumbent cycle ergometer at a 112º seat angle. Prior to testing, an intravenous line was established on the dorsum of the hand or antebrachium. Once an apical 4-chamber viewing window was established, the sonographer's arm was stabilized on an adjustable stand and the transducer kept in place at rest and for the duration of exercise. Image acquisition was preceded by a slow bolus 0.2 ml intravenous injection of commercial contrast agent (Definity®; Bristol-Myers Squibb, New York, NY, US) that was followed by a normal saline flush at a manual rate that optimized LV cavity opacification. Single-plane apical 4-chamber view cine images of 5 loops were then recorded to determine LV volumes (14). We elected to image using a single-plane view for determining LV volumes to ensure consistency in the viewing window between resting and exercise images. Exercise echocardiograms were obtained within the last 90 s of exercise. Heart rate was measured continuously by electrocardiogram.

2.2.6 Pacemaker Programming

Pacemaker device programming was standardized and implemented at the time of device implant. All subjects received a combined CRT-implantable cardiodefibrillator device (CRT-ICD) and 1 subject received a CRT device without an ICD based on clinical status. Device programming was designed to ensure atrial sensed ventricular pacing while

maintaining ventricular capture and LV-before-right ventricular (RV) stimulation. The base rate, which is the lowest intrinsic sinus rate detected prior to the CRT device setting the pacing rate, was programmed at 50 beats/min. The atrioventricular delay was set at 100 – 120 ms and was fixed to not rate adapt with changes in sinus rate. The interventricular delay was set to stimulate the LV 20 ms prior to RV stimulation. To avoid unwanted ICD shocks on testing days, the defibrillation threshold was programmed 20 beats/min above the estimated exercise heart rate based on age (*i.e.*, 220 – age) and clinical status. The ventricular tachycardia detection mode turned off for exercise testing. Settings were restored upon completion of exercise testing.

2.2.7 Curve Fitting

Breath-by-breath $\dot{V}O_2$ was filtered for aberrant breaths (22) and linearly interpolated to 1-s intervals, time aligned, averaged to 10-s intervals, superimposed and ensemble averaged to yield a single response profile for each subject. Curve fit parameter estimates for $\dot{V}O_2$ responses during the on-transient were determined using a first-order mathematical model of the form:

$$Y_{(t)} = Y_{(b)} + A \cdot [1 - e^{-(t-TD)/\tau}]$$

where Y is $\dot{V}O_2$ at a give time (t), b is the baseline (resting) value of $\dot{V}O_2$ over the last 60 s prior to exercise onset, A is the amplitude change in the $\dot{V}O_2$ response, τ is the time constant or time for $\dot{V}O_2$ to reach 63% of A, and TD is the time delay prior to the exponential onset of $\dot{V}O_2$. Steady-state $\dot{V}O_2$ was measured as the value over the last 60 s of exercise. Heart rate data were also filtered for aberrant beats (22), linearly interpolated to 1-s intervals, time aligned, averaged to 10-s intervals, superimposed and ensemble

averaged to yield a single response profile for each subject. Heart rate curve fit parameter estimates were determined in the same fashion as $\dot{V}O_2$.

Kinetic parameters for $\dot{V}O_2$ and heart rate were determined using non-linear regression and the iterative procedure of the computer program (Origin 7.5, OriginLab Corp., Northampton, MA, US) employed a Levenberg-Marquardt algorithm whereby the best fit was defined by minimization of the residual sum of squares. For $\dot{V}O_2$, the data-fitting window was extended from the phase II exponential onset to the end of exercise (300 s). Heart rate kinetics were determined from exercise onset to the end of exercise. The 95% confidence intervals for the estimation of phase II $\dot{V}O_2$ τ and heart rate τ were calculated using the method described by Lamarra et al. (22).

2.2.8 Cardiovascular Analyses

For determining ventricular volumes, endocardial borders were manually traced with papillary muscles and trabeculations included in the ventricular cavity using commercial software (Xcelera, Philips Healthcare, Andover, MA, US). LV EDV was measured as the largest cavity area prior to the onset of the QRS complex and LV ESV was measured as the smallest cavity area prior to mitral valve opening. Single-plane volumes were calculated using the disc summation method. LV EF was calculated as ((LV EDV – LV ESV)/LV EDV) × 100, stroke volume as LV EDV – LV ESV, and cardiac output as stroke volume × heart rate. Reported values were the average over 3–5 cardiac cycles. Manual brachial cuff blood pressure values were used to calculated mean arterial pressure. Systemic vascular resistance (SVR) was calculated as SVR = (mean arterial pressure/cardiac output) × 80.

2.2.9 Statistics

Paired *t*-tests were used to determine statistical differences between pre-CRT and post-CRT variables (SPSS 11.0.1, Chicago, IL, US). Data are presented as mean ± SD and $P < 0.05$ was considered statistically significant.

2.3 Results

2.3.1 Adverse Events

Ten subjects did not complete the study. One subject completed baseline testing and decline follow-up testing because of their HF symptoms. One subject completed baseline testing, but LV transvenous lead placement was unsuccessful and an epicardial lead was not considered based on the subject's clinical status. One subject had symptomatic hypotension upon arrival for the first testing day and the protocol was not conducted for safety; this subject declined to undergo further testing at a later date. One subject consented to study participation, but died prior to baseline testing and pacemaker implantation. Baseline testing was completed on 3 subjects who later had signs and/or symptoms of decompensated HF on their follow-up testing day. Another subject had signs and/or symptoms of decompensated HF on the baseline testing day. These 4 subjects were admitted to hospital the same day as testing and later died in hospital. One subject completed baseline testing and returned for follow-up testing, though was unable to perform their prescribed 10 W square-wave exercise protocol because of their HF symptoms. One subject completed peak exercise testing, though was implanted with a CRT-ICD device prior to baseline square-wave exercise testing based on clinical status and physician recommendation, and was subsequently hospitalized for device implant related complications.

2.3.2 Subject Characteristics

In total, 11 subjects completed this study (Table 2-1). Heart failure etiology was ischemic in 7 subjects and non-ischemic in 4 subjects. Subject medications are listed in Table 2-1 and medications (and respective dosages) did not change over the intervention period. All tests began at the same time of day (within ~0.5 hr) for pre-CRT and post-CRT time-points for square-wave exercise tests to account for potential effects of plasma concentration changes in medication. All subjects confirmed medication self-administration at their regular time on testing days and the day prior to testing. The CRT device in all subjects had a passive fixed right atrial lead placed in the atrial appendage, an RV active fixed lead placed in the apex, and a transvenous LV lead placed about the postero-lateral wall (n = 4) or lateral wall (n = 6). One subject received a LV lateral wall epicardial lead the same day following unsuccessful transvenous lead placement. Detailed findings from peak exercise testing are reported in Chapter 3.

2.3.3 Square-Wave Exercise

The exercise intensity for square-wave testing was 21 ± 8 W (range: 10 – 30 W). Individualized pre-CRT exercise intensities were used for post-CRT testing. The pre-CRT steady-state $\dot{V}O_2$ was 91 ± 7% of the ventilatory threshold (Table 2-1). No subjects exercised above the ventilatory threshold, and visual inspection of gas exchange data confirmed the absence of a further slow component rise in $\dot{V}O_2$ in all subjects. One subject completed only 3 post-CRT square-wave bouts because of fatigue.

2.3.4 $\dot{V}O_2$ kinetics

CRT did not affect resting $\dot{V}O_2$ ($Y_{(b)}$), the phase II $\dot{V}O_2$ time delay (TD), or the amplitude increase in $\dot{V}O_2$ (A) (all $P > 0.05$; Table 2-2). The steady-state $\dot{V}O_2$ during

square-wave moderate-intensity exercise did not change (pre-CRT: 0.72 ± 0.23 l/min; post-CRT: 0.71 ± 0.20; $P > 0.05$). CRT decreased the phase II $\dot{V}O_2$ time constant (τ) by 22% ($P < 0.05$; Table 2, Fig 2-1) and the overall $\dot{V}O_2$ mean response time (TD + τ) from 110 ± 23 s to 95 ± 18 s ($P < 0.05$). Based on the $\dot{V}O_2$ amplitude response, and a standard deviation of breath-to-breath fluctuation in $\dot{V}O_2$ of 0.021 l/min pre-CRT and 0.018 l/min post-CRT, the 95% confidence interval for the estimation of phase II $\dot{V}O_2$ τ was ±3.0 s pre-CRT and ±2.4 s post-CRT.

2.3.5 Heart Rate Kinetics

CRT decreased the resting ($Y_{(b)}$) heart rate by 5 beats/min ($P < 0.05$; Table 2-2). CRT did not significantly alter the heart rate time delay (TD) ($P > 0.05$; Table 2-2). CRT did decrease amplitude change (A) in heart rate (4 beats/min; Table 2-2) and the steady-state heart rate from 89 ± 20 beats/min to 80 ± 17 beats/min (both $P < 0.05$). CRT significantly decreased the heart rate time constant (τ) by 22% ($P < 0.05$; Table 2-2, Fig 2-2). Based on the heart rate amplitude responses in Table 2-2, and a standard deviation of beat-to-beat fluctuation in heart rate of 1.1 beats/min pre-CRT and 1.1 beats/min post-CRT, the 95% confidence interval for estimation of heart rate τ was ±2.1 s pre-CRT and ±4.6 s post-CRT.

2.3.6 Left Ventricular Function

LV volumes during both rest and exercise for both pre-CRT and post-CRT time points were measured in 7 of 11 subjects. In these subjects, CRT decreased resting LV EDV by 8% and LV ESV by 14%, and increased LV EF an absolute 5 percentage points (all $P < 0.05$; Fig 2-3). Resting stroke volume also increased 9 ml ($P < 0.05$; Fig 2-3). The post-CRT steady-state exercise LV EDV and LV ESV were 9% and 20% lower,

respectively, compared to pre-CRT steady-state exercise values ($P < 0.05$). CRT increased the exercise steady-state stroke volume by 31% and the steady-state cardiac output 27% (all $P < 0.05$; Fig 2-3). The change in moderate-intensity reserve (steady-state – rest) for LV volumes and stroke volume pre-CRT to post-CRT for individual subjects are shown in Fig. 2-4. LV ESV and stroke volume reserve increased from pre-CRT to post-CRT ($P < 0.05$), while LV EDV did not change ($P > 0.05$).

2.4 Discussion

We prospectively studied the effects of 6 mo of CRT on $\dot{V}O_2$ kinetics and exercise cardiovascular function in subjects with HF and reduced EF. The main new finding of this study was that CRT led to a significant speeding in phase II $\dot{V}O_2$ kinetics during the transition to moderate-intensity exercise (*i.e.*, exercise below the ventilatory threshold) from rest, thus reflecting a faster rate of oxidative phosphorylation to meet adenosine triphosphate demands during the transition to moderate-intensity exercise. Secondly, stroke volume during steady-state exercise was significantly increased, and this was due to a decrease in submaximal exercise LV ESV that was independent of cardiac preload, as the reserve in LV EDV did not increase from rest to exercise following CRT. Lastly, CRT improved heart rate measured as a lower resting and steady-state exercise heart rate. An unexpected finding was that CRT also resulted in faster heart rate kinetics, suggesting that autonomic control of heart rate during low-level exercise also changes with CRT. Cumulatively, the novel findings of this study indicate that the faster $\dot{V}O_2$ adaptation to moderate-intensity exercise following chronic CRT in subjects with HF may be the combined result of an enhanced exercise stroke volume response and faster heart rate kinetics.

2.4.1 $\dot{V}O_2$ Kinetics in Heart Failure and the Effects of CRT

Phase II $\dot{V}O_2$ kinetics have previously been shown to be prolonged in patients with HF and reduced EF (20, 25, 36, 42), and this may be mediated, in part, by impaired exercise cardiac function (43). At the onset of square-wave exercise, cardiac output increases rapidly and in an exponential manner at a rate that is often faster (21) or approximate (17) to $\dot{V}O_2$ kinetics in healthy subjects. Given that exercise cardiac output and muscle blood flow are tightly coupled (27), in addition to cardiac output kinetics having been shown to be slower than $\dot{V}O_2$ kinetics in patients with HF and reduced EF (18), supports the hypothesis that a slower O_2 delivery to exercising muscles may significantly contribute to the slowing in $\dot{V}O_2$ kinetics. However, little is known about the underlying cardiac mechanisms accounting for a delay in $\dot{V}O_2$ kinetics in patients with HF, and whether improving exercise cardiac function can reverse the impaired $\dot{V}O_2$ kinetics.

In a cross-sectional investigation, Matsumoto and colleagues (25) demonstrated in relatively less fit HF patients that cardiac output and $\dot{V}O_2$ kinetics were 54% and 38% slower, respectively, compared to relatively more fit HF patients. Notably, the slower cardiac output kinetics was well correlated with prolonged $\dot{V}O_2$ kinetics. In that same study (25), the kinetics of the arterial-venous O_2 content difference were similar between the less fit and more fit HF patients, suggesting that O_2 delivery and not O_2 extraction ability was a rate-limiting step for $\dot{V}O_{2p}$ kinetics. Consistent with an important cardiac role for affecting $\dot{V}O_2$ kinetics, Taniguchi et al. (42) showed that increasing LV EF (an 14% absolute) with 6 mo of β-blocker was associated with a 31% speeding in $\dot{V}O_2$ kinetics, suggesting that β-blockade may have conferred an improvement in exercise

stroke volume (3). As well, Koike et al. (20) demonstrated that both cardiac output and $\dot{V}O_2$ kinetics were 21% slower in patients with a lower (30 ± 3%) compared to those with a higher (40 ± 5%) LV EF, indicating a tight coupling between O_2 delivery and O_2 utilization that may be mediated by LV function. Notably, slower $\dot{V}O_2$ kinetics (–0.51, $p < 0.05$) and slower cardiac output kinetics (–0.33, $p = 0.02$) were associated with a lower LV EF (20). More recently, Sperandio et al. (36) demonstrated that the significantly slower $\dot{V}O_2$ and cardiac output kinetics in patients with HF and reduced EF also causes a "downstream" slowing in muscle microvascular O_2 delivery. A functional consequence of the central mediated slowing in O_2 delivery shown in previous reports of patient with HF and reduced EF is a perturbation in oxidative phosphorylation rate secondary to a reduction red blood cell flux (19, 31), thus causing a slowing in $\dot{V}O_2$ kinetics.

We extend these previous reports (20, 25, 36, 42) by demonstrating that improving exercise cardiac function by increasing LV ESV reserve and speeding heart rate kinetics, and presumably the rate of bulk O_2 delivery, can speed $\dot{V}O_2$ kinetics. We therefore infer from our study findings that the impaired LV ESV and heart rate responses to exercise incur a rate limiting affect on $\dot{V}O_2$ kinetics in patients with HF and reduced EF.

2.4.2 Effect of CRT on Heart Rate Kinetics

Previous studies have shown that patients with HF exhibit autonomic dysfunction as indicated by sympathoexcitation at rest (29), and during low-level exercise (28, 32). A major finding of our study was that heart rate kinetics were faster following CRT, and we suspect that this finding may be attributable to a change in cardiac autonomic control (2, 10, 13) that exhibited an effect during exercise.

In healthy individuals, the rapid increase in heart rate from rest to exercise onset is primarily due to a rapid reduction in parasympathetic activity that allows heart rate to accelerate quickly, and this effect predominates up to approximately 60% of the ventilatory threshold (46). During exercise above the ventilatory threshold, sympathetic nervous system activation accounts for further (and slower) increases in heart rate (46). Therefore, the shift from parasympathetic and sympathetic nervous control of heart rate during incrementally increasing exercise intensities likely accounts for the respective fast and slow heart rate kinetics reported in previous studies in young healthy individuals (16). We hypothesize that sympathoexcitation typically exhibited in patients with HF (28, 29, 32) may account, in part, for the slow heart rate kinetics that we found pre-CRT, and that CRT shifted the autonomic "profile" of cardiac control towards a more normalized parasympathetic control of heart rate at rest (2, 10, 13) and during moderate-intensity exercise. Consistent with this reasoning and indicative of enhanced resting vagal tone, Hamdan et al. (13) reported a significant reduction in muscle sympathetic nerve activity with CRT, Adamson et al. (2) found that CRT increased heart rate variability, and lastly Fantoni et al. (10) showed that CRT decreased resting heart rate 4 beats/min and increased heart rate variability. Similarly, we also found that CRT decreased resting heart rate 5 beats/min. However, our study extends these previous reports (2, 10, 13) by demonstrating that the shift towards greater parasympathetic heart rate control at rest may also contribute to a functional speeding in heart rate adaptation from rest to moderate-intensity exercise, measured as a faster heart rate τ.

