Left Ventricular Twisting Mechanics During Incremental Exercise: The Influence of Aerobic Fitness and Venous Return

by

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Abstract

The role left ventricular (LV) twisting mechanics play in the stroke volume response to incremental exercise is unknown. Furthermore, the influences of aerobic fitness and venous return on LV twisting mechanics during vigorous exercise have not been investigated previously. To examine this issue, LV twisting mechanics and haemodynamics were assessed in eight endurance-trained (VO₂ max = $68.1 \pm 5.6 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and eight normally active (VO₂ max = $50.1 \pm 5 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) males during incremental upright and supine exercise at rest and during heart rates of 110, 130, 150, and 170 bpm. LV twisting mechanics were measured via echocardiography, while haemodynamic measures were collected using impedance cardiography. During both incremental protocols, cardiac output increased continuously in both groups. Stroke volume (SV) and end-diastolic volume increased to a greater extent in endurance-trained athletes compared to normally active individuals during exercise in both postural positions (e.g., SV at 170 bpm supine: ET, 45%; NA, 30.5%; SV at 170 upright: ET, 44.7%; NA, 33.8%; p < 0.05). No differences in the response of LV twisting mechanics to incremental exercise in either posture existed between groups. During supine exercise, SV and LV systolic and diastolic twisting mechanics reached a plateau during sub-maximal exercise (110 - 150 bpm). During upright exercise, LV systolic twisting mechanics increased with each exercise stage until maximum, while LV diastolic twisting mechanics plateaued at approximately 110 bpm. These results indicate that aerobic fitness has minimal influence on LV twisting mechanics during exercise, while changes in cardiac loading resulting from changes in posture have a significant effect. It appears that at higher intensity exercise, LV twisting mechanics play a reduced role in maintaining cardiac function as compared to low to moderate intensity exercise, regardless of aerobic fitness and venous return.

Preface

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A version of Chapter IV will be submitted for peer review. C. Taylor Drury was responsible for writing the manuscript, while the co-authors made significant contributions to data collection and analysis, as well as edits to the manuscript. The data from this research investigation was obtained with approval from the UBC Clinical Research Ethics Board under Certificate H11-01893

Please see the first pages of these chapters to see footnotes with similar information

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List of Abbreviations

LV	Left Ventricle
2D	2-Dimensional
NA	Normally active individuals
ET	Endurance-trained individuals
VO ₂	Oxygen Consumption
VO ₂ max	Maximal Aerobic Power
MAP	Mean arterial blood pressure
AO	Aortic valve opening
Peak-EJ	Peak ejection of aortic blood flow
AVC	Aortic valve closure
MVO	Mitral valve opening
Peak-E	Onset of peak early diastolic filling

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To my family

Chapter I: Introduction

1.1 Background and Rationale

It is well documented that endurance exercise training results in cardiovascular adaptations that augment myocardial function under exercise conditions (Warburton et al., 1999a). Specifically, during incremental exercise, endurance-trained (ET) individuals are able to increase stroke volume to a greater extent than normally active (NA) controls (Gledhill et al., 1994). The exact mechanism for these diverging responses during incremental exercise remains unclear; however, it has recently been proposed that alterations in the twisting properties of the left ventricle (LV) between ET and NA individuals may play an important role (Esch & Warburton, 2009). LV twist during systole is composed of the concurrent counterclockwise rotation of the apex and clockwise rotation of the base, resulting in a wringing motion of the ventricle (Esch & Warburton, 2009; Phillips et al., 2011). In diastole, the stored potential energy from the systolic contractions is released, resulting in a rapid untwisting of the LV. These rotational properties of the LV are believed to help optimize both systolic ejection and diastolic filling, through the production of maximum LV pressure with minimal muscle shortening, and through rapid LV pressure decay, respectively (Sengupta et al., 2008a). LV twisting mechanics thereby serve as important aspects of LV function. It is believed that increases in these LV twisting parameters during exercise may enhance myocardial function, and that further improvements in LV twisting mechanics potentially present in ET individuals may explain their augmented cardiovascular function during exercise (Esch & Warburton, 2009). Accordingly, the primary objective of this thesis investigation is to examine the role LV twisting mechanics play in the stroke volume response to incremental exercise in ET and NA individuals. Furthermore,

the effect of changes in venous return, and thereby cardiac loading conditions on LV twisting mechanics during exercise were examined through manipulations in posture (upright vs. supine exercise).

1.2 Summary of Objectives

- To examine the influence of endurance-exercise training on LV twisting mechanics in young healthy males during incremental exercise
- To examine the influence of changes in volume loading conditions through manipulations in body position (upright vs supine) on LV twisting mechanics in young healthy males during incremental exercise
- To examine the relationship between stroke volume and LV twisting mechanics in individuals of differing fitness levels in young healthy males during incremental exercise

1.3 Hypotheses

- Endurance-trained males will have greater LV twisting mechanics during exercise conditions
- Increasing exercise intensity will result in greater LV twisting mechanics in both normally active and endurance-trained males
- Conditions of higher venous return (supine vs. upright) will result in greater LV twisting mechanics
- The stroke volume response to exercise will depend on fitness level and will be related to changes in LV twisting mechanics.

1.4 Overview of Document

Chapter II provides an introduction to the concept of LV twisting mechanics and its importance to LV function. The aspects of cardiac structure that allow for LV twist to occur is discussed, as well as a brief overview of the current methods of measuring LV twist and some of known factors that influence these rotational parameters. Chapter III consists of a systematic review of the existing literature on LV twisting mechanics and exercise. In addition to an indepth analysis of the changes in LV twisting mechanics according to exercise type, some overall trends and interesting observations are noted and examined. Chapter IV consists of the thesis investigation. In this chapter, the methodology and results are presented along with a thorough discussion of the findings and limitations. In Chapter V, future directions and recommendations for this field of research are provided, along with an overall concluding statement from the thesis investigation.

Chapter II: Introduction to LV Twisting Mechanics

The purpose of this chapter is to provide a brief introduction to the concept of LV twisting mechanics. The current techniques used to measure LV twisting mechanics are outlined, along with some of the physiological factors known to influence them.

2.1 LV Twisting Mechanics: Structure and Function

The left ventricle (LV) has three planes of motion: longitudinal, radial, and circumferential (Esch & Warburton, 2009). Circumferential motion of the LV is the result of the contraction and relaxation of obliquely oriented epicardial and endocardial myofibres (Streeter *et al.*, 1969). In the healthy human heart, these oblique contractions result in circumferential counterclockwise rotation at the apex, and clckwise rotation at the base, when the LV is viewed from the apex. The net result of these opposing rotations in the basal and apical planes is a wringing motion of the heart during systole, referred to as LV twist (Beyar & Sideman, 1985).

The obliquely oriented epicardial and endocardial myofibres that allow LV twist to occur are wound in opposing helixes; when viewed from the apex, the sub-endocardial layer forms a right-handed helix, and the sub-epicardial layer forms a left-handed helix (Sengupta *et al.*, 2008a). During systolic contractions, the endocardial fibers work to rotate the apex in a clockwise direction and the base in a counterclockwise direction, while the epicardial fibers contract to produce force in the opposite direction. Owing to the greater distance from the longitudinal axis of the LV, and therefore a greater lever arm, the epicardial fibers are able to produce more torque than the endocardial fibers and subsequently act as the dominant rotational force. This epicardial-dominant rotation therefore results in the observed counterclockwise rotation at the apex and clockwise rotation at the base (Taber *et al.*, 1996). During diastole, a rapid untwisting motion in

the opposite direction occurs (Nikolic *et al.*, 1990). Collectively, LV twist, the corresponding diastolic untwisting, and the apical and basal components of each parameter can be viewed as the twisting mechanics of the LV, and serve as important indicators of LV function.