Impaired cardiac output adaptation to exercise because of slower heart rate kinetics in patients with HF have previously been attributed, in part, to β-blocker use

(36). However, β-blocker use was not altered over the duration of the study in our subjects, thus any effect of β-blockade on heart rate kinetic parameter estimates would have been controlled for with our study design. In addition, it has previously been shown that β-blockade reduces the baseline (0 W cycling) and steady-state (100 W cycling) exercise heart rate in healthy young subjects, but does not affect the kinetics of heart rate during the transition to moderate-intensity exercise (15). Therefore, it is unlikely that β-blockade use confounded our study findings and rather emphasizes the added exercise cardiovascular benefit of CRT to standard (and optimal) pharmacologic therapy in patients with HF and reduced EF.

2.4.3 Effect of CRT on Resting LV Volumes

As previously shown, CRT was associated with reverse LV remodeling measured by a significant reduction in LV volumes and an increase in LV EF. Specifically, LV EDV decreased 8% and LV ESV decreased 14%, which is comparable to the 9% reduction in LV EDV and 11% reduction in LV ESV after 6 mo of CRT reported in the study by St John Sutton et al. (38), and is similar to the approximate 10% reduction in LV EDV and LV ESV reported by Saxon et al. (33), and the 10% reduction in LV EDV and 14% reduction in LV ESV reported by Stellbrink et al. (40), but is less than the 18% reduction in LV EDV and 25% reduction in LV ESV reported in the study by Yu et al. (47). Given the typically greater reduction in LV ESV compared to LV EDV associated with CRT, we found that LV EF increased an absolute 5%, which is similar to previous reports of an approximate absolute 4 to 5% increase in LV EF (1, 12, 38, 40), but is less than the absolute 11% increase found by Steendijk et al. (39). Also owing, in part, to the greater reduction in LV ESV versus LV EDV as previously detailed (38, 40, 47), we

found that resting stroke volume increased. Thus, relative to these larger studies, the magnitude of LV reverse remodeling that we report is comparable.

2.4.4 Effect of CRT on Sub-Maximal Exercise LV Function

Steady-state stroke volume response increased following CRT, which is consistent with a previous study showing optimized sequential biventricular pacing (LV before RV stimulation) increased stroke volume during submaximal cycle ergometry exercise compared to LV or simultaneous biventricular pacing (7). Our finding of an increase in exercise stroke volume was due primarily to enhanced systolic function as measured by a decrease in exercise LV ESV and increase in LV ESV reserve. The increase in LV ESV reserve was independent of an increase in cardiac preload as there was no change in LV EDV from rest to exercise. Compared to no pacing, acute LV pacing alone has been shown to increase LV EDV by 10 ml and stroke volume by 11 ml without a further reduction in LV ESV in patients with HF (6). These findings were attributed to LV pacing reducing the external constraint to LV filling by modulating a relatively earlier LV diastolic filling period prior to the RV (6). Compared to biventricular pacing, however, 6 mo of LV pacing alone has been shown to confer significantly less change in LV end-diastolic dimension (44), and this has been confirmed in a randomized multicenter trial (30). Our findings suggest that an enhanced Frank-Starling effect may not be present with sequential biventricular stimulation (LV before RV) during upright whole-body exercise compared to rest following chronic CRT.

Several factors may explain the lower LV ESV during exercise. Firstly, an improvement in β-adrendergic receptor sensitivity following CRT may increase myocyte sarcomere shortening rate (8), thus conferring an increase in contractility at rest (35, 39,

45), during dobutamine stress (45), and during atrial pacing (39). The lower exercise LV ESV may also be due, in part, to a reduction in intraventricular dyssynchrony (47). Lastly, the lower exercise LV ESV may also be secondary to a reduction in afterload that may be modulated by CRT (39), as we also found that SVR was lower post-CRT. Our study extends these previous reports by demonstrate that LV ESV is lower and LV ESV reserve higher during steady-state whole body exercise following CRT.

2.4.5 Limitations

This study has limitations. We did not investigate the time course of stroke volume throughout the exercise transient, and therefore we are not able to exclude a potential speeding in stroke volume adaptation as an additional mechanism attributing to our observation of faster $\dot{V}O_2$ kinetics in patients following CRT. We also did not control for or document physical activity in our study group during the CRT intervention period, and thus cannot discount potential skeletal muscle adaptations that may have occurred secondary to an improvement in physical function (26). Lastly, a methodologic disadvantage of imaging in a single-plane with our study group may be the potential overestimation of cardiac volumes compared to bi-plane imaging (37); however such possible error would be systematic from our pre- to post-CRT analyses, and thus would not affect our study findings. Accordingly, we have also reported reserve values to highlight the change LV function from rest to exercise pre- versus post-CRT. We also used a commercial contrast agent to further enhance the accuracy of our volume measures, as contrast has been shown to increase the accuracy and reproducibility of volume and LV EF determination, and increases the feasibility of single-plane imaging when compared to cardiac magnetic resonance imaging (24).

2.4.6 Conclusions

Chronic CRT reverses slow $\dot{V}O_2$ kinetics by increasing exercise stroke volume by reducing LV ESV and by causing a functional speeding in heart rate kinetics. The reduction in exercise LV ESV is independent of an increase in cardiac preload.

Table 2-1. Subject characteristics and peak exercise gas exchange

	n = 11
Age, yrs	59 ± 12
Male : female, n	8 : 3
Height, cm	169 ± 10
Mass, kg	84.1 ± 18.5
Body mass index, kg/m^2	29 ± 5
NYHA functional class	3.1 ± 0.3
Cardiovascular History	
Coronary artery disease, n (%)	7 (64)
Myocardial infarction, n (%)	4 (36)
Prior cardiac arrest, n (%)	2 (18)
Hypertension, n (%)	7 (64)
Medications	
β-blocker, n (%)	11 (100)
ACE or ARB, n (%)	11 (100)
Diuretic, n (%)	11 (100)
Digitalis, n (%)	5 (46)
Antiarrhythmic, n (%)	2 (18)
Anticoagulant, n (%)	7 (64)
Ventilatory Threshold	
$\dot{V}O_2$, l/min	0.79 ± 0.26
Power output, W	38 ± 16
Peak Exercise	
$\dot{V}O_2$, l/ min	1.08 ± 0.39
$\dot{V}CO_2/\dot{V}O_2$	1.23 ± 0.17
Power output, W	72 ± 25

Data are mean ± SD unless otherwise specified. NYHA, New York Heart Association; $\dot{V}O_2$, oxygen uptake; $\dot{V}CO_2$, carbon dioxide production. ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker.

Table 2-2. $\dot{V}O_2$ and heart rate kinetic parameter estimates

	$Y_{(b)}$	*A*	TD, s	τ, s
$\dot{V}O_2$, l/min				
Pre-CRT	0.30 ± 0.08	0.42 ± 0.18	41 ± 12	69 ± 21
Post-CRT	0.29 ± 0.08	0.42 ± 0.15	41 ± 13	54 ± 17*
Heart rate, beats/min				
Pre-CRT	70 ± 14	19 ± 9	0.1 ± 0.1	89 ± 12
Post-CRT	65 ± 13*	15 ± 7*	0.1 ± 0.1	69 ± 21*

Data are mean ± SD. $Y_{(b)}$, baseline; *A*, amplitude; TD, time delay; τ, time constant.
*Significantly different ($P < 0.05$) from Pre-CRT. n = 9 for heart rate data.

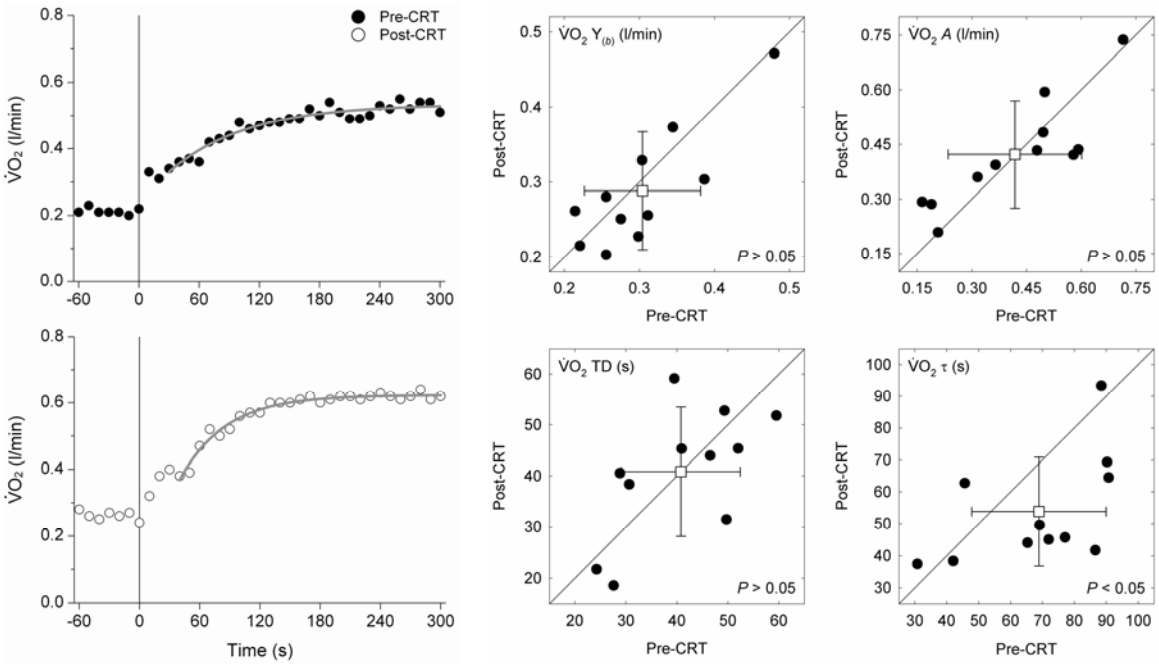

Figure 2-1. Oxygen uptake ($\dot{V}O_2$) responses during the transition to moderate-intensity exercise for a representative subject pre-CRT and post-CRT. Curve fits are also shown. Time 0 indicates exercise onset. Absolute exercise intensity was the same for pre-CRT and post-CRT testing. Panels to the right shown individual subject and mean ± SD data for kinetic parameter estimates.

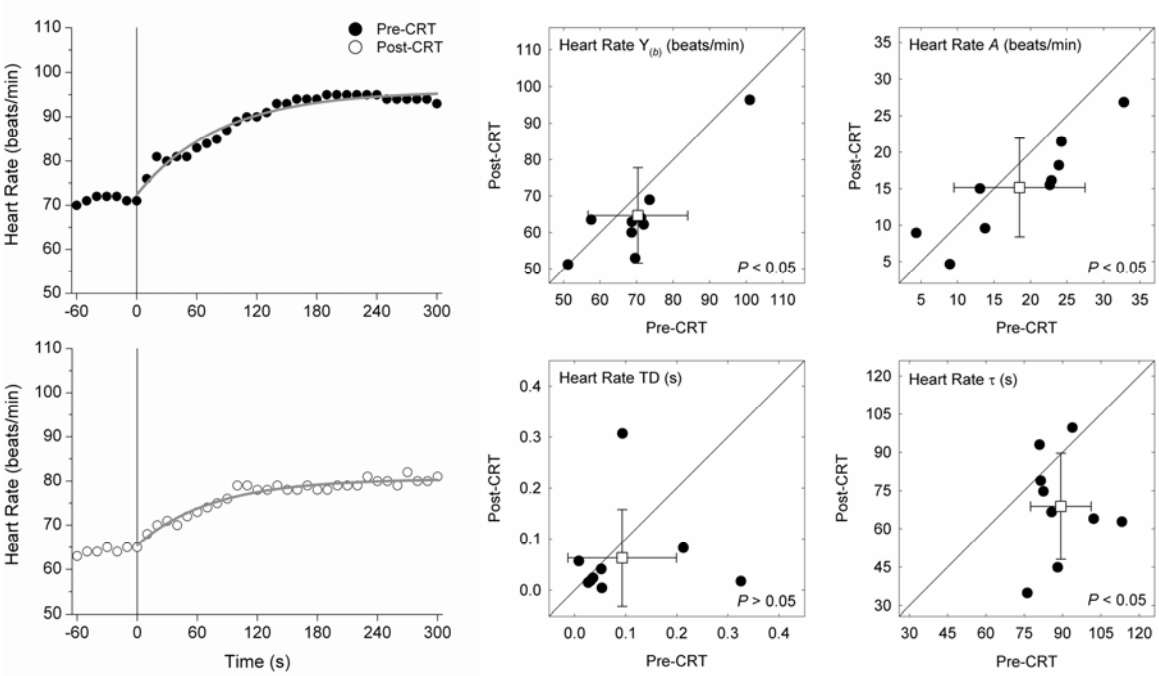

Figure 2-2. Heart rate responses during the transition to moderate-intensity exercise for a representative subject pre-CRT and post-CRT. Curve fits are also shown. Time 0 indicates exercise onset. Panels to the right shown individual subject and mean ± SD data for kinetic parameter estimates.

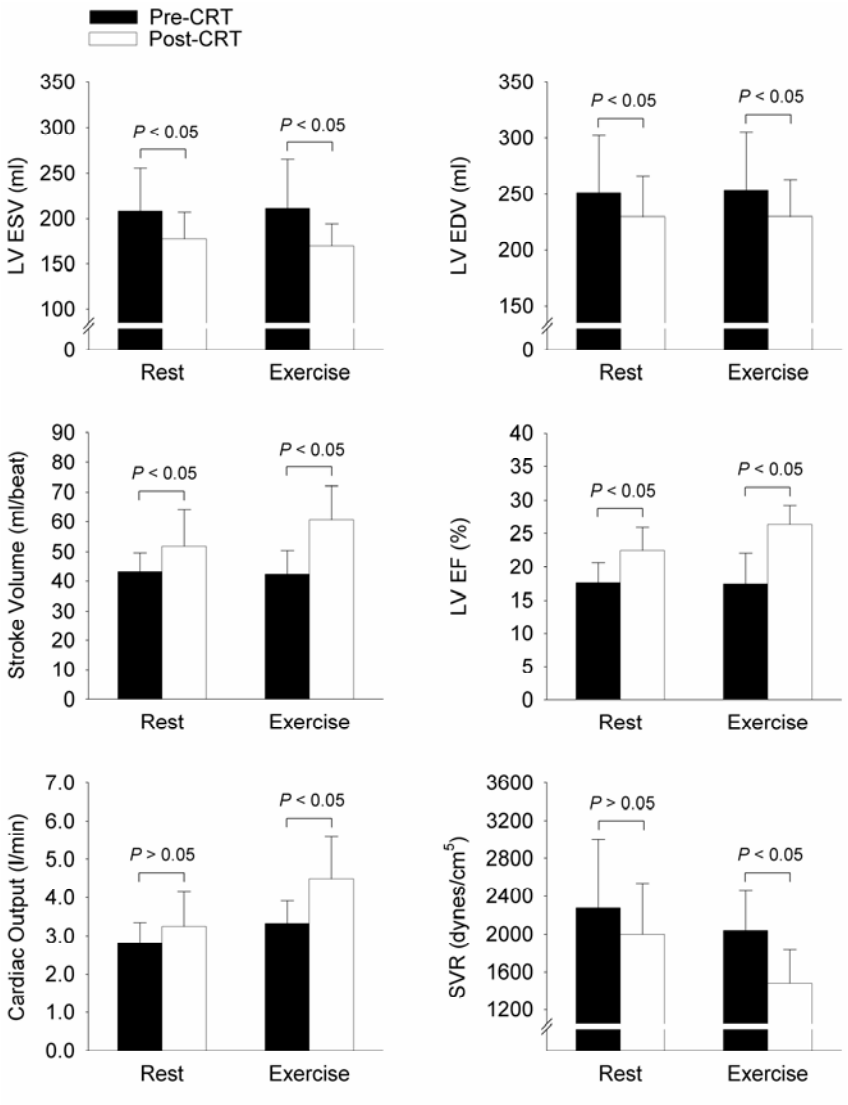

Figure 2-3. Effects of CRT on cardiovascular function at rest and during steady-state moderate-intensity exercise. LV ESV, left ventricular end-systolic volume; LV EDV, LV end-diastolic volume; LV EF, LV ejection fraction; SVR, systemic vascular resistance.

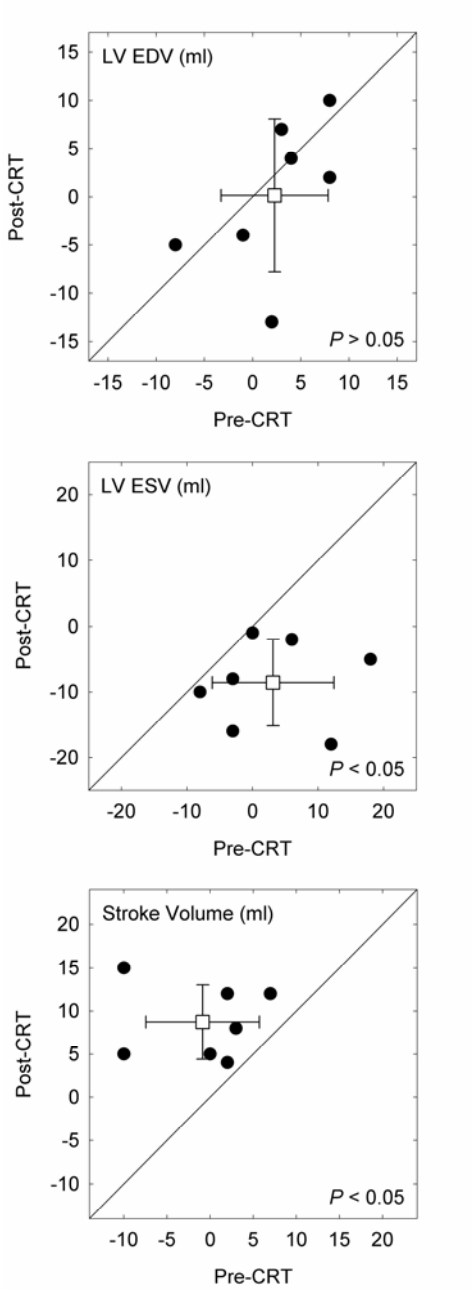

Figure 2-4. Effects of CRT on submaximal exercise cardiac reserve (steady-state exercise – rest). Panels show individual subject and mean ± SD data. LV EDV, left ventricular end-diastolic volume; LV ESV, LV end-systolic volume.

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Chapter 3

Cardiac Resynchronization Therapy Mediated Changes in Peak Exercise Left Ventricular Function and Post-Exercise Oxygen Uptake Kinetics

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3.1 Introduction

Several aspects of cardiopulmonary function during and following peak exercise are impaired in patients with heart failure (HF) and reduced ejection fraction (EF). In particular, peak pulmonary oxygen uptake ($\dot{V}O_2$) may be reduced by 30 to 50% (10, 21, 41), and the time for gas exchange and ventilation to recover from exercise may take upwards of 80% longer in patients with HF compared to healthy subjects (9, 10). These findings suggest that the maximum oxidative rate of the skeletal muscle is perturbed during exercise (22, 23). A reduction in O_2 availability (14, 22) secondary to a significant impairment in cardiac output may account for these observations (14, 21, 24, 41, 43).

Major trials have demonstrated that cardiac resynchronization therapy (CRT) increases peak $\dot{V}O_2$ in patients with drug refractory HF and reduced EF (1, 5, 12, 28, 47). Despite significant knowledge about the effects of CRT on resting left ventricular (LV) function, much less is known about the CRT mediated changes in LV function at peak exercise and the effects of CRT on the recovery of $\dot{V}O_2$ from peak exercise. Given that the delay in post-exercise $\dot{V}O_2$ has previously been associated with a delay in the time the restoration of skeletal muscle energy stores (9), and that this restoration is O_2 dependent (22), we suspect that a CRT mediated improvement cardiac output (and thus O_2 availability) may confer a speeding in post-exercise $\dot{V}O_2$.

Therefore, the aim of our study was to examine the CRT mediated improvements in peak exercise LV function, peak $\dot{V}O_2$, and recovery from peak exercise following

chronic (6 mo) of CRT. We tested the hypotheses that *1)* CRT would increase reserve and peak cardiac output, *2)* the increase in $\dot{V}O_2$ at peak exercise would be related to an increase in cardiac output reserve, *3)* CRT would decreased the time to exercise recovery as measured by a speeding in gas exchange and ventilation kinetics, and *4)* faster post-exercise $\dot{V}O_2$ kinetics would be associated with greater aerobic capacity.

3.2 Methods

3.2.1 Subjects

As described in Chapter 2, written and informed consent to participate in this investigation was provided by 21 subjects. The University of Alberta Hospital Research Ethics Board approved this study (Appendix A). Subjects met our hospital criteria for a CRT biventricular pacemaker, which included a diagnosis of New York Heart Association functional class III or IV HF with persistent symptoms despite stable and optimal medical therapy, a LV EF $\leq$ 35%, and a QRS duration > 120 ms consistent with interventricular conduction delay. Subjects further met our study criteria if they had a normal sinus rhythm and did not require atrial pacing, if their medications and HF symptoms had not changed in the previous 3 months, if they reported being able to perform stationary bicycle exercise, and had no change in medications while enrolled in our study. Subjects were excluded if they did not have a normal intrinsic sinus rhythm, the CRT device/lead wire implantation was not successful, or if HF symptoms/condition or comorbidities precluded exercise testing. Medications were not discontinued for testing.

3.2.2 Peak Exercise Protocol

For this study, subjects underwent exercise testing at baseline (pre-CRT) and 6 mo after CRT (post-CRT). Peak exercise testing to volitional fatigue was completed on a customized semi-recumbent (112º seat angle) electronically braked cycle ergometer (Corival, Lode, Groningen, The Netherlands). Following a 5-min resting measurement period, exercise began at 15 W for 1 min and was followed by 10 W/min increments. Exercise was terminated when subjects indicated they could no longer continue, or if subjects could no longer sustain a pedal rate of 50 revolutions/min. Upon exercise termination, subjects remained seated during a "quiet breathing and rest" period that was free of limb movement for 7 min. Recovery pulmonary gas exchange and ventilation were recorded during this period.

During exercise, subjects were provided standardized encouragement and assessment at regular intervals by an investigator. This included the questions "Are you feeling any dizziness, (abnormal) shortness of breath, or chest pain?", and "Do you feel that you can continue for about another 1 minute?". Subjects also pointed to a perceived exertion scale to aid in determining fatigue and answered questions with predetermined hand signals. As detailed in section *3.2.5 Measurement of Left Ventricular Function at Peak Exercise*, we wanted to assess LV function at peak exercise. The latter question served to aid in determining a subject's estimated remaining time of exercise. However, we were careful to not influence the time point of exercise termination by "suddenly" posing the latter question only when the subject was obviously nearing exercise termination. Thus, the latter question was asked a number of times early in the exercise protocol so as to not alert subjects that our measurements suggested they were nearing

exercise termination, thereby potentially signaling to them to terminate exercise prematurely.

3.2.3 Pulmonary Gas Exchange and Ventilation

Breath-by-breath pulmonary gas exchange and ventilation parameters were measured using a commercial system (SensorMedics® Vmax 229; VIASYS™ Healthcare Respiratory Technologies, Yorba Linda, CA, US). Prior to peak exercise, the low resistance, low deadspace (90 ml), bi-directional mass flow sensor was calibrated with a 3.0 L syringe across expected breathing frequencies. The paramagnetic O_2 analyzer and non-dispersive infrared CO_2 analyzer were calibrated using a 2-point calibration with known gas concentrations. We assessed peak $\dot{V}O_2$ and ventilation parameters (tidal volume, VT; breathing frequency, f_b; and minute ventilation, $\dot{V}E$), and recovery kinetics for $\dot{V}O_2$, carbon dioxide production ($\dot{V}CO_2$), and $\dot{V}E$. The ventilatory threshold was identified as the point of change in the $\dot{V}CO_2$ and $\dot{V}O_2$ slope (6). Peak $\dot{V}O_2$, and corresponding gas exchange and ventilation parameters, were the highest 30 s values within the last 1 min of exercise. A 12-lead electrocardiogram (CASE® 8000, GE Healthcare, Freiburg, DE), manual brachial cuff blood pressure, and pulse oximetry were also monitored throughout and during exercise and recovery every 2 min.

3.2.4 Contrast-Enhanced Echocardiography

Resting and peak exercise 2-dimensional echocardiograms (Vivid-*i*® or Vivid 7®; GE Medical Systems, Milwaukee, Wisconsin, US) were performed with subjects sitting on the semi-recumbent cycle ergometer at a 112º seat angle. As described in Chapter 2, an intravenous line was established on the dorsum of the hand or antebrachium. Once an apical 4-chamber viewing window was obtained, the sonographer's arm was stabilized on

an adjustable stand and the transducer kept in place at rest and for the duration of exercise. Image acquisition was preceded by a slow bolus 0.2 ml intravenous injection of commercial contrast agent (Definity®; Bristol-Myers Squibb, New York, NY, US) that was followed by a normal saline flush at a manual rate that optimized LV cavity opacification. Single-plane apical 4-chamber view cine images of 5 loops were then recorded to determine LV volumes. A single-plane view for determining LV volumes was used to ensure consistency in the viewing window between resting and peak exercise images.

3.2.5 Measurement of LV Function at Peak Exercise

Peak exercise echocardiograms were obtained within the approximate last 30-s of exercise. An investigator determined that a subject was nearing exercise termination based on $\dot{V}CO_2/\dot{V}O_2$, self-rated perceived exertion on a 10-point scale, and asking "Do you feel that you can continue for about another 1 minute?". When subjects indicated they were nearing volitional fatigue, we prepared for the peak exercise image acquisition, and this included a bolus injection of contrast agent as we have described in section *3.2.4*. There were no instances when exercise was terminated unexpectedly.

3.2.6 Pacemaker Programming

Pacemaker device programming was standardized and implemented at the time of device implant as previously described in Chapter 2. Briefly, all subjects received a combined CRT-implantable cardiodefibrillator device (CRT-ICD) and 1 subject received a CRT device without an ICD based on their clinical status. Device programming was designed to ensure atrial sensed ventricular pacing while maintaining ventricular capture and LV-before-RV stimulation. As previously described in Chapter 2, we programmed

the base rate to 50 beats/min, the atrioventricular delay fixed at 100 – 120 ms, and the interventricular delay to stimulate the LV 20 ms prior to RV stimulation. The defibrillation threshold was programmed 20 beats/min above the estimated peak exercise heart rate. The ventricular tachycardia detection mode was turned off for exercise testing. Settings were restored upon completion of exercise testing.

3.2.7 Curve Fitting

Breath-by-breath pulmonary gas exchange and ventilation was filtered for aberrant breaths (27), linearly interpolated to 1-s intervals, and averaged to 10-s intervals. As we have previously detailed (44), kinetic parameter estimates for $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ during peak exercise recovery were determined using a first-order mathematical model of the form:

$$Y_{(t)} = Y_{(peak)} - A \cdot [1 - e^{-(t-TD)/\tau}]$$

where Y is the respective parameter at any time (t), *peak* is the greatest value of Y over 30 s, A is the amplitude change in Y throughout recovery, τ is the time to reach a 63% change in Y, and TD is the time delay prior to the exponential change in Y.

Kinetic parameter estimates were determined using non-linear regression. The iterative procedure of the computer program (Origin 7.5, OriginLab Corp., Northampton, MA, US) employed a Levenberg-Marquardt algorithm whereby the best fit was defined by minimization of the residual sum of squares. The 95% confidence intervals of the estimated time constant for $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ were calculated using the method described by Lamarra et al. (27).

3.2.8 Cardiovascular Analyses

We determined ventricular volumes by manually tracing endocardial borders with the papillary muscles included in the ventricular cavity (Xcelera, Philips Healthcare, Andover, MA, US). LV EDV was measured as the largest cavity area prior to the onset of the QRS complex and LV ESV was measured as the smallest cavity area prior to mitral valve opening. Single-plane volumes were calculated using the disc summation method. LV EF was calculated as ((LV EDV – LV ESV)/LV EDV) × 100, stroke volume as LV EDV – LV ESV, and cardiac output as stroke volume × heart rate. We assessed reserve (peak – rest) LV EDV, LV ESV, stroke volume, heart rate, cardiac output, and LV EF. Data are the average over 3 cardiac cycles. Manual brachial cuff blood pressure values were used to calculated mean arterial pressure and systemic vascular resistance (SVR) was calculated as SVR = (mean arterial pressure/cardiac output) × 80.

3.2.9 Statistics

Paired *t*-tests were used to determine statistical differences between pre-CRT and post-CRT variables (SPSS 11.0.1, Chicago, IL, US). Correlation regression was used to compare the relationship between cardiac output reserve and peak $\dot{V}O_2$, peak $\dot{V}O_2$ and $\dot{V}O_2$ τ, and between $\dot{V}CO_2$ τ and $\dot{V}E$ τ (SigmaPlot 8.02, SPSS, Chicago, IL, US). Data are presented as mean ± SD and $P < 0.05$ was considered statistically significant.

3.3 Results

3.3.1 Adverse Events

One subject suffered cardiac arrest during pacemaker implant and was successfully resuscitated; this subject continued with the study without further pacemaker related or neurologic complications. Similar to the reasons detailed in Chapter 2, 9

subjects did not complete this study. Briefly, 1 subject completed baseline testing and decline follow-up testing because of their HF symptoms. One subject completed baseline testing, but LV transvenous lead placement was unsuccessful and an epicardial lead was not considered based on the subject's clinical status. One subject was hypotensive and symptomatic upon arrival for testing and the protocol was not conducted for safety; this subject declined further testing at a later date. One subject consented to study participation, but died prior to baseline testing and pacemaker implantation. Baseline testing was completed on 3 subjects who later had indications of decompensated HF on their follow-up testing day. Another subject had indications of decompensated HF on the baseline testing day. These 4 subjects were immediately seen by a cardiologist in the testing laboratory, admitted to hospital the same day as testing, and later died in hospital. One subject completed baseline testing and declined follow-up testing because of their HF symptoms.

3.3.2 Subject Characteristics

In total, 12 subjects completed this study (Table 3-1). The HF etiology was ischemic in 7 subjects and non-ischemic in 5 subjects. Subject medications are listed in Table 3-1. Medications and dosages did not change over the intervention period. Testing began at the same time of day (within ~0.5 hr) for pre-CRT and post-CRT time-points. All subjects confirmed medication self-administration at their regular time on testing days and the day prior to testing. The CRT device in all subjects had a passive fixed right atrial lead placed in the atrial appendage, a right ventricular active fixed lead placed in the apex, and a transvenous LV lead placed about the postero-lateral wall (n = 5) or

lateral wall (n = 7). One subject received a LV lateral wall epicardial lead the same day following unsuccessful transvenous lead placement.

3.3.3 Resting LV Function

Changes in resting LV function reported here are similar to our findings detailed for this study cohort in Chapter 2. Briefly, CRT was associated with LV reverse remodeling as indicated by a significant 23 ± 22 ml (range: –57 to 2 ml) reduction in LV EDV and a 29 ± 29 ml (range: –63 to 12 ml) reduction in LV ESV (Table 3-2). There was a trend increase of an absolute 4 ± 6 % (range: –8 to 11 %) in resting LV EF ($P = 0.052$; Table 3-2). Stroke volume increased 6 ± 12 ml (range: –19 to 22 ml; $P > 0.05$; Table 3-2). Resting heart rate decreased significantly (Table 3-2) and there was no change in resting SVR (Table 3-2).

3.3.4 Peak Exercise $\dot{V}O_2$ and LV Function

All subjects tolerated peak exercise testing without any adverse events or decrease in O_2 saturation. $\dot{V}O_2$ at the ventilatory threshold was higher post- (10.6 ± 2.4 ml/kg/min) compared to pre-CRT (9.4 ± 2.1 ml/kg/min; $P < 0.05$). Peak $\dot{V}O_2$ increased 2.0 ± 2.4 ml/kg/min (range: –2.9 to 5.9 ml/kg/min) post-CRT ($P < 0.05$; Table 3-2). There was no effect of CRT on peak exercise ventilation (Table 3-2). Peak exercise power output increased 9 ± 15 W (range: –20 to 30 W) post-CRT ($P = 0.059$; Table 3-2).

Peak exercise LV EDV and LV ESV were lower post-CRT ($P < 0.05$; Table 3-2). LV EDV and LV ESV reserve were not statistically different from pre- to post-CRT (Fig 3-1). There was no change in peak exercise heart rate ($P > 0.05$; Table 3-2); heart rate reserve increased 6 ± 11 beats/min ($P > 0.05$; Fig 3-1). Stroke volume reserve (Fig 3-1) and stroke volume at peak exercise (Table 3-2) were significantly greater post-CRT.

There was a 1.9 fold increase in cardiac output from rest to peak exercise pre-CRT (range of cardiac output reserve: 1.2 to 5.2 l/min) compared to a 2.3 fold increase post-CRT (range of cardiac output reserve: 2.3 to 6.4 l/min). Peak exercise cardiac output was higher post-CRT ($P < 0.05$, Table 3-2; Fig 3-2). SVR was significantly lower at peak exercise post-CRT (Table 3-2). Cardiac output reserve was related to $\dot{V}O_2$ at peak exercise ($r = 0.48$, $P < 0.05$; Fig 3-3).