LV twisting mechanics help optimize both systolic and diastolic function. Systolic LV twist helps normalize myocardial sarcomere shortening across the ventricle, resulting in reduced shear stress between the endocardial and epicardial fiber layers, and correspondingly a reduction in myocardial oxygen demand (Arts *et al.*, 1982). As a result, LV twist allows for maximal LV pressures to be generated with minimal energy cost, and therefore helps improve systolic efficiency (Beyar & Sideman, 1985). During diastole, the rapid untwisting that occurs is believed to be caused by the release of elastic potential energy accumulated during systolic contractions (Fukuda *et al.*, 2001). This potential energy is thought to arise from the compression of spring-like cardiac proteins such as titin (Granzier *et al.*, 2005), and the release of shear strains accumulated between the sub-endocardial and sub-epicardial myofibre layers (Hui *et al.*, 2007). This early diastolic untwisting enhances the generation of the intraventricular pressure gradient and works to draw blood from the left atrium into the LV, a process known as diastolic suction, thereby enhancing passive diastolic filling and allowing diastolic filling to occur at lower atrial pressures (Rademakers *et al.*, 1992).

2.2 Measuring LV Twisting Mechanics

The twisting motion of the LV was first described by William Harvey (1628) and has since been measured and examined over the past few centuries (Sengupta *et al.*, 2008a). Early research involved implanting various myocardial markers in the epicardium, such as radiopaque metallic markers that were tracked using cine-fluoroscopy (Arts *et al.*, 1993), or small implanted crystals tracked using specialized external receivers (sonomicrometry) (Bell *et al.*, 2000). Given the invasive nature of these procedures, early research was therefore restricted to cardiac surgeries and animal models. More recently, newer imaging techniques including magnetic resonance imaging (MRI) and ultrasound have been developed that allow for LV twisting mechanics to be measured non-invasively.

MRI is considered by many to be the gold standard measure of LV twisting mechanics, and is often used in the validation of newer procedures (Notomi *et al.*, 2005a; Notomi *et al.*, 2005b). The technique involves collecting short axis images at the level of the apex and mitral valve of the left ventricle. Specific regions of the imaged myocardium are then 'tagged' and their movement is tracked between two time points (Epstein, 2007). MRI provides high spatial resolution and precision, owing to the exceptional image quality, yet has limited temporal resolution due to the inability to acquire images in quick succession (as compared to echocardiography) (Sengupta *et al.*, 2008a; Esch & Warburton, 2009). As a result of the high cost of MRI and the limited temporal resolution, its use is not as widespread as echocardiography (particularly during exercise).

The use of echocardiography to measure LV twisting mechanics also requires the collection of short axis images at the apical and basal level. Initially, tissue Doppler echocardiography was used to quantify apical and basal rotation by integrating the rotational velocities; yet the angle-dependence of the Doppler measurements was a significant limitation of this procedure (Notomi *et al.*, 2005b). Today, the most common echocardiographic measurements of LV twisting mechanics consist of collecting two-dimensional ultrasound images which are then analyzed using specialized software called speckle-tracking analysis (e.g., EchoPAC, GE Healthcare) in order to quantify apical and basal rotation and their respective velocities (Kim *et al.*, 2007). In brief, speckle-tracking analysis is the measurement of acoustic markers (speckles) created via

interference between the ultrasound waves and microscopic structures within the myocardium. These speckles, located within the myocardium, are then tracked frame-by-frame throughout the cardiac cycle to produce a measure of rotational displacement and velocity (Burns et al., 2008b). Speckle-tracking analysis has been validated previously against sonomicrometry and MRI (Helle-Valle et al., 2005; Notomi et al., 2005a), and has become the most widely used technique in the field. However, despite its widespread use, speckle-tracking analysis has some significant limitations. Accurate speckle-tracking analysis is highly dependent on the quality of the ultrasound image, and is therefore susceptible to image movement and through-plane motion of the speckles (Notomi et al., 2005a). Furthermore, there exists significant variability in the reported values of resting LV twist (Weyman, 2007). Part of this variability could be attributed to the importance of the location of echocardiographic image collection, as it has previously been demonstrated that manipulating the location of the point of apical image collection can significantly change the calculated value of LV twist (van Dalen et al., 2008). This becomes very important when evaluating the ability of speckle-tracking analysis to measure LV twisting mechanics during exercise (Phillips & Warburton, 2012).

2.3 Factors That Influence LV Twisting Mechanics

Many physiological factors have been examined for their influence on LV twisting mechanics (for reviews see Esch and Warburton (2009) and Sengupta *et al.* (2008a)). Those most pertinent to this thesis investigation include changes in loading conditions, sympathetic activity, contractility, heart rate, and age, all having been previously shown to influence LV twisting mechanics.

The influence of exercise on LV twisting mechanics has become a topic of considerable research. As exercise combines increases in sympathetic activity, contractility, heart rate, and

often changes in loading conditions (all while varying in both intensity and duration), its effect on LV twisting mechanics are not clear. The existing literature concerning the influence of exercise on LV twisting mechanics in healthy individuals has been investigated via systematic review (see Chapter III).

The changes in LV twisting mechanics as a result of manipulated loading conditions remains controversial. Gibbons-Kroeker et al. (1995), in open-chested dogs, first reported that increases in preload had no effect on peak LV twist, while increases in afterload reduced apical rotation. In contrast, Dong et al. (1999), using perfused canine hearts, demonstrated that peak LV twist increased in response to increases in preload. However, Dong and colleagues (1999) also confirmed that increases in afterload result in reductions in peak LV twist. In another canine heart model, LV twist was again found to decrease following increases in afterload (MacGowan et al., 1996). In contrast, the results of cardiac loading manipulations in human models have been varied. Volume loading via saline infusion produced no change in peak LV twist in two separate investigations in transplanted human hearts (Hansen et al., 1991; Moon et al., 1994). These same investigators also reported that increases in afterload via administration of methoxamine resulted in no changes to LV twist or diastolic untwist (Hansen et al., 1991; Moon et al., 1994). In healthy individuals, a similar saline infusion protocol resulted in increases in apical rotation, peak LV twist, and peak early diastolic untwisting rate (Weiner et al., 2010b). However, in older individuals (age: 66 ± 8 yr), no changes in systolic LV twisting mechanics and a reduction in diastolic twisting mechanics were reported in response to saline infusion (Burns et al., 2010). In the same study population, a reduction in both afterload and preload via administration of glyceryl trinitrate augmented both systolic and diastolic LV twisting mechanics (Burns et al., 2010). In response to volume unloading via lower body negative pressure (LBNP), peak apical

rotation and LV twist increased in healthy normally active males (Hodt *et al.*, 2011). However, LBNP to a similar extent has also been shown not to affect systolic LV twisting mechanics in normally active males and endurance-trained athletes, while at the same time inducing divergent diastolic responses (Esch *et al.*, 2010). A recent investigation using postural changes to manipulate loading conditions (head-up and head-down tilting) reported no change in any LV twisting mechanic parameter during the protocol (Nelson *et al.*, 2011). This diverse array of responses in LV twisting mechanics to changes in cardiac loading in humans draws attention to the need for further research in this area. In contrast to the relative consistency present in the animal literature, the widespread disagreement present in the human literature suggests that the dynamic mechanisms in which the cardiovascular system responds to perturbations in cardiac loading impedes the ability to measure the effects of cardiac loading on LV twisting mechanics in isolation. Indeed, Dong *et al.* (1999) suggested that the variable responses that occur following alterations in preload or afterload in 'preparations with intact circulations' may account for some of the variability in the literature.