3.3.5 Post-Exercise $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ kinetics

CRT significantly improved the time constant (τ) for $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ over a 7-min recovery period following peak exercise (Table 3-3). Given the higher peak exercise gas exchange values post-CRT, the amplitude decrease (A) in $\dot{V}O_2$ and $\dot{V}CO_2$ throughout peak exercise recovery was also greater post-CRT (Table 3-3). Figure 3-2 illustrates exercise and recovery $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ responses to CRT and corresponding exponential curve fits for a representative subject. Individual time constants for $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ pre- versus post-CRT are also shown in Fig. 3-2. Correlation-regression analysis indicated that an increase in peak $\dot{V}O_2$ was related to a faster $\dot{V}O_2$ recovery time constant ($r = –0.46$, $P < 0.05$; Fig 3-3). Additionally, $\dot{V}CO_2$ and $\dot{V}E$ recovery kinetics were also correlated ($r = 0.80$, $P < 0.05$; Fig 3-3).

3.3.6 Parameter Estimation Confidence Intervals for τ

Visual inspection of peak exercise recovery data and the appropriateness of the curve fit to the data, and inspection of the residual sums of squares values indicated that our modeling approach and procedures adequately described the time course change in $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ over the 7-min recovery period. Based on the $\dot{V}O_2$ amplitude response (Table 3-3), and a standard deviation of breath-to-breath fluctuation in $\dot{V}O_2$ of

0.60 ml/kg/min pre-CRT and 0.34 ml/kg/min post-CRT, the 95% confidence interval for the estimation of $\dot{V}O_2$ τ was ±2.6 s pre-CRT and ±1.7 s post-CRT. Based on the $\dot{V}CO_2$ amplitude response (Table 3-3), and a standard deviation of breath-to-breath fluctuation in $\dot{V}CO_2$ of 0.60 ml/kg/min pre-CRT and 0.50 ml/kg/min post-CRT, the 95% confidence interval for the estimation of $\dot{V}CO_2$ τ was ±2.2 s pre-CRT and ±1.9 s post-CRT. Lastly, based on the $\dot{V}E$ amplitude response (Table 3-3), and a standard deviation of breath-to-breath fluctuation in $\dot{V}E$ of 1.78 L/min pre-CRT and 2.00 L/min post-CRT, the 95% confidence interval for the estimation of $\dot{V}E$ τ was ±2.2 s pre-CRT and ±2.6 s post-CRT.

3.4 Discussion

In this prospective study, we examined the effects of chronic CRT on peak exercise left ventricular reserve function, and the relationship between peak exercise cardiopulmonary function and post-exercise $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ recovery kinetics in patients with HF. The novel findings of this investigation were that *1)* CRT increased reserve and peak cardiac output, *2)* CRT increased $\dot{V}O_2$ at peak exercise and this was related to an increase in cardiac output reserve, *3)* CRT decreased the time to exercise recovery as measured by a speeding in $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ recovery kinetics within the first 7 min post-exercise, and *4)* faster post-exercise $\dot{V}O_2$ kinetics were associated with greater aerobic capacity. Cumulatively, we demonstrate that chronic CRT increases peak exercise systolic function and aerobic capacity, and improves the early recovery from peak exercise measured as a speeding in $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ kinetics.

3.4.1 Effect of CRT on Resting LV Function

As reported for this study cohort in Chapter 2, CRT was associated with reverse LV remodeling as evidenced by a significant reduction in resting LV EDV and LV ESV,

and a 4 percentage point increase in LV EF (Table 3-2). The magnitude of the changes in LV EDV, LV ESV, and LV EF that we found are comparable to reports from major clinical trials that assessed peak $\dot{V}O_2$ and resting LV function following CRT (1, 5, 28, 39, 47).

3.4.2 Factors Affecting Peak $\dot{V}O_2$ in Heart Failure and the Effects of CRT

Peak $\dot{V}O_2$ is upwards of 50% lower in patients with HF and reduced EF compared to healthy controls (21, 41). The impairment in peak $\dot{V}O_2$ can be attributed, in part, to a concomitant reduction in peak cardiac output (41) that is secondary to a decrease in heart rate and a reduction in both LV ESV reserve and use of the Frank-Starling mechanism (thus reducing stroke volume) (26, 35, 41).

Several studies have previously shown that CRT improves exercise capacity in patients with HF measured as an average increase in peak $\dot{V}O_2$ ranging from 1.1 to 3.1 ml/kg/min (1, 3, 4, 8, 12, 17, 28). We also found that CRT increased exercise capacity as measured by a 9% increase (2.0 ± 2.4 ml/kg/min) in peak $\dot{V}O_2$. However, the mechanistic basis for the previously reported improvement in exercise capacity associated with CRT has not been well studied. To the best of our knowledge no investigation has simultaneously assessed LV function and $\dot{V}O_2$ during peak whole-body exercise in HF patients undergoing CRT. Using contrast enhanced 2-dimensional echocardiography, we found that peak and reserve cardiac output increased following CRT. The increase in cardiac output was primarily due to an increase in peak and reserve stroke volume reserve, and likely a small salutary increase in heart rate reserve (see *3.4.3 Mechanistic Basis for Improved Peak Exercise Cardiac Output* for detailed discussion).

In their study, Duncan et al. (12) reported that the change in resting LV end-systolic dimension accounted for 22% of the variance in the change in peak $\dot{V}O_2$. Similarly, we found that an increase in cardiac output reserve accounted for only 23% of the variance in peak $\dot{V}O_2$. Together, these data suggest that the CRT mediated changes in peak $\dot{V}O_2$ are not restricted to solely improvements in resting and exercise LV function (*i.e.*, reduction in LV ESV, and an increase in stroke volume and cardiac output), as a reduction in limb blood flow (14, 41) and an unfavorable shift in skeletal muscle fiber composition (11, 40) and reduction in cross sectional area (21) also occurs in HF. Thus, other factors not measured in the current study that could contribute to the increase in peak $\dot{V}O_2$ secondary to a CRT modulated reduction in sympathoexcitation (2, 15, 20) include a reversal of chronic skeletal muscle underperfusion, reversal of skeletal muscle myopathy, and a subsequent shift towards greater oxidative metabolism (30).

3.4.3 Mechanistic Basis for Improved Peak Exercise Cardiac Output

The increase in cardiac output at peak exercise post-CRT is attributable to the combined effects of a smaller reduction in LV EDV reserve and a greater increase in LV ESV reserve. The net effect of these changes in LV EDV and LV ESV reserve significantly increased stroke volume reserve and stroke volume at peak exercise. Given that LV EDV reserve did not increase at peak exercise, we believe that the small increase in LV ESV reserve was not because of an increase in cardiac preload. The increase in LV ESV that we did observe may be due, in part, to a reduction in LV afterload (16, 19), as we found that SVR was significantly lower at peak exercise post-CRT. It is also noteworthy that although not significant, heart rate reserve increased subsequent to a

reduction in resting heart rate, which is consistent with previous findings (3). It is likely that this small (6 beats/min) increase also facilitated an increase in cardiac output reserve.

Others have shown that CRT improves LV systolic function and preserves diastolic function during simulated exercise and cycle ergometry exercise. During LV catheterization and biventricular pacing at 100 and 120 beats/min, Steendijk et al. (38) showed that CRT increased cardiac output with a small reduction in LV ESV and significant increase in contractility (dP/dt_{max}) compared to biventricular pacing at 80 beats/min. Using low-dose dobutamine infusion, Valzania et al. (45) also showed that CRT was associated with a greater increase in contractility (LV systolic tissue velocity), aortic velocity time integral, and cardiac output. Lastly, Ennezat et al. (13) found that CRT increased LV contractility during cycle ergometry exercise. Similar to our observation, Steendijk et al. (38) also showed that LV EDV decreased to a lesser degree post-CRT compared to pre-CRT during increased pacing rates. This latter finding may be attributable to enhanced diastolic function measured as an increase in early and late diastolic tissue velocity and diastolic filling time (45, 46).

Given the current study findings and those of previous reports (13, 38, 45, 46), we conclude that the increase in peak exercise cardiac output following chronic CRT is attributable to an increase in LV ESV reserve that is modulated, in part, by increased LV contractility, a reduction in LV afterload, and preserved, but not enhanced, cardiac preload.

3.4.4 Effects of CRT on Post-Exercise $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ kinetics

Several investigators have shown that the post-exercise recovery of $\dot{V}O_2$ is delayed following both submaximal and maximal exercise in patients with HF (7, 9, 10,

18, 31, 34, 36). An important mechanism thought to be responsible for the attenuation in recovery $\dot{V}O_2$ kinetics is a delay in the post-exercise restoration of phosphocreatine (9) that is mediated by a reduction in O_2 availability (22, 23, 25, 43). Given previous reports that the rate of phosphocreatine restoration post-exercise reflects the maximum rate of oxidative adenosine triphosphate synthesis (23, 33), and that this process is highly O_2 dependent (14, 22, 23), we confirmed our hypothesis that increasing the maximal rate of oxidative phosphorylation by increasing cardiac output with CRT would, in addition to increasing peak $\dot{V}O_2$, also speed $\dot{V}O_2$ kinetics following exercise. Our finding that an increase in peak $\dot{V}O_2$ following CRT was correlated with faster post-exercise $\dot{V}O_2$ kinetics further supports this conclusion.

Although we did not evaluate post-exercise cardiovascular function in the present study, others have shown that cardiac output (and its determinants) are impaired throughout exercise recovery, and this may contribute to the prolonged recovery of $\dot{V}O_2$ kinetics in HF. For example, Koike et al. (25) found that heart rate following sub-maximal exercise was slower in patients with a lower compared to higher LV EF, and that this was associated with slower $\dot{V}O_2$ kinetics. However, this contrasts other reports that post-exercise heart rate kinetics are not impaired in HF patients compared to healthy controls following peak exercise despite slower $\dot{V}O_2$ kinetics (9, 34). Tanabe et al. (43) reported a lower cardiac output at peak exercise and slower cardiac output recovery following exercise in patients with more severe compared to less severe HF, and the impaired cardiac output was correlated with slower $\dot{V}O_2$ kinetics. In addition, Tanabe et al. (43) reported higher SVR through recovery in patients with more severe HF, suggesting that a greater post-exercise LV afterload may contribute, in part, to lower a

stroke volume and cardiac output in those patients. Consistent with the deleterious effect that vascular dysfunction may have on post-exercise $\dot{V}O_2$ kinetics, Guazzi et al. (18) found that phosphodiesterase-5 inhibition improved flow mediated endothelial function and post-exercise $\dot{V}O_2$ kinetics in patients with HF. Whether CRT confers a beneficial cardiac output and vascular effect throughout the early post-exercise recovery period (first 7 min) was not directly measured in our investigation. However, we reason that if O_2 availability throughout peak exercise recovery did not improve following CRT, then this would be reflected as no change in post-exercise $\dot{V}O_2$ kinetics.

We found that CRT also decreased the recovery time for $\dot{V}CO_2$ and $\dot{V}E$ kinetics. Prolonged $\dot{V}CO_2$ kinetics may be attributed to a circulatory delay throughout exercise recovery (42) or to a relatively early onset of the lactate accumulation (32). Our findings that CRT increased the ventilatory threshold and increased peak cardiac output suggest that CRT reversed a circulatory delay (thus clearing CO_2 at a faster rate) and reduced the early reliance on non-oxidative energy sources during exercise. A consequence of the faster clearance of CO_2 is a faster rate of recovery for $\dot{V}E$, and indeed, we found that $\dot{V}CO_2$ and $\dot{V}E$ kinetics were well correlated.

3.4.5 Limitations

This study had limitations. We did not assess cardiac function throughout the exercise recovery period, and thus the exact affect of CRT on LV function during the first 7 min of recovery remains unknown. As indicated in Chapter 2, cardiac imaging was performed using a single-plane and this could affect absolute values for cardiac volumes (37). As we have noted, such error would be systematic from our pre- to post-CRT analyses. Therefore, we have also reported reserve values to highlight the change LV

function from rest to peak exercise pre- versus post-CRT. To further increase the feasibility of our imaging technique, we used a commercial contrast agent (29).

3.4.6 Conclusions

In this study we demonstrate that the CRT mediated changes in LV function at peak exercise include a preservation of LV EDV reserve and a greater increase in LV ESV reserve that subsequently increases peak and reserve stroke volume and cardiac output. The decrease in peak exercise LV ESV may be the combined effects of increased contractility and reduced LV afterload. We also demonstrate that CRT decreases the recovery time of $\dot{V}O_2$ following peak exercise, and that this related to an increase in aerobic capacity.

Table 3-1. Subject characteristics

	n = 12
Age, yrs	56 ± 15
Male : female, n	9 : 3
Height, cm	169 ± 9
Mass, kg	83.3 ± 17.8
Body mass index, kg/m^2	29 ± 5
NYHA functional class	3.1 ± 0.3
Cardiovascular History	
Coronary artery disease, n (%)	7 (58)
Myocardial infarction, n (%)	4 (33)
Prior cardiac arrest, n (%)	2 (17)
Hypertension, n (%)	8 (67)
Medications	
β-blocker, n (%)	12 (100)
ACE or ARB, n (%)	12 (100)
Diuretic, n (%)	12 (100)
Digitalis, n (%)	6 (50)
Antiarrhythmic, n (%)	2 (17)
Anticoagulant, n (%)	7 (58)

Data are mean ± SD unless otherwise specified. NYHA, New York Heart Association; $\dot{V}O_2$, oxygen uptake; $\dot{V}CO_2$, carbon dioxide production. ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker.

Table 3-2. Effect of CRT on pulmonary gas exchange, ventilation, and cardiovascular function at rest and peak exercise

	Rest		Peak Exercise	
	Pre-CRT	Post-CRT	Pre-CRT	Post-CRT
Power output, W	–	–	72 ± 24	81 ± 25
$\dot{V}O_2$, ml/kg/min	3.8 ± 0.5	3.8 ± 0.6	12.9 ± 3.2	14.9 ± 3.5*
$\dot{V}CO_2$, ml/kg/min	3.3 ± 0.5	3.5 ± 0.8	15.9 ± 4.5	18.0 ± 4.2*
$\dot{V}CO_2/\dot{V}O_2$	–	–	1.23 ± 0.16	1.22 ± 0.09
$\dot{V}E$, l/min	13 ± 4	13 ± 3	55 ± 11	56 ± 11
VT, l	0.66 ± 0.19	0.64 ± 0.15	1.54 ± 0.47	1.51 ± 0.42
f_b, breaths/min	20 ± 5	20 ± 4	37 ± 7	39 ± 7
LV EDV, ml	253 ± 43	230 ± 30*	248 ± 48	228 ± 33*
LV ESV, ml	207 ± 42	178 ± 26*	196 ± 49	162 ± 25*
Stroke volume, ml	46 ± 8	52 ± 10	50 ± 12	65 ± 14*
Heart rate, beats/min	67 ± 9	62 ± 8*	113 ± 19	114 ± 15
Cardiac output, l/min	3.1 ± 0.8	3.2 ± 0.7	5.8 ± 1.4	7.4 ± 1.7*
LV EF, %	19 ± 4	23 ± 4	22 ± 6	29 ± 5*
MAP, mmHg	70 ± 8	64 ± 64	72 ± 9	72 ± 9
SVR, dyn/s/cm^5	2258 ± 594	2105 ± 507	1041 ± 252	836 ± 219†

Data are mean ± SD. $\dot{V}O_2$, pulmonary oxygen uptake; $\dot{V}CO_2$, carbon dioxide output; $\dot{V}E$, minute ventilation; VT, tidal volume; f_b, breathing frequency; LV EDV, left ventricular end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; MAP, mean arterial pressure; SVR, systemic vascular resistance. *Significantly different ($P < 0.05$) from Pre-CRT values for respective columns. $^\dagger P = 0.053$. n = 10 for cardiovascular data.

Table 3-3. $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}E$ kinetics

	τ, s		*A*	
	Pre-CRT	Post-CRT	Pre-CRT	Post-CRT
$\dot{V}O_2$, ml/kg/min	83 ± 22	67 ± 14*	8.7 ± 3.1	10.6 ± 3.8*
$\dot{V}CO_2$, ml/kg/min	140 ± 40	119 ± 44*	11.8 ± 3.8	14.2 ± 4.3*
$\dot{V}E$, l/min	127 ± 27	108 ± 41*	35 ± 9	37 ± 9

Data are mean ± SD. τ, time constant; *A*, amplitude; $\dot{V}O_2$, pulmonary oxygen uptake; $\dot{V}CO_2$, carbon dioxide output; $\dot{V}E$, minute ventilation.*Significantly different ($P < 0.05$) from Pre-CRT. n = 11.

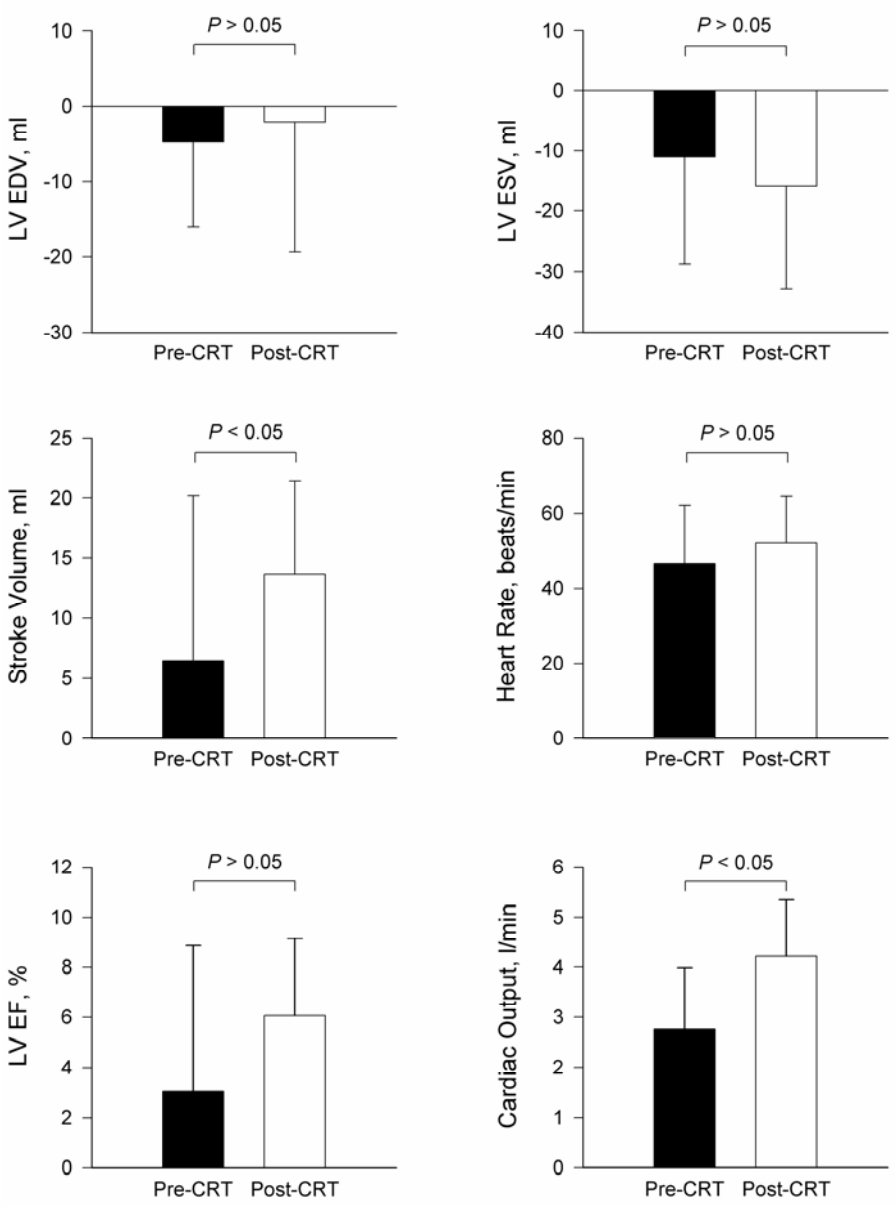

Figure 3-1. Cardiac reserve function. Values were calculated as peak – rest. LV EDV, left ventricular end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction. Data are mean ± SD. n = 10.

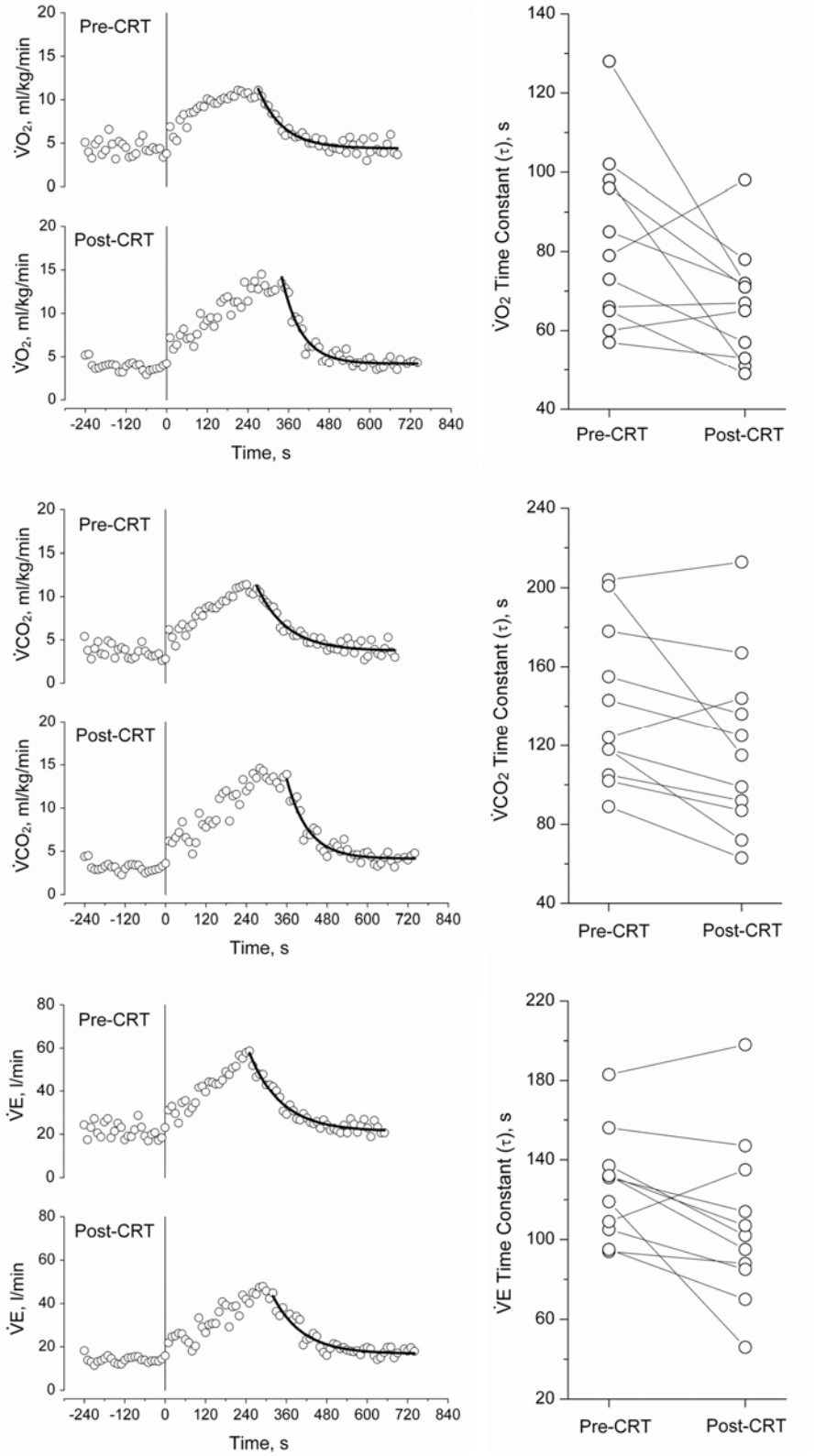

Figure 3-2. Representative subject exercise and recovery gas exchange and ventilation following CRT. Individual time constants and curve fits are shown. $\dot{V}O_2$, oxygen uptake; $\dot{V}CO_2$, carbon dioxide output, $\dot{V}E$, minute ventilation. Time 0 is exercise onset. n = 11.

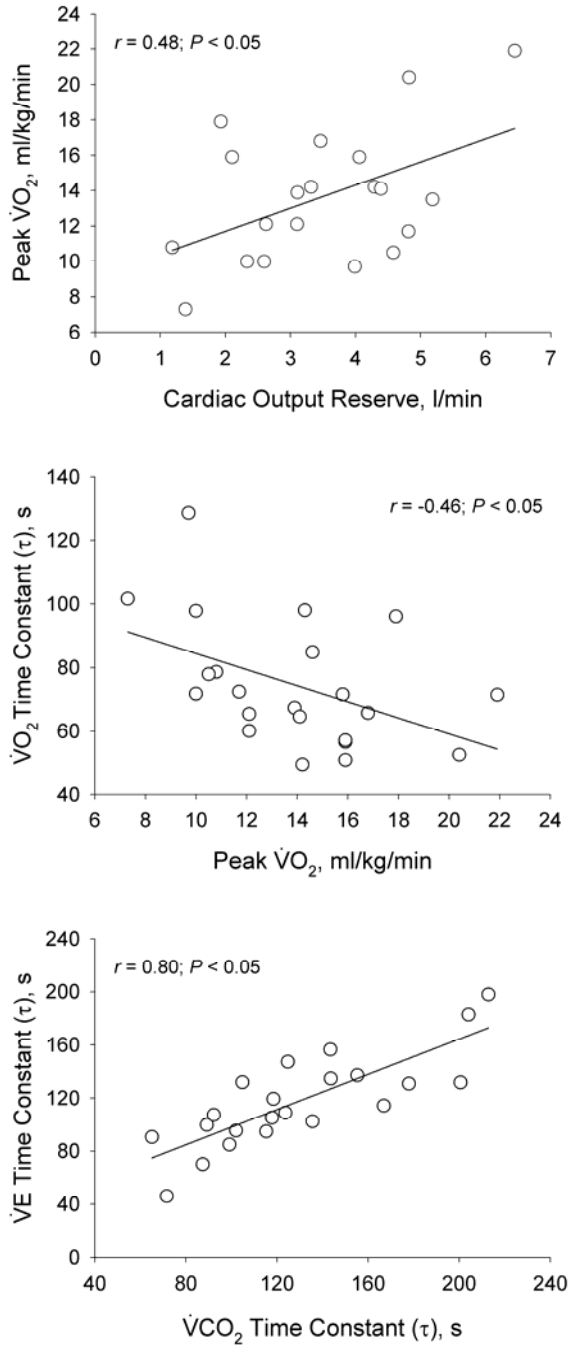

Figure 3-3. Correlation regression findings. $\dot{V}O_2$, pulmonary oxygen uptake; $\dot{V}CO_2$, carbon dioxide output; $\dot{V}E$, minute ventilation. Figures include data points for pre- and post-CRT findings. n = 10 for cardiac output reserve versus peak $\dot{V}O_2$.

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Chapter 4

Effect of Acute High-Intensity Interval Exercise on Post-Exercise Biventricular Function in Mild Heart Failure

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4.1 Introduction

Heart failure (HF) is marked by severe exercise intolerance that is attributable, in part, to abnormal cardiac function (17, 29-31, 34, 38). Current exercise rehabilitation guidelines (13, 27, 35, 40) recommend that clinically stable HF patients perform moderate-intensity continuous aerobic exercise (*i.e.*, continuous exercise at 50 to 80% of peak capacity for upwards of 45 min) to improve peak oxygen uptake ($\dot{V}O_2$). A recent large-scale randomized control trial reported modest improvements in self-reported health and survival with this type of training (9, 25). However, Wisløff et al. (39) demonstrated that 12 wks of high-intensity interval training (HIT) (*i.e.*, alternating 4-min bouts of exercise at 90 to 95% of peak capacity with 3 min of recovery) was more effective than continuous aerobic exercise for improving peak $\dot{V}O_2$ and resting ventricular-vascular coupling in older patients with HF and reduced ejection fraction (EF). Despite this potential longer-term benefit, the acute effects of HIT on biventricular function in patients with HF and reduced EF have not been described.

Several aspects of heart function are impaired during exercise in HF patients, such as the reserve in LV end-systolic volume (ESV) and end-diastolic volume (EDV) (30), and the ability to increase systolic twist and diastolic untwisting rate (23). Twist refers to

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the opposite short axis rotation of the myocardium measured in apical and basal views during ventricular contraction (like wringing out a wet towel), with untwisting occurring during early diastole (33). The inability of the failing LV to substantially reduce ESV and increase LV twist because of impaired systolic reserve and/or reduced LV preload (4) may also blunt an increase in LV untwisting rate, and this may further impair diastolic filling (3, 14) during or following HIT.

The aim of this study was to assess biventricular function using cardiac magnetic resonance imaging (cMRI) prior to, and immediately following acute HIT in clinically stable patients with non-ischemic mild HF. We tested the hypothesis that immediately following acute HIT, HF patients would have a reduction in biventricular EF as the result of an increase or no change in ESV and a decrease in EDV. A secondary hypothesis was that HF patients would have reduced diastolic function, comprising of reductions in filling rate, mitral annular tissue velocity, and LV peak untwisting rate immediately following acute high-intensity interval exercise.

4.2 Methods

4.2.1 Subjects

Twelve non-ischemic HF patients were recruited from the heart function clinic at the Mazankowski Alberta Heart Institute. Study inclusion criteria were New York Heart Association (NYHA) function class I or II HF, LV EF <50 %, clinically stable HF defined by no change in symptoms or medications during the previous 3 mo, and normal sinus rhythm. The University of Alberta Health Research Ethics Board approved this study and all subjects provided written and informed consent prior to study enrolment (Appendix B).

4.2.2 Exercise Testing Protocols

Subjects underwent 2 days of testing under the supervision of a cardiologist. On the first testing day, subjects completed an incremental exercise test to fatigue on a treadmill (Series 2000 Treadmill, GE Healthcare, Freiburg, DE) in order to determine peak exercise heart rate and peak $\dot{V}O_2$. Following a 2-min standing rest period, the protocol began with a 3-min warm-up at a walking speed that was pre-selected by study subjects. The protocol continued until volitional fatigue at the same constant walking speed with a pre-selected increase in gradient ranging between 2% and 3% every 1 min, based on subject ability. A 12-lead electrocardiogram (CASE® 8000, GE Healthcare, Freiburg, DE), manual brachial cuff blood pressure (BP), and pulse oximetry were monitored and recorded. Breath-by-breath gas exchange and ventilation parameters were also measured (SensorMedics® Vmax 229; VIASYS™ Healthcare Respiratory Technologies, Yorba Linda, CA, US).

On the second testing day, subjects completed a baseline cMRI assessment (see below) that was immediately followed by HIT treadmill exercise. The HIT protocol was the same as described by Wisløff et al. (39). Briefly, the protocol began with a standing 4-min rest period and then a 3-min warm-up at the same walking speed as previously selected from the peak exercise test. Following, the gradient was increased to elicit a heart rate response approximating 95% of peak heart rate for 4 min. The treadmill speed and gradient were then decreased for a 3-min recovery period. Four intervals and 4 recovery periods were performed. A 12-lead electrocardiogram, manual brachial cuff BP, pulse oximetry, and gas exchange and ventilation parameters (in the last 1 min of each stage) were again monitored and recorded. Immediately following the last recovery

period, subjects were rapidly transported by an investigator via wheelchair to the MRI center that was located approximately 50 m from the exercise testing site for post-exercise cMRI image acquisition that began 6 ± 2 min immediately following HIT (hereafter termed "immediately post-exercise"). A second identical imaging protocol (+30min) was performed with a midpoint scan time of 30 ± 4 min following exercise termination.

4.2.3 cMRI Protocol

Cardiac imaging was performed using a 1.5-T MRI scanner (Siemens Sonata, Erlangen, DE) as previously described by our group (2, 6, 22, 32). Images were electrocardiogram gated (3-lead) and acquired at end-expiratory breath holds in the order described below. LV and right ventricular (RV) volumes were measured from short-axis cine images spanning the entire length of both ventricles using a steady-state free precession sequence. Short-axis phase contrast cines, for the measurement of through-plane filling velocities, were acquired at the level of the mitral annulus to calculate early (E) and late atrial (A) filling blood velocities. Peak E and A transmitral filling rates were calculated from summation of the through-plane velocities across the mitral valve area. Peak systolic (S'), early (E'), and late (A') mitral and tricuspid annular velocities were assessed on the free wall sides of each chamber from 4-chamber steady-state free precession cines. Short-axis grid myocardial tissue tagging was applied to the LV base (level of mitral valve), at the mid-ventricular position, and at the LV apex (1 cm from true apex based on 2-, 3-, and 4-chamber views and always keeping LV chamber in view for cardiac cycle duration). Apical, mid, and basal slice locations were used in the calculation of peak circumferential strain and peak circumferential strain rate. Grid tags

were applied with a 200 ms delay following the electrocardiogram R-wave to ensure tag persistence throughout diastole.