The effects of changes in contractility and heart rate on LV twisting mechanics have been more conclusive. Positive inotropic and chronotropic stimulation in both animal and human models has consistently resulted in increased peak LV twist (Hansen *et al.*, 1991; Moon *et al.*, 1994; Gibbons Kroeker *et al.*, 1995; Dong *et al.*, 1999). However, the extent to which LV twisting mechanics will increase with continual increases in contractility and heart rate remains unknown. Previous research has demonstrated a plateau or a decrease in LV twisting mechanics at around 130 to 150 bpm in both animal and human models (Gibbons Kroeker *et al.*, 1995; Stöhr *et al.*, 2011c).

LV twisting mechanics are known to increase across the human lifespan from infancy to adulthood (Notomi *et al.*, 2006b). Research has shown that as age progresses, there is an increase in peak LV twist and a decrease in diastolic untwisting as compared to younger individuals (>60 yr vs. <40 yr) (Takeuchi *et al.*, 2006). Similarly, Burns *et al.* (2008a) reported higher resting peak LV twist in older individuals (>60 yr). Some believe these age-related changes in LV twisting mechanics to be related to reduced sub-endocardial myofibres shortening during systole, therefore reducing the force acting in opposition to the sub-epicardial rotation and resulting in greater LV twist (Lumens *et al.*, 2006).

The influence of chronic endurance training on LV twisting mechanics is not well understood, and even less so are the effects of endurance training on LV twisting mechanics during exercise. Endurance training is well known to result in an increase in resting blood volume (Convertino *et al.*, 1980; Warburton *et al.*, 2000), which in turn results in greater LV end-diastolic volume and therefore increased LV preload (Warburton et al., 2000). As previously discussed, some investigators have reported augmented LV twisting mechanics in response to increases in preload, and therefore it could be expected that ET athletes have higher resting LV twisting mechanics. However, ET individuals also have lower resting heart rates (Katona et al., 1982). As heart rate and contractility have been linked directly to changes in LV twisting mechanics, it may be that in fact ET athletes have lower resting LV twisting mechanics. To our knowledge, only five studies have measured resting LV twisting mechanics in both ET and NA individuals, yielding inconclusive results. Two investigations examined elite cyclists and found conflicting evidence. One study showed lower LV twisting mechanics (Nottin et al., 2008), while the other investigation reported increased LV twist and basal rotation (De Luca et al., 2011) in cyclists versus control participants. Professional soccer players were also found to have

lower resting LV twisting mechanics (Zócalo *et al.*, 2008). In two other separate conflicting investigations, individuals of higher aerobic fitness were found to have both reduced apical rotation (and a trend towards reduced LV twist (p = 0.09)) (Stöhr *et al.*, 2012), as well as similar LV twisting mechanics in comparison to normally active individuals (Esch *et al.*, 2010). While the presence of such variability in the literature highlights the need for further research, it is important to consider underlying factors such as cardiac remodeling when interpreting these results. Structural adaptations in the endocardium and epicardium resulting from chronic endurance training are likely to influence the rotation properties of the LV. The degree of structural remodeling present in a given study population would therefore present an additional source of variability. Moreover, all data in this field must be interpreted carefully owing to the inherent difficulties in the measurements (especially during exercise conditions).

2.4 Conclusion

The recent technological improvements in cardiac imaging have allowed the assessment of LV twisting mechanics to become increasingly widespread. While LV twist and untwisting are clearly important indicators of systolic and diastolic function, our knowledge of their impact across a wide range of physiological stressors is lacking. In particular, our understanding of the effects of exercise, aerobic training, and cardiac loading on LV twisting mechanics is insufficient and requires further investigation.

Chapter III: Left Ventricular Twist and Exercise in Healthy Individuals: A Systematic Review

The purpose of this chapter is to review systematically the existing literature concerning the changes in LV twisting mechanics during exercise in healthy individuals. Research papers are categorized and discussed in detail and concluding comments are provided. A version of this chapter has been accepted for publication with the following co-authors (in order): C. Taylor Drury, Shannon S.D. Bredin, Aaron A. Phillips, and Darren E.R. Warburton.

3.1 Introduction

During exercise, LV twisting mechanics may play an important role in augmenting cardiac function. It is well understood that the increases in chronotropic stimulation that occur with exercise result in reduced diastolic filling time, requiring a compensatory increase in diastolic filling in order to maintain cardiac output. As inotropy also increases during exercise, more potential energy is produced and stored in myocardial proteins during systole through vigorous twisting contractions, resulting in greater diastolic untwisting and therefore allowing for diastolic filling to occur more rapidly (Notomi *et al.*, 2006a). As diastolic untwisting plays a major role in diastolic filling, and relies heavily on LV twist, it is clear that the twisting mechanics of the LV are integral to cardiac function during exercise. The measurement of these twisting mechanics under exercise conditions is therefore critical to an accurate understanding of the relationship between exercise and heart function.

Recent improvements in echocardiography and cardiac MRI have allowed the twisting mechanics of the LV to be measured and quantified in healthy individuals (Helle-Valle *et al.*, 2005; Notomi *et al.*, 2005a). Correspondingly, there has been a rapid increase in the number of

papers examining the changes in LV twist and diastolic untwisting resulting from exercise. In light of this, we feel that a systemic assessment of the overall findings from these articles is required. Two recent narrative reviews have discussed changes in various indicators of LV function that occur following acute and prolonged bouts of exercise (George *et al.*, 2010; Oxborough *et al.*, 2010a); however, to our knowledge no systematic review exists examining the effects of all forms of exercise interventions on LV twisting mechanics. Accordingly, the primary purpose of this review is to summarize systematically and evaluate the existing literature examining the effects of exercise on LV systolic and diastolic twisting mechanics in healthy individuals. We aim to provide clarity to the effects of different exercise durations and intensities on LV twisting mechanics, and hypothesize that acute short-term exercise will induce an increase in these LV parameters, while prolonged exercise will cause a transient decrease.

3.2 Methods

3.2.1 Search Strategy:

An extensive literature search on the effects of exercise on LV systolic and diastolic twisting mechanics was conducted in the following electronic databases (from 1950 – January 2012): MEDLINE, EMBASE, Cochrane Library, ACP Journal Club, DARE, CCTR, CMR, HTA, NHSEED, Academic Search Complete, CINAHL, PsycINFO, and SPORTDiscus. Search terms were divided into three categories: 1) exercise, 2) LV, and 3) twisting mechanics. The exercise search terms used were developed previously in systematic reviews conducted by our research group (Warburton *et al.*, 2010). See Table 3.1 for a complete list of the Medical Subject Headings (MeSH) and keywords used.

Search #	Searches (<i>March</i> 13 ^{<i>m</i>} , 2011)	Results					
1	exp. Physical Fitness/	18174					
2	exp. Motor Activity/	93010	щ				
3	exp, Physical Endurance/	19700	Xer				
4	exp. Exercise/ 54165						
5	exp. Physical Exertion/	50171	Pa				
6	exp. Sports/	89073	ram				
7	exp. Exercise Therapy/	22408	lete				
8	exp. Exercise Tolerance/	6138	ß				
9	exp. Health Behavior/	75536					
10	exp. Heart Ventricles/	59094	Lef Pa				
11	exp. Ventricular Function, Left/	22147	t Vo aran				
12	Exp. Ventricular Function/	39642	entr nete				
13	Myocardial.mp	299096	icle rs				
14	Rotation\$.mp	68499					
15	Recoil\$.mp	2248	_V] Para				
16	Twist\$.mp	9749	Гwi ame				
17	Untwist\$.mp	404	stin				
18	Torsion\$.mp	16973	, QO				
	1 2 2 4 5 6 7						
19	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	329205	_				
20	10 or 11 or 12 or 13	353080	_				
21	14 or 15 or 16 or 17 or 18	93704	_				
22	19 or 20 or 21	43	-				

 Table 3.1: Results of the MEDLINE literature search using the OVID Interface.

3.2.2 Screening:

A total of 127 articles were found through the literature search. Duplicates, review articles, conference abstracts, articles not in English, letters to the editor, studies investigating only pathological conditions (without data on healthy individuals), and investigations that did not report data on LV twisting mechanics were excluded, leaving 14 articles remaining. In addition, four articles were found via manual cross-referencing and the authors' knowledge of the subject area, resulting in a total of 18 articles for final review (Figure 3.1).



Figure 3.1: Flow chart of literature search process

3.2.3 Quality Assessment and Level of Evidence:

Two reviewers (TD and AP) assessed all articles for methodological quality and level of evidence in duplicate and any disagreements were settled through consultation with a third reviewer (DW) until 100% consensus was achieved. All systematic review related processes were overseen and directed by a senior investigator specializing in systematic reviews (SB). Methodological quality was determined using the Downs and Black Quality Index checklist (Downs & Black, 1998), as our review did not include any randomized controlled trials. The Quality Index checklist was modified according to Prince *et al* (2008) (and used previously by our research group (Warburton *et al.*, 2010)) to incorporate only the most relevant questions from the original checklist. Each article was assigned a score out of 15, with higher scores indicating greater levels of methodological quality. Level of evidence was assessed using a 5-point scale (Eng *et al.*, 2007) (modified from Sackett *et al* (2000)). In brief, Level 1 (the highest level of evidence for research trials) corresponds to a randomized controlled trial of high quality. Level 2 refers to either a randomized controlled trial of lower quality, a prospective controlled trial, or a cohort study. Level 3 is a case control study design. Level 4 refers to a pre-post, posttest, or a case series study design. Level 5 (the lowest level of evidence) can be either an observational, clinical consensus, or case report design.

3.3 Results

The 18 included articles involved a total of 324 healthy participants (276 men, 48 women) with an age range of 19 to 70 years. The articles were categorized by their exercise type into four groups: acute sub-maximal exercise (9 studies, 147 total participants) (Notomi *et al.*, 2006a; Burns *et al.*, 2008a; Esch *et al.*, 2009; Tan *et al.*, 2009; Doucende *et al.*, 2010; Stöhr *et al.*, 2011a; Stöhr *et al.*, 2011b; Stöhr *et al.*, 2011c; Stöhr *et al.*, 2012); prolonged endurance exercise (5 studies, 102 total participants) (Nottin *et al.*, 2009; Chan-Dewar *et al.*, 2010; Oxborough *et al.*, 2010b; Hanssen *et al.*, 2011; Nottin *et al.*, 2012); acute maximal exercise (3 studies, 60 total participants) (Tischler & Niggel, 2003; Neilan *et al.*, 2006; Scott *et al.*, 2010); and chronic endurance exercise (1 study, 15 total participants) (Weiner *et al.*, 2010a). See Table 3.2 for an overall summary and Tables 3.3, 3.4, 3.5, and 3.6 for a comprehensive summary of the articles in each exercise category (supplemental tables). The articles examined were of low to moderate

methodological quality, with a mean Downs and Black score of 10.61 ± 0.85 out of 15 (range 9 – 12). The articles were published over a nine year period (2003 - 2012).

					Systolic Parameters				Diastolic Parameters	
Study	# Subjects (male)	Exercise Mode	Age (SD)	Twist	Apical Rotation	Basal Rotation	TTP Twist	Untwisting Rate	TTP Untwisting Rate	
Acute Sub-Maximal Exercise										
Notomi et al. 2006	n = 20 (12)	Supine cycling	34 (7)	\uparrow	\uparrow	\uparrow		\uparrow	\downarrow	
Burns et al. 2008	n = 14 (9)	Supine cycling	Young: 40 Old: 60	$\uparrow \\ \leftrightarrow$				$\stackrel{\uparrow}{\leftrightarrow}$		
Esch et al. 2009	n = 11 (11)	Semi-supine cycling	Young: 35 (8) Old: 60 (0)	$\uparrow \\ \leftrightarrow$			$\stackrel{\downarrow}{\leftrightarrow}$	$\stackrel{\uparrow}{\leftrightarrow}$		
Tan et al. 2009	n = 27 (8)	Semi-supine cycling	70 (7)		\uparrow			1		
Doucende et al. 2010	n = 20 (20)	Semi-supine cycling	25 (9)	\uparrow	\uparrow	\uparrow	\leftrightarrow	\uparrow	\leftrightarrow	
Stohr et al. 2011a	n = 10 (10)	Knee Extensions	21 (2)	\leftrightarrow	\leftrightarrow	\leftrightarrow		\leftrightarrow		
Stohr et al. 2011b	n = 9 (9)	Supine cycling	26 (4)	\uparrow	\uparrow	\uparrow		↑	\downarrow	
Stohr et al. 2011c	n = 8 (8)	Knee Extensions	20 (2)	\leftrightarrow	\leftrightarrow	\leftrightarrow		\leftrightarrow	\uparrow	
Stohr et al. 2012	n = 28 (28)	Supine cycling	ET: 21 (3) NA: 21 (2)	↑ ↑	↑ ↑	$\uparrow \\ \uparrow$		↑ ↑		
Prolonged End	urance Exercis	e								
Nottin et al. 2009	n = 23 (23)	Triathlon	40 (9)	\leftrightarrow	\downarrow	\downarrow	\uparrow	\downarrow	\uparrow	
Chan Dewar et al. 2010	n = 14 (14)	Marathon	32 (10)	S-epi A S-end A	$\begin{array}{ccc} \leftrightarrow & \leftrightarrow \\ \leftrightarrow & \leftrightarrow \end{array}$	\leftrightarrow \leftrightarrow				
Oxborough et al. 2010	n = 17 (17)	Marathon	33 (6)	\leftrightarrow	\leftrightarrow	\leftrightarrow		\downarrow		
Hanssen et al. 2011	n = 28 (28)	Marathon	41 (5)	\uparrow					\leftrightarrow	
Nottin et al. 2011	n = 20 (20)	Upright cycling	25 (5)	\leftrightarrow	\leftrightarrow	\leftrightarrow	\leftrightarrow	\leftrightarrow	\uparrow	
Acute Maximal	Exercise									
Tischler et al. 2003	n = 25 (14)	Treadmill	35.6 (9)	\uparrow						

Table 3.2: Overall summary table of the effects of exercise on select systolic and diastolic LV twisting mechanics.

				Systolic Parameters				Diastolic Parameters	
Study	# Subjects (male)	Exercise Mode	Age (SD)	Twist	Apical Rotation	Basal Rotation	TTP Twist	Untwisting Rate	TTP Untwisting Rate
Neilan et al. 2006	n = 17 (12)	Rowing	37 (NR)	\uparrow	\leftrightarrow	\uparrow			
Scott et al.	n = 18(18)	Upright	ET: 29 (6)	\leftrightarrow	\downarrow	\leftrightarrow	\uparrow	\downarrow	\uparrow
2010	II = 18(18)	cycling	NA: 35 (7)	\leftrightarrow	\leftrightarrow	\leftrightarrow	\leftrightarrow	\leftrightarrow	\leftrightarrow
Chronic Endurance Exercise									
Weiner et al. 2010	n = 15 (15)	Endurance exercise training	18.6 (0.5)	Ŷ	\uparrow	\leftrightarrow	\leftrightarrow	\uparrow	\leftrightarrow

TTP, time to peak; ET, endurance-trained athletes; NA, normally active un-trained individuals; S-epi, sub-epicardium; S-end, sub-endocardium; NR, not reported

3.3.1 Acute Sub-maximal Exercise

Nine studies investigated the effects of acute sub-maximal exercise on systolic and diastolic LV twisting mechanics (147 total participants, approximate mean ages: 20-70). All investigations measured LV function at rest and during exercise. Seven investigations utilized either supine or semi-supine bicycling as their exercise mode (Notomi *et al.*, 2006a; Burns *et al.*, 2008a; Esch *et al.*, 2009; Tan *et al.*, 2009; Doucende *et al.*, 2010; Stöhr *et al.*, 2011c; Stöhr *et al.*, 2012), while the two remaining investigations utilized a unilateral knee extensor exercise protocol (Stöhr *et al.*, 2011a; Stöhr *et al.*, 2011b).