4.2.4 Data Analysis

All cMRI data were analyzed offline using custom software (MATLAB, MathWorks, Natick, MA, US) (2, 6, 22, 32, 37). The greatest left atrial (LA) volume just prior to mitral valve opening was measured by tracing the LA endocardial border from 2-, 3-, and 4-chamber cine images and delineating atrial height and width for respective chamber views. LV and RV volumes at end-systole and end-diastole were determined with short-axis stack steady-state free precession images by method of disks using Simpson's rule. Endocardial borders were manually traced with papillary muscles included in the ventricular cavities. Employing the same procedure as illustrated in Fig. 1 by Cheng-Baron et al. (2), long-axis images were used to define the LV base (at the level of the mitral annulus) and apex so as to allow for the fractional inclusion of respective slices. The same procedure was used for determining volumes in the RV. Stroke volume and EF were calculated from cardiac volumes for both ventricles. Cardiac output was calculated as stroke volume × heart rate. Volume flow rates were calculated as the product of the sum of velocities over the filling orifice and the pixel cross-sectional area (22). Peak annular tissue velocities were determined from 4-chamber cines by manually tracking the lateral (free-wall) annular position throughout the cardiac cycle.

Short-axis tagged cines for basal and apical slices (as defined above) were used to determine myocardial tissue deformation with custom image morphing software as we have previously reported (2, 6, 22, 37). The angle of rotation, Φ, for apical (Φ_{apex}) and basal (Φ_{base}) slices was calculated as the average rotation of each point in a slice relative

to a reference phase, diastasis (5). Twist curves, θ(t), were the difference between apical and basal rotation and were calculated as $\theta = \Phi_{apex} - \Phi_{base}$. Untwisting rate, dθ/dt, was calculated as the discrete time derivative of the twist versus time curve. Peak twist and untwisting rate and peak rotation and rotation rates were measured. We calculated the difference in the time to peak untwisting rate and circumferential strain rate (untwist-strain rate interval) as a measure of diastolic function (32). Isovolumic relaxation (IVR) times were calculated using a previously described method by our group (2).

Gas exchange data from the HIT and peak exercise protocol are reported as 30-s averages. Heart rates reported for the HIT protocol are the steady-state values from the last 30 s of the exercise interval. Peak exercise heart rates are the instantaneous values from the 12-lead electrocardiogram at exercise termination. Peak $\dot{V}O_2$ and heart rate were referenced to predicted values (15). Systemic vascular resistance (SVR) was calculated as SVR = (mean arterial pressure/cardiac output) × 80. Non-invasive LV contractility was estimated by single-point end-systolic elastance (Ees) (1).

4.2.5 Statistics

Non-parametric repeated measures comparisons with the Freidman test were used to determine statistical differences between baseline, immediately post-exercise, and +30min (MedCalc 11.3.1.0, MedCalc Software, Mariakerke, BE). Based on previous reports (4, 32, 39, 41), correlation regression was used to establish the relationship between twist with LV ESV, twist and LV EF, and LA volume with LV EDV (SigmaPlot 8.02, SPSS, Chicago, IL, US). All data are presented as mean ± standard deviation and $P < 0.05$ was considered statistically significant.

4.3 Results

Peak $\dot{V}O_2$ testing was terminated because of volitional fatigue in all except 1 subject for whom it was stopped because of self-reported dizziness (peak heart rate: 64% predicted) – this subject completed the remaining study protocol symptom free. One subject completed the peak $\dot{V}O_2$ test and voluntarily withdrew from the study upon commencing the baseline cMRI protocol because of claustrophobia. A second subject was excluded because of ventricular bigeminy that began during the last recovery period of the HIT protocol and persisted intermittently throughout the post-exercise cMRI assessment – this reflected a 9% event rate in the 11 subjects who performed HIT. A third subject was excluded because of a large atrial septal defect.

In total, 9 subjects were included in this study (Table 4-1). Cardiac related medications included β-blocker (n = 8), angiotensin converting enzyme inhibitor (n = 9), diuretic (n = 5), lipid lowering agent (n = 3), and anticoagulant (n = 3). Cardiovascular risk factors and comorbidities included smoking history (n = 3), hypertension (n = 1), diabetes (n = 1), and dyslipidemia (n = 3). All subjects reported participating in structured physical activity that included walking a minimum of 2 times/wk.

4.3.1 High-Intensity Interval Exercise

All 9 subjects completed the HIT protocol with no adverse events. Mean values over the 4 interval and recovery bouts for $\dot{V}O_2$, heart rate, mean arterial pressure, treadmill speed, and treadmill gradient during the high-intensity interval exercise protocol are listed in Table 4-1. Self-reported exertion in 1 subject was low for their prescribed exercise intensity, we therefore further increased that subject's heart rate above 95% of their peak exercise heart rate (which was 76% of predicted maximum),

likely achieving an intensity closer to their true maximum. Accordingly, the average HIT heart rate for the study group was just above 95% of peak values (Table 4-1). The average HIT heart rate for the other 8 subjects was 93 ± 4% of peak heart rate.

4.3.2 Systolic Function

Compared to baseline, LV ESV decreased by 6% immediately post-exercise and 7% at +30min (both $P < 0.05$), while LV EF increased an absolute 2.4% from baseline to +30min ($P < 0.05$; Table 4-2, Fig 4-1). LV systolic annular velocity (S') increased 21% immediately post-exercise and remained elevated at +30min (both $P < 0.05$; Table 4-2). LV stroke volume did not significantly change. Similar trends were observed for RV function (Table 4-2, Fig 4-2). LV twist was not significantly different after exercise (Table 4-2, Fig 4-3) and the change in LV ESV and twist from baseline to immediately post-exercise and +30min were not related ($P > 0.05$), and neither was the change in twist and LV EF at +30min ($P > 0.05$).

4.3.3 Heart Rate and Blood Pressure

Heart rate was elevated above baseline immediately post-exercise and at +30min ($P < 0.05$; Table 4-2). Mean arterial pressure and SVR decreased significantly immediately post-exercise and remained lower at +30min ($P < 0.05$; Table 4-2).

4.3.4 Diastolic Function

Baseline diastolic dysfunction was moderate (grade II) for our study group based on E', E/A, and LA volume values reported in Table 4-3, and a resting E/E' (septal and lateral E' average) of 9.4 ± 4.4 (19). Table 4-3 shows that LV early and late filling velocity and filling rate, and peak early diastolic annular velocity in the LV and RV remained unchanged following acute HIT. A reduction in LA volume (Table 4-2) was

significantly related to a concomitant decline in LV EDV (Table 4-2, Fig 4-1) immediately post-exercise ($r = 0.84$, $P < 0.05$). LV apical rotation rate during early diastole did not significantly change (both $P > 0.05$), whereas basal rotation rate increased 23% immediately post-exercise and remained 18% elevated above baseline at +30min (both $P < 0.05$; Table 4-3, Fig 4-4). Similarly, LV peak untwisting rate increased 24% immediately post-exercise and remained 18% elevated above baseline at +30min (both $P < 0.05$; Table 4-3, Fig 4-4).

4.4 Discussion

The main finding of this study, contrary to our hypothesis for ESV and EF, was that a single bout of HIT did not decrease immediate post-exercise biventricular systolic or diastolic function in clinically stable non-ischemic patients with mild HF. Rather, we observed a decrease in biventricular ESV commensurate with an increase in LV systolic annular velocity immediately following acute high-intensity interval exercise. By +30min we observed a significant increase in LV EF. Secondly, we observed that diastolic function immediately following acute HIT was preserved, despite significant volume unloading measured by a reduction in LA volume and LV EDV. The preserved diastolic function was likely due to increased LV recoil because of a reduction in LV ESV, which was reflected as an increase in the rate of LV untwisting.

4.4.1 Effects of Acute High-Intensity Interval Exercise on Systolic Function in Health and Heart Failure

Acute HIT has varying effects on post-exercise global LV systolic function. More fit subjects have been shown to have a reduction in LV EF (32) or no change in LV EF (21, 28) immediately post-exercise, whereas normally active healthy subjects have no, or

minimal, change in the immediate post-exercise LV EF (32). To date, no studies have examined the acute effects of HIT on post-exercise biventricular function in patients with mild HF.

During exercise, patients with HF exhibit an increase or no change in exercise LV ESV (30) that is due to impaired contractility, increased afterload, and reduced LV EDV (17, 31, 34). In contrast, our findings show that acute HIT was associated with a decrease in LV ESV immediately post-exercise and at +30min, with a concomitant increase in LV EF by +30min (Table 4-2, Fig 4-1) and similar changes found for the RV (Table 4-2, Fig 4-2). This decline may be due, in part, to a reduction in afterload (11), as SVR was lower throughout recovery (Table 4-2). Alternatively, the lower ESV may be due to enhanced myocardial contractility as single-point Ees and S' were higher immediately after exercise. Our findings extend the prior work of Wisløff et al. (39) who found that 12 wks of HIT was associated with a favourable change in resting LV S', ESV, EF, and vascular function in older ischemic HF patients.

4.4.2 Effect of Acute High-Intensity Interval Exercise on Diastolic Function

Decreasing LV pressure during IVR aids in the generation of a transmitral pressure gradient and thus LV suction and filling (18), and this has been shown to be impaired in HF (29) potentially because of impaired untwisting rate (7, 38). We found that LV peak untwisting rate increased immediately post-exercise in most (8/9) subjects ($P < 0.05$; Table 4-3, Fig 4-4). The enhanced LV untwisting rate may have facilitated the maintenance of diastolic function following acute high-intensity interval exercise by increasing LV suction (23, 24), and this may have been modulated in part by the

reduction in LV ESV (Table 4-2, Fig 4-1) (4, 23) via a greater storage and release of elastic energy from titin (12).

Our finding of an increase in basal rotation rate immediately post-exercise in 7/9 subjects (Table 4-3, Fig 4-4.) is consistent with Fuchs et al. (10) who found that HF patients (EF: 26%) treated for 6 mo with pharmacologic therapy increased resting basal rotation rate and not apical rotation rate. Together, these findings suggest that functional reserve in basal rotation rate remains and that this preserved regional function may be especially important for LV untwisting rate and LV filling during or immediately following exercise in patients with varying degrees of LV EF depression.

Our finding that biventricular E' did not increase immediately post-exercise (Table 4-3) contrasts a previous report in HF subjects in which E' increased by 38% immediately following (3.7 ± 2.4 min) incremental exercise (29). In the present investigation, despite a significant reduction in LV ESV and subsequent increased LV recoil immediately post-exercise, the lack of change in E' may be explained by the reduction in venous return and thus filling pressure (8, 26). This is consistent with our finding of a significant reduction in LA volume (Table 4-2) that correlated with changes in LV EDV immediately post-exercise. The increased left and right atrial A' (Table 4-3) was unanticipated given that LA volume was significantly reduced immediately post-exercise, and subsequently A' would be expected to decrease (20). The elevated A' may be due to inertia from early filling residual flow, especially given the narrowed time interval of these events immediately post-exercise because of an elevated heart rate (Table 4-2).

4.4.3 Role of LV Rotation on Post-Exercise LV Function in Heart Failure

LV twist is greater with an incrementally lower LV ESV and is adversely affected by a reduction in LV EDV and contractility, and changes in LV twist have also been shown to correlate with LV EF (4). However, others have shown that LV EF can increase without a change in LV twist (41) or with only a change in LV basal rotation, and not LV apical rotation, in subjects with HF (10). In the present study, changes in LV ESV and twist were not correlated and peak twist marginally increased in 6/9 subjects immediately post-exercise (Fig 4-3), likely due to an increase in sympathetic stimulation (4). It is unlikely, however, that these small changes in LV twist significantly contributed to the increase in LV EF at +30min.

Diastolic events from our tagged MRI analyses show that the timing of LV untwisting aided in preserving LV filling. Because LV untwisting serves to aid in early LV filling and thus precedes filling (36), LV untwisting rate should precede circumferential strain rate as this provides time to generate a basal to apical pressure gradient allowing for an enhanced suction effect in the LV (23). In the present investigation, given there was no reduction in the time interval between untwisting rate and circumferential strain rate (untwist-strain rate interval, Table 4-3), we conclude that diastolic filling was preserved, in part, because enhanced LV peak untwisting rate preceded LV filling immediately following acute HIT, likely aiding in the development and preservation of LV suction post-exercise.

4.4.4 Clinical Relevance

Currently, HIT is not recommended for HF patients (13, 16, 27, 35, 40), because exercise intensity requirements may not be attainable or sustainable, and/or because of

the potential for inducing acute LV dysfunction and exacerbating HF symptoms. Our findings suggest that in physically active patients with clinically stable non-ischemic mild HF (NYHA functional class I/II) that *1)* acute HIT (*e.g.*, 12% gradient and 4 km/h at a heart rate approximating 95% of peak) can be safely completed in a supervised medical setting, *2)* without exacerbating HF symptoms, *3)* while maintaining or increasing biventricular function immediately post-exercise and for upwards of 30 min post-exercise. Taken together, these findings suggest that in a supervised setting, that acute HIT may be a viable alternative form of exercise in clinically stable patients with mild non-ischemic HF.

4.4.5 Limitations

This was a small sample of clinically stable non-ischemic HF patients. Our findings are limited to those with NYHA functional class I or II HF and reduced EF and associated moderate diastolic dysfunction who participate in regular physical activity. We did not measure biventricular function during exercise, and thus uncertainty remains regarding the biventricular responses during HIT in patients with non-ischemic HF. Our cMRI measurements were made with subjects in the supine position, and thus postural changes may have had an affect on cardiac loading conditions. However, cardiac assessment using other commonly employed modalities such as echocardiography often requires subjects to be repositioned supine as well, and so our study findings are best compared to such studies employing similar methods.

4.4.6 Conclusions

Acute HIT is not associated with a decrease in biventricular function immediately following exercise in physically active patients with clinically stable non-ischemic mild

HF. Our finding of an immediate post-exercise increase in ESV may be attributable to a reduction in SVR and enhanced contractility. These effects persist for upwards of 30 min post-exercise and likely account for a significant increase in LV EF. We also conclude that diastolic function is not impaired following HIT in patients with mild HF, despite a significant reduction in volume loading. The preserved LV filling immediately post-exercise in patients with mild HF may be modulated, in part, by enhanced LV untwisting rate that precedes LV filling.

Table 4-1. Subject characteristic, peak exercise, and high-intensity interval exercise gas exchange and heart rate

	n = 9
Age, yrs	49 ± 16
Male : female, n	6 : 3
Height, cm	172 ± 13
Mass, kg	86.3 ± 13.8
Body mass index, kg/m^2	29.0 ± 2.7
NYHA functional class	1.2 ± 0.4
Peak Exercise	
Heart rate, beats/min	148 ± 28
Range, beats/min	111 – 193
% predicted	88 ± 15
$\dot{V}O_2$, ml/kg/min	27.3 ± 8.8
Range, ml/kg/min	10.2 – 39.4
% predicted	87 ± 28
$\dot{V}CO_2/\dot{V}O_2$	1.06 ± 0.09
Treadmill speed, km/h	4.1 ± 1.4
Treadmill grade, %	20.0 ± 6.1
High-Intensity Interval Exercise	
Interval	
Heart rate, beats/min	141 ± 24
% peak	96 ± 10
$\dot{V}O_2$, ml/kg/min	22.9 ± 7.1
% peak	85 ± 9
MET	6.6 ± 2.0
MAP, mmHg	99 ± 16
Treadmill speed, km/h	4.1 ± 1.1
Treadmill gradient, %	12.2 ± 4.1
Recovery	
Heart rate, beats/min	111 ± 16
% peak	76 ± 13
$\dot{V}O_2$, ml/kg/min	12.2 ± 3.6
% peak	47 ± 14
MET	3.5 ± 1.0
MAP, mmHg	99 ± 17
Treadmill speed, km/h	2.0 ± 0.5
Treadmill gradient, %	0.0 ± 0.0

Data are mean ± standard deviation unless otherwise specified. NYHA, New York Heart Association; $\dot{V}O_2$, oxygen uptake; $\dot{V}CO_2$, carbon dioxide production; MET, metabolic equivalent; MAP, mean arterial pressure. Interval and recovery data are the averaged values across the 4 respective interval and recovery periods.