Systolic Parameters: Acute sub-maximal exercise was found to result primarily in augmented LV systolic twisting mechanics (including LV twist, twisting rate, systolic apical and basal rotation, and apical and basal rotation rate) in individuals below age 40 (Notomi *et al.*, 2006a; Burns et al., 2008a; Esch et al., 2009; Doucende et al., 2010; Stöhr et al., 2011c; Stöhr et al., 2012). However, two investigations reported no change in any of these parameters in response to sub-maximal exercise in individuals of this age group (Stöhr et al., 2011a; Stöhr et al., 2011b). This disagreement is most likely due to the use of a weak exercise stimulus in these two outlying investigations, as unilateral knee extensor exercises did not induce increases in either stroke volume or ejection fraction, two indices of cardiac function that were found to increase in all other investigations in this category. Interestingly, one investigation examined the changes in LV twisting mechanics during sub-maximal exercise between endurance-trained and normally active individuals (Stöhr et al., 2012). This investigation reported that all measured systolic LV twisting mechanics increased from rest to exercise in both groups, but found no evidence of group differences in any LV twisting mechanic parameter, aside from lower apical rotation, and a trend towards lower LV twist (p = 0.09) at rest and during exercise in the endurance-trained group

compared to the normally active group (Stöhr *et al.*, 2012). In addition, sub-maximal exercise was also found to primarily result in no change in LV systolic twisting mechanics in individuals above age 40 (Burns *et al.*, 2008a; Esch *et al.*, 2009), although one investigation did report increased peak apical rotation in an older population during semi-recumbent cycling (Tan *et al.*, 2009). This discrepancy is potentially attributable to differences in the selected sample populations, as the older populations examined by Burns *et al.*, (2008a) and Esch *et al.*, (2009) were on various cardiac and blood pressure lowering medications, while the population examined by Tan *et al.*, (2009) was free of any cardiovascular medications. The absence of medication potentially reflects a healthier cardiovascular system in which LV function may have more closely resembled that of younger individuals in the ability augment systolic twisting mechanics in response to the exercise perturbation.

Diastolic Parameters: Consistent with the increase in LV systolic twisting mechanics, diastolic twisting mechanics (including untwisting rate, time to peak untwisting rate, and diastolic apical and basal rotation rates) were generally reported to increase during sub-maximal exercise in individuals below age 40 (Notomi *et al.*, 2006a; Burns *et al.*, 2008a; Esch *et al.*, 2009; Doucende *et al.*, 2010; Stöhr *et al.*, 2011c; Stöhr *et al.*, 2012). The same two investigations which utilized a lower exercise intensity reported no change in diastolic twisting mechanics (Stöhr *et al.*, 2011a; Stöhr *et al.*, 2011b). In endurance-trained and normally active individuals, sub-maximal exercise induced an increase in all measured LV diastolic twisting mechanics, yet there was no difference in any diastolic twisting mechanic parameter between groups at rest or during exercise (Stöhr *et al.*, 2012). In individuals above age 40, sub-maximal exercise resulted primarily in impaired diastolic untwisting (increased time to peak untwisting rate, failure to augment peak untwisting rate) (Burns *et al.*, 2008a; Esch *et al.*, 2009). However, the same investigation that reported

contradictory improvements in systolic twisting mechanics in a potentially healthier older population, also found conflicting evidence of increased peak untwisting rate in these individuals (Tan *et al.*, 2009). The percentage of LV untwisting that occurred prior to mitral valve opening, a marker of early diastolic function and an essential aspect of diastolic suction, was found to be primarily unchanged in individuals below age 40 yr (Notomi *et al.*, 2006a; Esch *et al.*, 2009; Doucende *et al.*, 2010). The two studies to report this measure in those older than 40 yr found conflicting evidence, as Esch *et al.*, (2009) reported a decrease – further supporting their finding of impaired diastolic twisting mechanics – while Tan *et al.*, (2009) reported no change in the amount of untwisting occurring at any point during diastole. The percentage of LV untwisting occurring prior to mitral valve opening is of great interest because any LV untwisting that occurs after mitral valve opening does not contribute to LV pressure decay and is therefore less efficient (Notomi *et al.*, 2006a).

Conclusion: There is consistent support from level 4 and level 2 (Notomi *et al.*, 2006a; Burns *et al.*, 2008a; Doucende *et al.*, 2010; Stöhr *et al.*, 2011c; Stöhr *et al.*, 2012) evidence that submaximal exercise results in enhanced systolic and diastolic LV twisting mechanics in individuals below age 40. The conflicting results present in the two level 4 studies likely arise from the use of low intensity exercise protocols (Stöhr *et al.*, 2011a; Stöhr *et al.*, 2011b). As nine investigations have examined the effects of sub-maximal exercise on LV twisting mechanics in younger individuals, the results can be interpreted to be relatively conclusive. However, the evidence in older individuals is less clear, and more work is needed examining LV twist during exercise across the human lifespan. Regardless, future studies should utilize comparable modes of exercise and note the clinical health of their participants. It is evident that the changes in systolic and diastolic LV twisting mechanics during sub-maximal exercise are influenced by age,

as younger individuals are able to augment their LV function during exercise, while older individuals are not.

3.3.2 Prolonged Endurance Exercise

The effects of prolonged endurance exercise on resting LV systolic and diastolic twisting mechanics were investigated by five studies (102 total participants, approximate mean ages: 30-40). The exercise protocols included three marathon races (involving 42.2 km of running) (Chan-Dewar *et al.*, 2010; Oxborough *et al.*, 2010b; Hanssen *et al.*, 2011), one ultra-long triathlon race (involving a 3.8 km of swimming, 186 km of cycling, and 42.2 km of running) (Nottin *et al.*, 2009), and one 120 minute continuous cycling protocol (Nottin *et al.*, 2012). All investigations examined the changes in LV twisting mechanics pre- and post-exercise, with one investigation specifically examining the changes in the sub-endocardial and sub-epicardial layers of the myocardium (Chan-Dewar *et al.*, 2010).

Systolic Parameters: Prolonged endurance exercise primarily resulted in impaired LV systolic twisting mechanics. This was evident in the form of decreased peak systolic apical and basal rotations, increased time to peak apical and basal rotation, increased time to peak apical and basal rotation rates, a slight decrease in peak LV twist (p = 0.09) delayed time to peak LV twist, and a decreased amount of LV twist occurring at the time of aortic valve closure (Nottin *et al.*, 2009; Nottin *et al.*, 2012). In contrast, however, one investigation reported augmented systolic twisting mechanics (increases in peak LV twist and twisting rate) (Hanssen *et al.*, 2011). As previously discussed, preload has been demonstrated to influence systolic twisting mechanics, and therefore this disagreement could be the result of change sin preload pre- and post-exercise. Accordingly, the two investigations that reported impaired systolic twisting mechanics also reported decreases in preload (Nottin *et al.*, 2009; Oxborough *et al.*, 2010b), while the

investigation that reported augmented systolic twisting mechanics reported no change in preload (Hanssen *et al.*, 2011). Finally, prolonged endurance exercise was also found to largely exert no effect on systolic twisting mechanics in the sub-endocardial and sub-epicardial layers of the myocardium, apart from an increase in peak sub-endocardial apical rotation rate (Chan-Dewar *et al.*, 2010).

Diastolic Parameters: Prolonged endurance exercise resulted primarily in impaired diastolic twisting mechanics. This was evident through a decrease in peak untwisting rate, an increase in time to peak untwisting rate, a decrease in peak diastolic apical and basal rotation rates, and a decrease in the amount of LV untwisting that occurred during isovolumic relaxation (indicating less efficient diastolic filling) (Nottin et al., 2009; Oxborough et al., 2010b; Nottin et al., 2012). Interestingly, the diastolic impairments observed after 120 min of endurance exercise (Nottin et al., 2012) were less severe than those observed after 850 min (Nottin et al., 2009), suggesting a potential dose-response relationship between exercise duration and diastolic impairment. In addition, LV twist (Oxborough et al., 2010b) and systolic apical rotation (Hanssen et al., 2011) were reported to remain elevated during early diastole, indicating a reduction in LV relaxation time and therefore a reduced time for diastolic untwisting and subsequent filling. These findings could also be interpreted as an increased time to peak LV twist, therefore suggesting an impairment in systolic twisting mechanics. Furthermore, Hanssen et al., (2011) reported no evidence of impaired diastolic twisting function, yet found a global decrease in diastolic filling. This finding, coupled with the elevated systolic apical rotation during early diastole, suggests that diastolic impairment may not always manifest in alterations diastolic twisting mechanics. Finally, prolonged endurance exercise resulted in no changes in the twisting mechanics of the sub-endocardium and sub-epicardium (Chan-Dewar et al., 2010).

Conclusion: Level 4 evidence (indicating available evidence but without comparable groups) exists indicating that that prolonged endurance exercise induces impaired systolic and diastolic LV twisting mechanics (Nottin et al., 2009; Oxborough et al., 2010b; Nottin et al., 2012). Conflicting level 4 evidence exists indicating that prolonged endurance exercise results in augmented systolic twisting mechanics and unaltered diastolic twisting mechanics (Hanssen et al., 2011). This investigation, however, also reported elevated measures of systolic twisting mechanics during diastole, suggesting a form of diastolic impairment consistent with previous reports. Finally, Level 4 evidence demonstrates that prolonged endurance exercise largely exerts no change in either systolic or diastolic twisting mechanics in the sub-endocardial and subepicardial layers of the myocardium. As there have only been five studies examining the changes in twisting mechanics after prolonged endurance exercise, the need for further research is clear. However, the relative consistency in the observed results tends to support the observed trends in the data. Of particular interest is the apparent effect of changes in preload on LV systolic twisting mechanics, a finding potentially resulting from excessive fluid loss or exercise-induced hypotension which can occur during exercise of this duration and intensity.

3.3.3 Acute Maximal Exercise

Three articles investigated the effects of acute maximal exercise on resting LV twisting mechanics (60 total participants, approximate mean ages: 30-40). All investigations measured LV function before after exercise and each utilized a different exercise intervention, yet all reported achieving a maximal effort from their respective participants.

Systolic Parameters: In response to maximal exercise, LV systolic twisting mechanics were found to increase, in the form of increases in peak LV twist, peak basal rotation, and a trend towards increased peak apical rotation (p = 0.07) (Tischler & Niggel, 2003; Neilan *et al.*, 2006).
Interestingly, one investigation that examined repeated bouts of maximal intensity exercise showed differing results. After performing 14 one-minute bouts at maximal exercise (separated by 2 minutes of recovery), no change in LV systolic twisting mechanics occurred in their untrained group, while the endurance-trained group experienced decreases in peak apical rotation rate and a delay in the time to peak twist (Scott *et al.*, 2010). This disagreement is potentially due to the increased duration and intensity of the exercise protocol in comparison to the protocols involving single-bouts at maximal intensity, and draws similarities to the apparent dose-response relationship between twisting mechanics and exercise duration found during prolonged endurance exercise.

Diastolic Parameters: Diastolic LV twisting mechanics were only examined in one investigation, which reported evidence of reduced peak untwisting rate and an increased time to peak untwisting rate in endurance-trained individuals, but not in untrained participants (Scott *et al.*, 2010). This investigation also reported a reduced time interval between peak diastolic untwisting and LV filling (measured as peak circumferential strain rate) in endurance-trained individuals. As noted by the authors, peak diastolic untwist and LV filling are distinctly separated under normal resting conditions, as myocardial relaxation occurs before ventricular filling (Nagel *et al.*, 2000), and a reduction in this time interval indicates impaired diastolic function. Interestingly, additional evidence exists that maximal exercise can also result in an attenuation of more traditional markers of LV diastolic function in endurance-trained participants. Neilan *et al.*, (2006) showed that there is a reversal in diastolic filling pattern in these individuals, perhaps suggesting that highly trained athletes are more susceptible to diastolic impairment following maximal exercise.

Conclusion: There is level 4 evidence that acute maximal exercise can result in augmented LV systolic twisting mechanics (Tischler & Niggel, 2003; Neilan *et al.*, 2006). There is also level 2 evidence that this same exercise type, albeit a more intense exercise protocol, can impair both systolic and diastolic twisting mechanics in endurance-trained individuals while exerting no changes in untrained participants (Scott *et al.*, 2010). As only three studies exist examining the effects of acute maximal exercise on LV twisting mechanics, and each investigation utilized a different exercise protocol and varying subject populations, more research is necessary that incorporates standardized exercise protocols and consistent population samples. Despite these inconsistencies, it appears that endurance-trained individuals may experience a reduction in both systolic and diastolic LV twisting mechanics after maximal exercise while untrained individuals do not.

3.3.4 Chronic Endurance Exercise

One study investigated the effects of chronic endurance exercise on resting LV systolic and diastolic twisting mechanics in elite athletes (15 total participants, mean age: 19 yr) (Weiner *et al.*, 2010a), utilizing 90 days of endurance exercise training (approximately 13.6 hr per week) as their exercise protocol. Measures of LV twisting mechanics were taken at rest before and after the training program.

Systolic Parameters: Systolic LV twisting mechanics were found to be augmented following chronic endurance exercise in the form of increases in peak LV twist and peak systolic apical rotation (Weiner *et al.*, 2010a).

Diastolic Parameters: Chronic endurance exercise resulted in enhanced LV diastolic twisting mechanics in the form of increased peak untwisting rate, increased peak diastolic apical rotation

rate, and an increase in the percentage of untwisting occurring during isovolumic relaxation (Weiner *et al.*, 2010a). This increase in early diastolic untwisting is likely the result of the increased LV systolic twist, which would generate greater elastic potential energy for release during early diastole.

Conclusions: There is level 4 evidence that chronic endurance exercise results in augmented LV systolic and diastolic twisting mechanics (Weiner *et al.*, 2010a). Although this is the only study of its kind, prior investigations have examined resting LV systolic and diastolic twisting mechanics in elite athletes and untrained individuals (as previously discussed) reporting reductions in peak LV twist (Nottin *et al.*, 2008; Zócalo *et al.*, 2008) and LV diastolic untwisting (Zócalo *et al.*, 2008), as well as no change in LV diastolic twisting mechanics (Nottin *et al.*, 2008) in elite athletes. This disagreement, recognized by Weiner *et al.*, (2010a), was attributed to differences in study populations and study designs, as Nottin *et al.*, (2008) and Zócalo *et al.*, (2008) examined slightly older individuals and used a cross-sectional study design that could have collected data from the athletes while they were in a period of detraining.

3.4 Discussion

Significant contention exists regarding changes in LV twisting mechanics occurring in response to exercise. This debate has resulted in several publications (e.g., Esch & Warburton (2009), George *et al.*, (2010), Oxborough *et al.*, (2010a), Weiner and Baggish (2011), Phillips and Warburton (2012)). The purpose of this review was to summarize systematically the existing published evidence examining the influence of exercise on LV twisting mechanics in healthy individuals. Separation of the articles according to exercise type was essential in order to adequately compare investigations, and yielded mixed results, with no category having complete

agreement. Yet despite these observed inconsistencies, some intriguing trends were found in the literature.