Table 4-2. Cardiac volumes, cardiovascular and systolic function

	Baseline	Post Ex	+30min
Heart rate, beats/min	71 ± 13	87 ± 12*	81 ± 13*†
Cardiac output, l/min	5.5 ± 1.0	6.2 ± 0.7	6.1 ± 0.8
MAP, mmHg	93 ± 15	87 ± 11*	85 ± 11*
SVR, dynes/s/cm^5	1426 ± 452	1138 ± 199*	1120 ± 201*
Left Atrium			
Volume, ml	109 ± 29	99 ± 32*	102 ± 31†
Left Ventricle			
EDV, ml	228 ± 62	214 ± 65	217 ± 70
ESV, ml	149 ± 53	140 ± 59*	139 ± 61*
SV, ml	78 ± 15	74 ± 17	78 ± 18
EF, %	36 ± 7	37 ± 10	38 ± 10*†
Twist, °	8.2 ± 3.6	9.3 ± 2.8	9.1 ± 4.0
Basal rotation, °	–1.5 ± 1.0	–2.0 ± 1.4	–1.9 ± 1.1
Apical rotation, °	7.0 ± 4.1	7.5 ± 3.3	7.4 ± 4.5
Circumferential strain, %	–0.10 ± 0.02	–0.12 ± 0.05	–0.11 ± 0.03
S', cm/s	5.3 ± 1.6	6.7 ± 2.5*	6.1 ± 1.9*
Ees, mmHg/ml	0.83 ± 0.35	0.93 ± 0.48	0.93 ± 0.51
Right Ventricle			
EDV, ml	158 ± 22	145 ± 24	148 ± 30
ESV, ml	82 ± 25	72 ± 22	72 ± 20
SV, ml	76 ± 14	73 ± 14	77 ± 21
EF, %	49 ± 10	51 ± 9	52 ± 9
S', cm/s	7.0 ± 1.8	7.4 ± 1.2	7.0 ± 1.4

Data are mean ± standard deviation. MAP, mean arterial pressure; SVR, systemic vascular resistance; Ees, single-point end-systolic elastance; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction; S', peak systolic annular velocity. *Significantly different ($P < 0.05$) from baseline. †Significantly different ($P < 0.05$) from immediately post-exercise (post ex).

Table 4-3. Biventricular diastolic function

	Baseline	Post Ex	+30min
Left Ventricle			
IVR time, ms	82 ± 21	71 ± 24*	77 ± 19*
Untwisting rate, °/s	–93 ± 27	–123 ± 48*	–114 ± 40*
Basal rotation rate, °/s	39 ± 16	51 ± 16*	48 ± 16*
Apical rotation rate, °/s	–56 ± 42	–78 ± 60	–72 ± 48
Circumferential strain rate, %/s	0.73 ± 0.22	0.80 ± 0.32	0.77 ± 0.21
Untwist-strain rate interval, ms	81 ± 41	101 ± 62	69 ± 51
E, cm/s[§]	35 ± 11	38 ± 15	37 ± 16
A, cm/s[§]	29 ± 15	30 ± 10	29 ± 11
E/A[§]	1.86 ± 1.88	1.44 ± 1.00	1.52 ± 1.24
E filling rate, ml/s[§]	377 ± 93	357 ± 115	367 ± 91
A filling rate, ml/s[§]	280 ± 144	260 ± 103	252 ± 121
E', cm/s	5.5 ± 2.0	5.6 ± 2.2	4.6 ± 1.4
A', cm/s	3.1 ± 2.1	6.1 ± 2.8*	4.9 ± 3.0
Right Ventricle			
E', cm/s	6.4 ± 2.9	5.5 ± 2.1	6.5 ± 2.0
A', cm/s	7.8 ± 2.8	11.4 ± 3.7*	8.6 ± 3.5†

Data are mean ± standard deviation. IVR, isovolumic relaxation; E', peak early diastolic annular velocity; A', peak late diastolic annular velocity. [§]Reported for 5 subjects because of wave fusion in 4 subjects.*Significantly different ($P < 0.05$) from baseline. †Significantly different ($P < 0.05$) from immediately post-exercise (post ex).

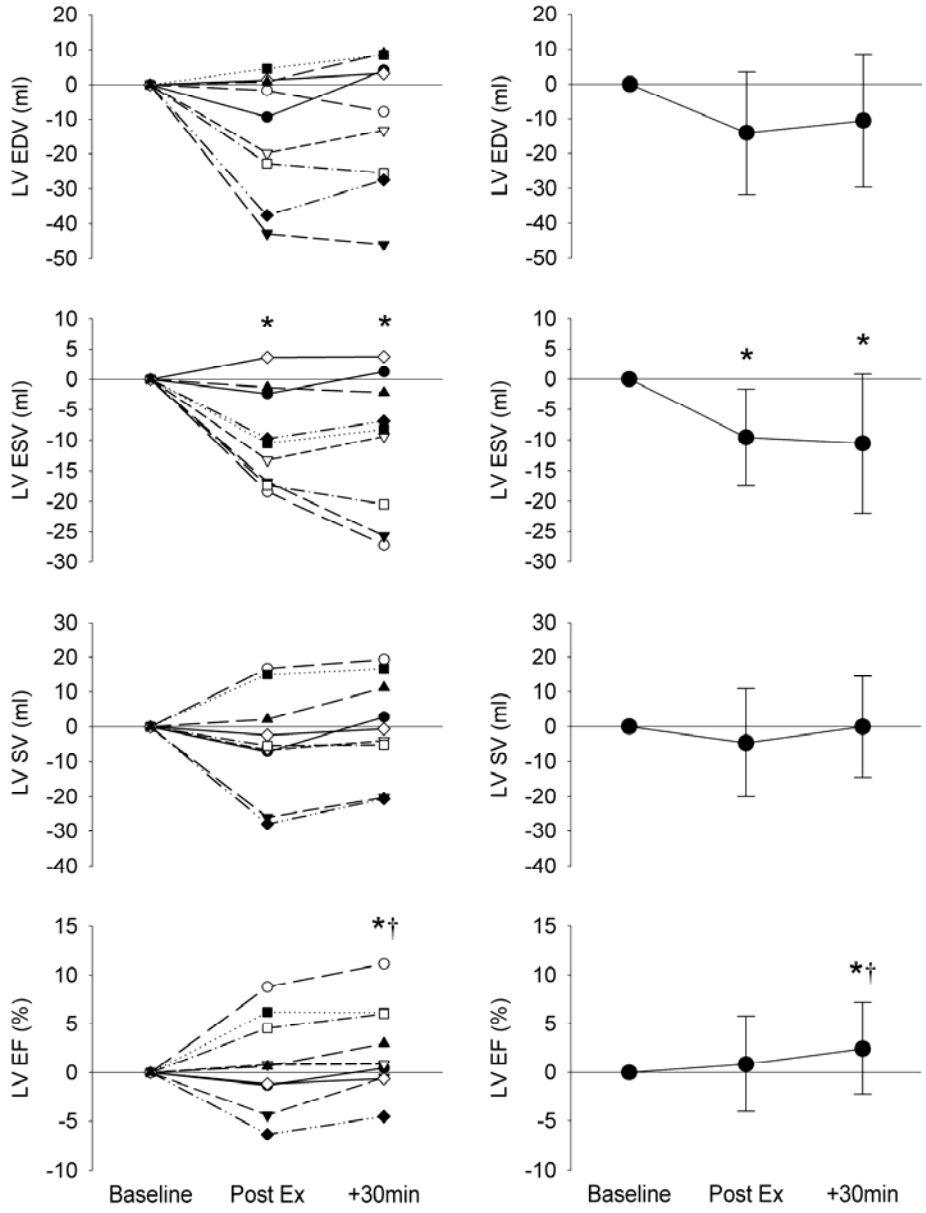

Figure 4-1. Change in left ventricular (LV) volumes from baseline to immediately post-exercise (post ex) and +30min for individual subjects (panels in left column). Group mean (± standard deviation) responses are also shown (panels in right column). EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction. *Significantly different ($P < 0.05$) from baseline. †Significantly different ($P < 0.05$) from post ex.

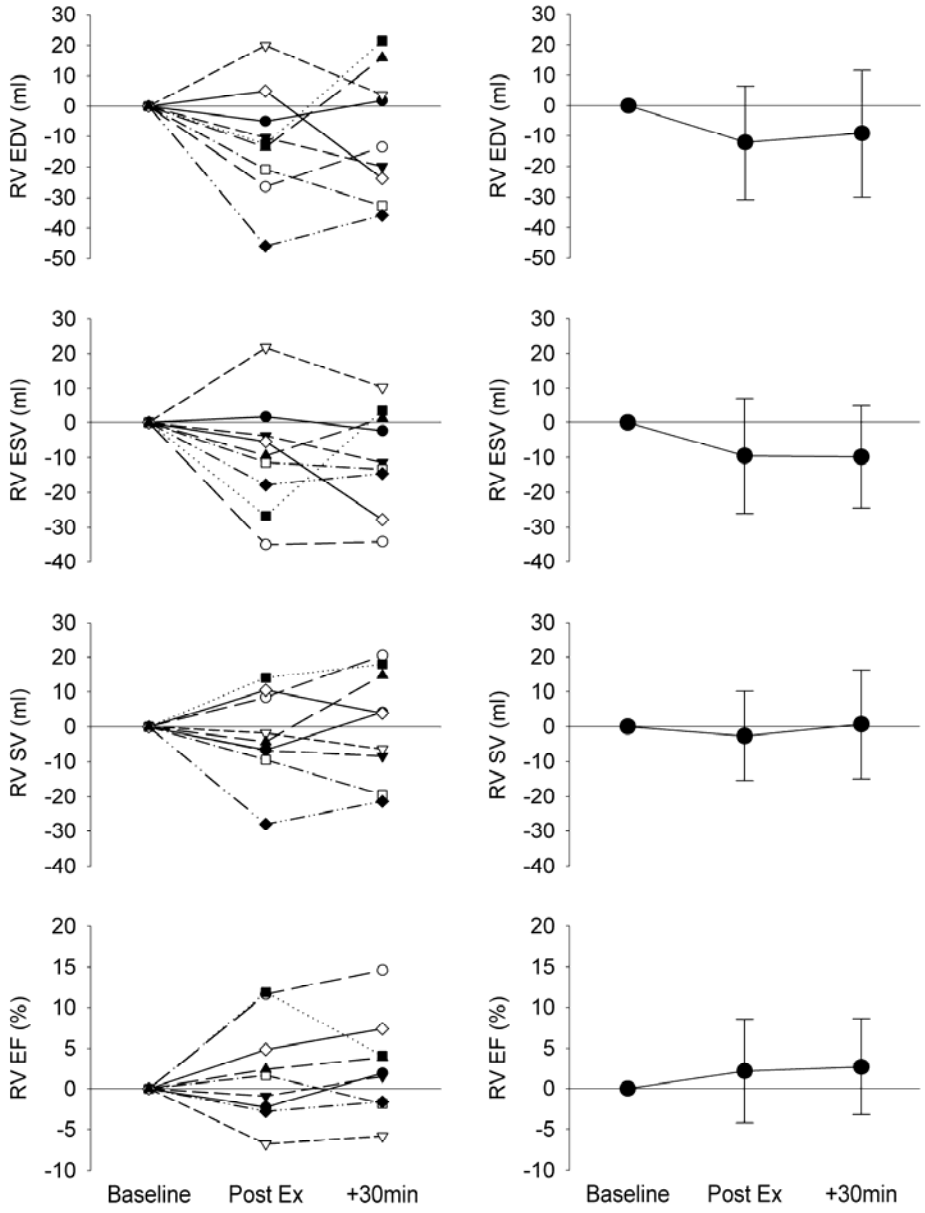

Figure 4-2. Change in right ventricular (RV) volumes from baseline to immediately post-exercise (post ex) and +30min for individual subjects (panels in left column). Group mean (± standard deviation) responses are also shown (panels in right column). EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction.

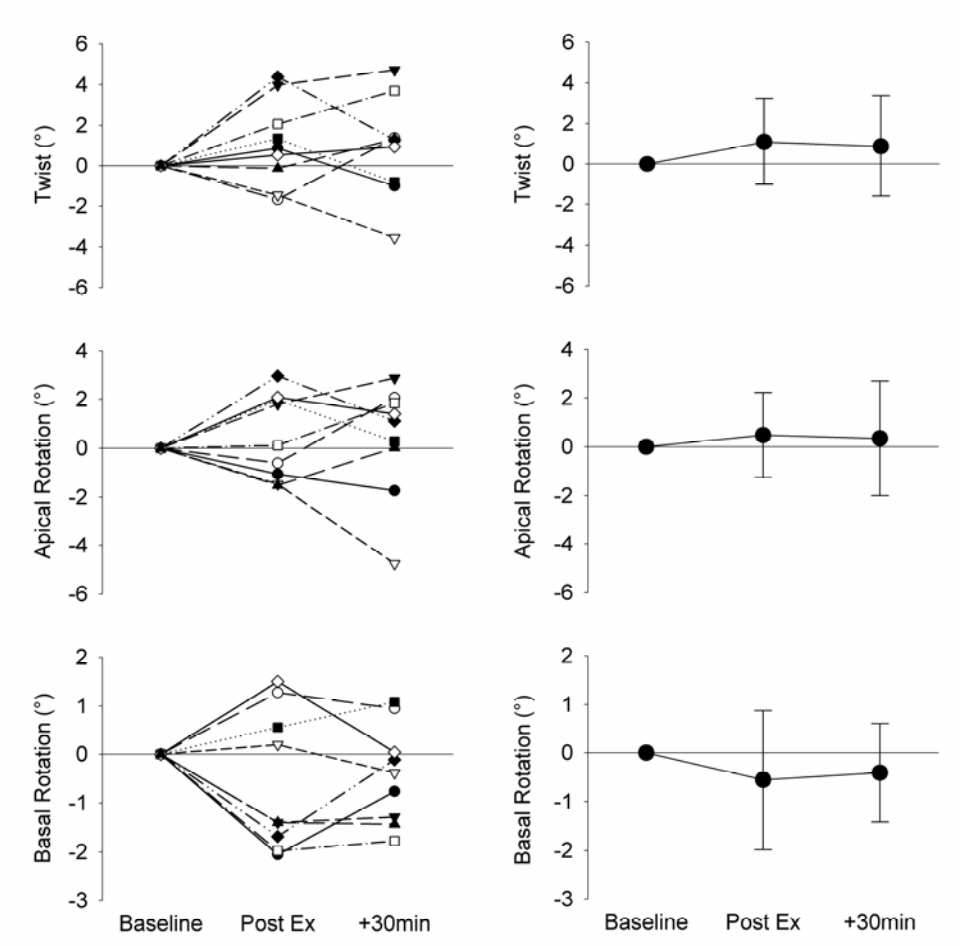

Figure 4-3. Change in left ventricular apical and basal rotation, and twist from baseline to immediately post-exercise (post ex) and +30min for individual subjects (panels in left column). Group mean (± standard deviation) responses are also shown (panels in right column).

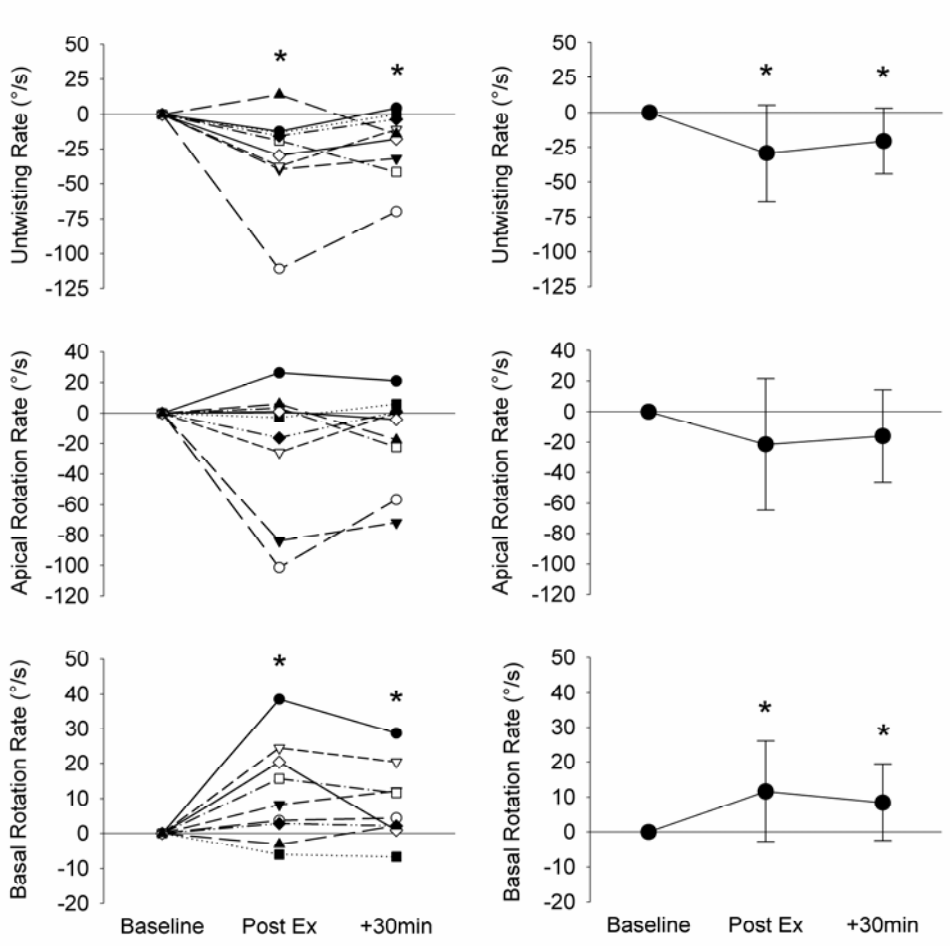

Figure 4-4. Change in left ventricular apical and basal rotation rate, and untwisting rate from baseline to immediately post-exercise (post ex) and +30min for individual subjects (panels in left column). Group mean (± standard deviation) responses are also shown (panels in right column). *Significantly different ($P < 0.05$) from baseline.