Firstly, sub-maximal exercise appears to result in augmented LV systolic and diastolic twisting mechanics in only younger individuals (below age 40). Given that exercise produces increases in heart rate and contractility, both previously demonstrated to increase LV twisting mechanics, this finding can be expected. However, the increases in venous return (preload) and systolic blood pressure (often used as an indicator of afterload) that also occur with exercise, both of which have been demonstrated to influence LV twisting mechanics through opposing mechanisms, could account for some of the observed result variability. With regards to the effects of age on LV twisting mechanics during exercise, previous research has demonstrated that LV twisting mechanics increase with age (Nakai *et al.*, 2006; Notomi *et al.*, 2006b); yet the inability of older individuals to enhance LV twisting mechanics during exercise has not been fully explained. One theory attributes this age-related change to a decreased 'twisting reserve' in older individuals. Older individuals have been found to have higher resting LV twist, which could therefore limit the capacity of the LV to further twist/untwist during exercise (Burns *et al.*, 2008a), yet more research is needed to thoroughly investigate this theory.

Secondly, prolonged endurance exercise appears to impair both LV systolic and diastolic twisting mechanics. LV function during systole and diastole has been well documented to decrease following endurance exercise through traditional measures such as ejection fraction and E/A ratios (Shave *et al.*, 2008; Oxborough *et al.*, 2010a), thereby providing support for this observed decrease in twisting mechanics. Interestingly, there also appears to be a dose-response relationship between the duration and intensity of endurance exercise and the level of twisting impairment. This is supported by previous research using traditional measures of LV function

which demonstrate that increases in exercise duration and intensity are related to the level of cardiac function impairment (Middleton *et al.*, 2006). Changes in cardiac loading after endurance exercise, manifested as changes in end-diastolic volume were also found to potentially exert an effect on systolic twisting mechanics, supporting the idea that LV twisting mechanics are indeed load dependent.

Finally, a general trend found throughout all exercise types is the linkage between the systolic and diastolic components of LV twisting and untwisting. In other words, if systolic twisting was impaired (or improved), it resulted in impaired (or improved) diastolic untwisting, respectively. This finding suggests that the systolic-diastolic rotational coupling of the LV, through the production and release of elastic potential energy (Notomi *et al.*, 2006a) holds true for the various exercise modalities. In fact, systolic-diastolic LV rotational coupling has also been widely reported in various heart diseases (Esch & Warburton, 2009). As it appears that systolic function cannot be altered without similar implications on diastolic function, or vise versa, the connectedness between systole and diastole through LV twisting mechanics provides an important avenue for future cardiac research (Pasipoularides, 2011).

Methodological Considerations:

The presence of conflicting evidence in many of the exercise categories is potentially explained by some important methodological considerations. The methodological quality of the included investigations was low to moderate, and the evidence was primarily rated at level 4. Methodological quality could be improved in future studies through the use of control groups (absent in 15 of the 18 studies), and their absence in the current body of literature is difficult to explain – perhaps due to unreported challenges such as an increased amount of time required to analyze echocardiographic images, or difficulty with participant recruitment. In addition, there was significant variability in the exercise protocols and subject characteristics present within each exercise type. The inconsistent durations and intensities of the exercise protocols across studies of the same exercise type are also likely to account for some of the observed conflicting results. As increases in exercise duration and intensity have already been demonstrated to relate directly to changes in cardiac function during endurance exercise (Middleton et al., 2006), it is conceivable that variations in the duration and intensity of the exercise protocols used in the other exercise types could exert similar effects. The use of different exercise protocols also creates different conditions of cardiac loading. In the sub-maximal exercise category, for example, participants exercised in the supine, semi-supine, and upright postural positions - each resulting in differing levels of venous return and therefore variations in cardiac preload. Given the aforementioned potential influence of changes in cardiac loading on LV twisting mechanics, the use of inconsistent exercise protocols is an important methodological consideration. In addition, as aerobic fitness may also influence LV twisting mechanics, participant training status should therefore be carefully controlled for during an investigation. Another potential confounding factor and methodological consideration is the use of sample populations consisting of mixed sexes, as females are known to exhibit altered cardiac responses to both acute (Davis et al., 2000) and prolonged (Scott et al., 2007) exercise in comparison to males. Finally, the inherent limitations of each cardiac imaging technique must also be considered. The use of trained personnel to collect and analyze the data in order to reduce measurement error and result variability is essential.

3.5 Conclusions

The measurement of LV twisting mechanics during exercise is becoming increasingly prevalent and has resulted in considerable debate. The study of the rotational properties of the LV provides important insight into cardiac function during exercise that traditional measures of LV function cannot. Despite some important methodological considerations present in the available literature, there are significant trends in each exercise category that should be considered. Most importantly, the rotational coupling of the LV between systole and diastole holds true in all exercise types, as LV systolic and diastolic twisting mechanics were impaired (or improved) concomitantly. Future research should include standardized exercise protocols and consistent subject characteristics in order to limit the methodological-induced variability in the observed results.

Table 3.3: Effects of acute sub-maximal	exercise on systolic and dia	astolic LV twisting mechanics.

Author, Country, Study Design and Level of Evidence, Quality score	Population	Methods	Outcome	Additional Notes	Interpretations
Notomi et al 2006 USA Pre-post = Level 4 D&B Score = 11/15	N = 20 (12 males) Mean age: 34±7 yrs Characteristics: Healthy volunteers	EI: Submaximal supine bicycle (25W start with 25W increases every 2min) MP: before and during exercise (HR=100bpm) OM: LV systolic apical and basal rotation, twist, twisting rate, time to peak twist, diastolic untwisting rate, time to peak untwisting rate MT: Doppler tissue imaging	- LV systolic apical and basal rotation, twist, twisting rate and diastolic untwisting rate increased. Time to peak untwisting rate decreased	- No change in percentage of LV untwisting occurring prior to mitral valve opening	- Sub-maximal exercise enhances LV systolic and diastolic twisting function
Burns et al 2008 Australia Pre-post = Level 4 D&B Score = 11/15	N = 14 (9 males) Mean age: Young = 40 yrs, Old = 60 yrs Characteristics: Patients undergoing clinically indicated stress tests	EI: Submaximal supine bicycle (50W start with 25W increases every 3min) MP: before and at peak exercise OM: LV twisting, twisting rate, diastolic untwisting rate MT: 2D echo with STA	 Young: LV twist and diastolic untwisting rate increased. Time to peak twist decreased Old: no change in LV twist, diastolic untwisting rate, or time to peak untwisting rate 	- Older population on various cardiac medications to treat hypertension and lipid problems	- Sub-maximal exercise enhances twisting function in younger populations and impairs systolic and diastolic twisting function in older populations
Esch et al 2009 Canada Prospective controlled trial = Level 2 D&B Score = 10/15	N = 11 (all males), 6 old (O) and 5 young (Y) Mean age: O = 60 ± 9 yrs, Y = 35 ± 8 yrs Characteristics: O VO ₂ peak= 36.3 ± 10.7 ml/kg/min, Y VO ₂ peak= 51.1 ± 10.4 ml/kg/min	EI Submaximal semi- supine bicycle (20min at 80% ventilatory threshold) MP: before and at peak exercise OM: LV systolic apical and basal rotation, twist, twisting rate, diastolic untwisting rate MT: 2D echo with STA	 Young: LV twist and diastolic untwisting rate increased. Time to peak twist decreased Old: no change in twist and diastolic untwisting rate 	 Percentage of LV diastolic untwisting occurring prior to mitral valve opening decreased in Old group, no change in Young group Older population on various cardiac medications to treat hypertension and lipid problems 	- Sub-maximal exercise enhances twisting function in younger populations and impairs systolic and diastolic twisting function in older populations