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Chapter 5

General Discussion and Conclusions

5.1 General Discussion and Conclusions

Heart failure (HF) with reduced ejection fraction is characterized in part by a significant decrease in exercise capacity (5, 12, 37), often measured objectively as a reduction peak oxygen uptake ($\dot{V}O_2$). Regrettably, HF is associated with a poor 5-yr survival rate following the initial diagnosis (20). Given that peak $\dot{V}O_2$ and left ventricular (LV) function are reduced in these patients, coupled with the important association between exercise capacity and survival (25), suggests that interventions that can maximize a potential improvement in LV function (and subsequently $\dot{V}O_2$) may also confer an improvement in survival (10, 19, 22, 23, 35). Therefore, detailed study on interventions (and their underlying mechanisms) that can improve LV function and $\dot{V}O_2$ in patients with HF is warranted.

In order to better understand the mechanisms that regulate exercise LV function and $\dot{V}O_2$, and how cardiac resynchronization therapy (CRT) and high-intensity interval training (HIT) may affect these exercise determinants, this thesis merged three important fields of research that included the study of ventricular function in HF, the study of pulmonary gas exchange kinetics in HF, and the study of HF rehabilitation. By merging these three fields, the goals of this thesis were to better understand *1)* the interaction of CRT mediated changes in LV function on $\dot{V}O_2$ characteristics and *2)* the acute effects of HIT on biventricular function in HF patients were met.

Based on strong evidence that the rate of $\dot{V}O_2$ adaptation to exercise in patients with HF may be mediated by an O_2 availability limitation that is secondary to a reduction

in LV function (16, 17, 34), coupled with evidence that patients with HF maintain a certain degree of metabolic reserve (7), the study in Chapter 2 tested the hypothesis that improving sub-maximal exercise LV function with CRT would speed $\dot{V}O_2$ kinetics during the transition to moderate-intensity exercise. There were several important and novel findings from this study. Firstly, CRT led to a significant speeding in phase II $\dot{V}O_2$ kinetics, which suggests that a faster rate of oxidative phosphorylation occurred to meet adenosine triphosphate demands. This effect was likely mediated by an increase in O_2 availability, and thus conferred a faster adaptive metabolic rate. Secondly, the steady-state exercise stroke volume increased secondary to a decrease in exercise LV end-systolic volume (ESV). The further decrease in exercise LV ESV was independent of an increase in cardiac preload and may have been due, in part, to a reduction in afterload. Lastly, CRT improved the heart rate response to exercise, most notably measured as a speeding in heart rate kinetics. This latter finding was particularly intriguing, as it suggests that autonomic control of heart rate during low-level exercise also changes with CRT, which extends previous reports of improved autonomic function while at rest (2, 8, 11). Cumulatively, the findings of Chapter 2 provide the first integrated cardiac and metabolic basis for how CRT may reduce exercise fatigue during even regular activities of daily living. However, given the restriction of the study findings relying on LV volumes for making conclusions about systolic function, a more detailed investigation of the effects of CRT on exercise LV function is certainly needed. In addition, further study on heart rate control during exercise in patients with HF following CRT would confirm or refute the conclusion that CRT alters exercise autonomic function.

Although nearly a decade has passed since the first study findings that CRT increases peak $\dot{V}O_2$ (1, 3, 6, 21, 40), the CRT mediated changes in peak exercise LV function have remained elusive. Moreover, given that peak $\dot{V}O_2$ and post-exercise $\dot{V}O_2$ kinetics are a function of maximal oxidative rate in the skeletal muscle (13, 14), and that this is mediated by O_2 availability (7, 12, 16, 37, 38), it has remained unknown whether CRT can reverse the attenuated recovery from peak exercise that has been previously reported in HF patients (4, 5). Accordingly, the study in Chapter 3 investigated the effects of CRT on peak exercise LV function, peak $\dot{V}O_2$, and post-exercise $\dot{V}O_2$ kinetics. CRT was found to increased reserve and peak cardiac output secondary to an increase in stroke volume that was mediated by a preservation of cardiac preload and greater reduction in LV ESV. Expectedly, the increase in cardiac output reserve was associated with an increase in peak $\dot{V}O_2$. An additional novel finding of Chapter 3 was that CRT decreased the time to recovery from peak exercise, measured by a speeding in $\dot{V}O_2$ and ventilation kinetics. The significant relationship found between peak $\dot{V}O_2$ and post-exercise $\dot{V}O_2$ kinetics further suggests that the CRT mediated increase in peak cardiac output conferred an increase in the maximal rate of oxidative phosphorylation of the skeletal muscle. However, similar to Chapter 2, further study on LV function at peak exercise is warranted to clarify the mechanistic basis for the improved peak stroke volume. Given that the variance accounted for in the correlation analyses of Chapter 3, it is possible that improvements in blood flow and skeletal muscle metabolism occurred during the follow-up period (24). Thus, these factors should be considered in future investigations.

An additional and obvious limitation to the studies in Chapter 2 and 3 that warrants discussion is the high incompletion rate that was due to mortality, HF

complications, and clinical intervention. However, this incompletion rate is not overly surprising given that the Pacing Therapies in Congestive Heart Failure (PATH-CHF) study (36) reported a similar 40% drop-out rate by their 6-mo follow-up period in their small cohort of 42 subjects. Further, in the large Multicenter InSync Randomized Clinical Evaluation (MIRACLE), approximately 42% of 528 subjects who underwent device implantation did not complete the 6-mo follow-up $\dot{V}O_2$ study (1). Compared with those studies, individuals in the present investigation were younger, with a slightly lower LV EF and peak $\dot{V}O_2$, and were requested to undergo more intensive exercise testing (multiple gas exchange exercise tests and exercise contrast echocardiography) likely requiring greater physical effort and time commitment. Six subjects in the study in Chapter 2 and 5 subjects in the study in Chapter 3 did have baseline testing completed, however their data was not included as the study design did not include an intention to treat analysis. Notably, within approximately 1 yr of study termination, 1 subject was awaiting cardiac transplantation, 2 subjects underwent cardiac transplantation, and another subject died from their HF, further highlighting the clinical severity of HF in our study group.

During the course of the investigations in Chapters 2 and 3, Wisløff et al. (39) released their study findings demonstrating that 12 wks of HIT had greater benefit on peak $\dot{V}O_2$ and resting LV function than moderate-intensity continuous aerobic exercise in patients with HF. Following soon after, findings from the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study confirmed only modest improvements in self-reported health and survival with continuous aerobic exercise in patients with HF (9, 27). However, given the potential for more broad use of

HIT in patients with HF since the findings of Wisløff et al. (39), and the unknown and varying affects of acute HIT on ventricular function in patients with HF (18, 26, 29-33), the study in Chapter 4 investigated the effects of acute HIT on post-exercise biventricular function in patients with non-ischemic mild HF. Based on previous reports above, it was hypothesized that acute HIT may decrease LV function post-exercise. Rather, it was observed that HIT decreased biventricular ESV, increased LV systolic annular velocity, and increased LV EF. In addition, diastolic function immediately following acute HIT was preserved, likely due to increased LV recoil. Given the study findings of Chapter 3, it was concluded that in a supervised setting, acute HIT may be a safe and effective form of exercise for LV reverse remodelling in clinically stable patients with mild non-ischemic HF. However, given that ventricular function was not measured during exercise, uncertainty remains regarding the effects of HIT on cardiac function during exercise. The findings of Chapter 4 are limited to patients with mild non-ischemic HF.

5.2 An Important Focus for Heart Failure Rehabilitation

Two major common findings across the studies of Chapters 2, 3, and 4 were that 1) the increase in LV ESV reserve/further reduction in LV ESV compared to baseline values was independent of an increased reliance on the Frank-Starling mechanism, and 2) a decrease in LV afterload was associated with an improvement in LV ESV. This latter finding is consistent with pharmacologic studies demonstrating a beneficial antiremodeling effect of ACE inhibition (19) and β-blockade (10). It is clear then that one potential and very important mechanism contributing to reverse remodelling associated with chronic exercise in patients with HF (15) is a reduction in LV afterload that may be sustained for some time period following exercise termination. But does this confer

survival benefit? Chronic unloading of the heart with pharmacologic therapy has proven to reduce mortality (23, 35). Interestingly, combined aerobic exercise training and CRT has been shown to further improve LV systolic function compared to CRT alone in optimally medicated HF patients (28). Given the greater vascular and ventricular benefit of HIT compared to continuous aerobic exercise (39), coupled with the modest findings of the HF-ACTION trial (9), it is reasonable to assume an even greater reverse remodelling benefit for HF patients with CRT who perform HIT, which may be associated with an even greater LV afterload reduction effect with this type of exercise. Based on the findings from this thesis, future investigations employing a randomized control design to evaluate the added LV reverse remodelling and survival benefit of HIT versus continuous aerobic exercise in stable and optimally medicated HF patients with CRT is warranted.

5.3 References

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APPENDIX A: Ethics Certificate of Approval

Health Research Ethics Board

213 Heritage Medical Research Centre
University of Alberta, Edmonton, Alberta T6G 2S2
p.780.492.9724 (Biomedical Panel)
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p.780.492.0459
p.780.492.0839
f.780.492.7808

ETHICS APPROVAL FORM

Date of HREB Meeting: January 27, 2006

Name(s) of Principal Investigator(s): Dr. Robert G. Haennel

Department: Physical Therapy

Title: The effects of cardiac resynchronization therapy on oxygen uptake kinetics in heart failure

Protocol:

The Health Research Ethics Board (Biomedical Panel) has reviewed the protocol involved in this project which has been found to be acceptable within the limitations of human experimentation. The REB has also reviewed and approved the patient information material and consent form.

The Research Ethics Board assessed all matters required by section 50(1)(a) of the Health Information Act. Subject consent for access to identifiable health information is required for the research described in the ethics application, and appropriate procedures for such consent have been approved by the REB Panel.

Specific Comments:

D. W. Morrish, M.D., PhD
Chairman of Health Research Ethics Board
Biomedical Panel

MAR - 8 2006
Date of approval release

This approval is valid for one year

Issue #6213

UNIVERSITY OF ALBERTA Capital Health CARITAS HEALTH GROUP

Health Research Ethics Board

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ETHICS APPROVAL FORM

Date: January 2007

Name(s) of Principal Investigator(s): Dr. Robert Haennel

Department: Faculty of Rehabilitation Medicine

Title: The effects of cardiac resynchronization therapy on oxygen uptake kinetics in heart failure

The Health Research Ethics Board (Biomedical Panel) has reviewed the protocol involved in this project which has been found to be acceptable within the limitations of human experimentation. The REB has also reviewed and approved the patient information material and consent form.

Specific Comments:

D. W. Morrish, M.D., PhD
Chairman, Health Research Ethics Board
Biomedical Panel

This approval is valid for one year

Issue: **#6213**

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Capital Health
Edmonton and area

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Health Research Ethics Board

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ETHICS APPROVAL FORM

Date: January 2008

Name(s) of Principal Investigator(s): Dr. Robert Haennel

Department: Medicine

Title: The effects of cardiac resynchronization therapy on oxygen uptake kinetics in heart failure

The Health Research Ethics Board (Biomedical Panel) has reviewed the file on this project, for which all documentation is currently up to date. The research has been found to be acceptable within the limitations of human experimentation.

Specific Comments: This is the annual re-approval and is valid for one year. Next year, a few weeks prior to its expiration, a Progress Report will be sent to you for completion. If no major issues are identified, your approval will be renewed for another year.

For studies where investigators must obtain informed consent, signed copies of the consent form must be retained, as should all study related documents, so as to be available to the HREB on request. They should be kept for the duration of the project and for at least seven years following its completion. In the case of clinical trials approved under Division 5 of the Food and Drug Regulations of Health Canada, study records must be retained for 25 years.

S.K.M. Kimber, MD, FRCPC
Chair, Health Research Ethics Board
Biomedical Panel

Issue: #6213

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Edmonton and area

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APPENDIX B: Ethics Certificate of Approval

From: hero@ualberta.ca [mailto:hero@ualberta.ca]
Sent: March-12-09 9:39 AM
To: Haykowsky, Mark
Subject: HERO: Ethics Application has been approved

UNIVERSITY OF ALBERTA
EDMONTON, ALBERTA, CANADA

Ethics Application has been Approved

ID:	Pro00004461
Title:	Acute Effect of Aerobic Interval Exercise on Left Ventricular Function in Heart Failure
Study Investigator:	Mark Haykowsky
	This is to inform you that the above study has been approved.
Description:	Click on the link(s) above to navigate to the HERO workspace.
	Please do not reply to this message. This is a system-generated email that cannot receive replies.

University of Alberta
Edmonton Alberta
Canada T6G 2E1

APPENDIX C: Arterial-Venous O_2 Content Difference Reserve

Table. Arterial-venous O_2 content difference reserve

	Pre-CRT	Post-CRT
Arterial-venous O_2 content difference reserve, ml/dl	8 ± 6	6 ± 4

Data are mean ± SD. Data are from Chapter 3 and are calculated as peak – rest.
*Significantly different ($P < 0.05$) from Pre-CRT. n = 10.

APPENDIX D: Relation between Stroke Volume and O_2-Pulse

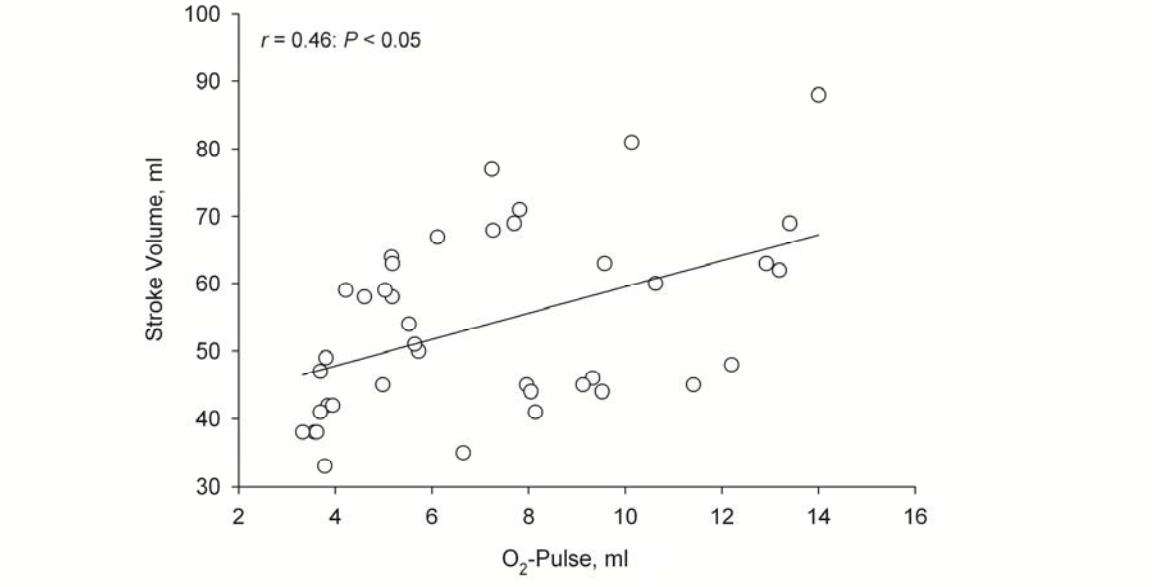

Figure. Relationship between O_2-pulse and stroke volume at rest and at peak exercise pre- and post-CRT. Data are from Chapter 3. n = 10.