Author, Country, Study Design and Level of Evidence, Quality score	Population	Methods	Outcome	Additional Notes	Interpretations
Tan et al 2009 United Kingdom Pre-post = Level 4 D&B Score = 12/15	N = 27 (8 males) Mean age: 70 ± 7 yrs Characteristics: no prior medical history and receiving no medications	EI: Symptom limited, fatigue or dyspnea, submaximal semi- recumbent bicycle (to a max HR of 100bpm) MP: before and during submaximal exercise OM: LV systolic apical rotation, diastolic untwisting rate MT: 2D echo with STA	- LV systolic apical rotation and diastolic untwisting rate increased	 No change in percentage of LV untwisting occurring prior to mitral valve opening Population was not on any medications 	 Sub-maximal exercise enhances systolic and diastolic twisting function in older populations Disagreement potentially due to sampling of healthier older population
Doucende et al 2010 France Pre-post = Level 4 D&B Score = 11/15	N = 20 (all males) Mean age: 25 ± 9 yrs Characteristics: sedentary males, no reported regular training habits	EI: Submaximal semi- supine bicycle (6min stages at 20% (W1), 30% (W2), and 40% (W3) VO ₂ max) MP: before exercise and during each stage (W1, W2, W3) OM: LV systolic apical and basal rotation, apical and basal rotation rate, twist, twisting rate, time to peak twist, diastolic apical and basal rotation rate, untwisting rate, time to peak untwisting rate MT: 2D echo with STA	- LV systolic apical and basal rotation, apical and basal rotation rate, twist, twisting rate, diastolic apical and basal rotation rate, and untwisting rate increased with each stage	- No change in percentage of LV untwisting occurring prior to mitral valve opening	- Sub-maximal exercise enhances systolic and diastolic twisting function

Author, Country, Study Design and Level of Evidence, Ouality score	Population	Methods	Outcome	Additional Notes	Interpretations
Stohr et al 2011a United Kingdom Pre-post = Level 4 D&B Score = 10/15	N = 10 (all males) Mean age: 21 ± 2 yrs Characteristics: recreationally active individuals	EI: Submaximal unilateral knee extensor exercises (12 min at 21±2W) MP: before and during last 8 min of exercise OM: LV systolic apical and basal rotation, apical and basal rotation rate, twist, twisting rate, diastolic apical and basal rotation rate, untwisting rate MT: 2D echo with STA	- No change in any LV systolic or diastolic twisting mechanic measurement	- Exercise stimulus did not induce increases in stroke volume or ejection fraction	 Sub-maximal exercise does not enhance systolic or diastolic twisting function. Disagreement potentially due to weak exercise stimulus
Stohr et al 2011b United Kingdom Pre-post = Level 4 D&B Score = 10/15	N = 8 (all males) Mean age: 20 ± 2 yrs Characteristics: active individuals	EI: Submaximal unilateral knee extensor exercises (15 min at 23±2W) MP: before and during last 10 min of exercise OM: LV systolic apical and basal rotation, apical and basal rotation rate, twist, twisting rate, diastolic apical and basal rotation rate, untwisting rate, time to peak untwisting rate MT: 2D echo with STA	 No change in any LV systolic or diastolic twisting mechanic measurement Time to peak untwisting rate increased 	- Exercise stimulus did not induce an increase in stroke volume	 Submaximal exercise does not result in changes to systolic and diastolic twisting function Weak exercise stimulus potential reason for this finding

Author, Country, Study Design and Level of Evidence, Quality score	Population	Methods	Outcome	Additional Notes	Interpretations
Stohr et al 2011c United Kingdom Pre-post = Level 4 D&B Score = 9/15	N = 9 (all males) Mean age: 26 ± 4 yrs Characteristics: recreationally active individuals	EI: Submaximal supine bicycle (4 min stages at 10%, 30%, 50%, 70%, and 90% peak power) MP: before and during each stage OM: LV systolic apical and basal rotation, apical and basal rotation rate, twist, twisting rate, time to peak twisting rate, diastolic apical and basal rotation rate, untwisting rate, time to peak untwisting rate MT: 2D echo with STA	 - LV systolic apical and basal rotation, apical and basal rotation rate, twist, twisting rate, diastolic apical and basal rotation rate, and untwisting rate increased - LV twist, twisting rate, and untwisting rate plateaued at ~50% peak power - Time to peak diastolic apical rotation rate and untwisting rate decreased - Time to peak diastolic basal rotation rate increased 	- Stroke volume and end diastolic volume plateaued at ~30% and ~50% peak power, respectively	- The enhancement of systolic and diastolic twisting function during exercise plateaus at sub- maximal intensities
Stohr et al 2012 United Kingdom Pre-post = Level 4 D&B Score = 11/15	N = 28 (all males) 14 endurance-trained (ET), 14 normally active (NA) Mean age: ET= 21 ± 3 yrs & N= 21 ± 2 yrs Characteristics: Groups divided <i>post</i> <i>hoc</i> . ET: VO ₂ peak= 63 ± 7 ml/kg/min, NA: VO ₂ peak= 49 ± 5 ml/kg/min,	EI: Submaximal supine bicycle (5 min at 40% peak power) MP: before and during last 3 min of exercise OM: LV systolic apical and basal rotation, apical and basal rotation rate, twist, twisting rate, diastolic apical and basal rotation rate, untwisting rate MT: 2D echo with STA	 LV systolic apical and basal rotation, apical and basal rotation rate, twist, twisting rate, diastolic apical and basal rotation rate, and untwisting rate increased in both ET and NA LV systolic apical rotation was lower at rest and during exercise in ET vs. NA 	 Slightly lower LV twist at rest and during exercise in ET vs. NA (p=0.09) No between group differences in LV structure, heart rate, or stroke volume 	- ET individuals have reduced twisting function during submaximal exercise compared to NA individuals despite similar haemodynamics

D&B = Down's and Black Quality Index Score, EI = exercise intervention, MP = measurement period, OM = outcome measures, MT - measurement technique, STA = speckle tracking analysis, ET = endurance-trained individuals, NA = normally active individuals

Table 3.4: Effects of	prolonged endurance e	exercise on LV systolic a	and diastolic twisting mechanics.
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Author, Country, Study	Population	Methods	Outcome	Additional Notes	Interpretation
Design and Level of					
Nottin et al 2009 France Pre-post – Level 4	N = 23 (all males) Mean age: 40 ± 9 yrs Characteristics: Trained individuals (Mean	EI: Ultra-long triathlon (3.8km swim, 186km cycle, 42.2km run) MD: 858 min	- LV systolic apical and basal rotation, and diastolic untwisting rate	- LV twist decreased but not significantly (p=0.09)	- Ultra-long triathlon induces impaired systolic and diastolic twisting function
D&B Score = 11/15	training = 12 ± 3 hrs/week for 12 ± 6 yrs)	MP: before and 40 ± 15 min after race completion OM: LV systolic apical and basal rotation, apical and basal rotation rate, twist, time to peak twist, time to peak systolic apical and basal rotation, diastolic apical and basal rotation rate, untwisting rate, time to peak untwisting rate MT: 2D Echo with STA	- Time to peak twist, times to peak systolic apical and basal rotation, and time to peak untwisting rate increased	closure decreased - Loss of rapid LV untwisting during isovolumic relaxation time	
Chan-Dewar et al 2010 United Kingdom Pre-post = Level 4 D&B Score = 11/15	N = 14 (all males) Mean age: 32 ± 10 yrs Characteristics: Non- elite runners (Range of personal best marathon times: 157-268 min, range of training mileage in month prior to race: 10-60 miles)	EI: Marathon (42.2km) MD: 229 ± 38 min MP: before and within 60 min after race completion OM: LV systolic apical and basal rotation, apical and basal rotation rate, twist, diastolic apical and basal rotation rate in sub-endocardium and sub-epicardium MT: 2D Echo with STA	- Systolic apical rotation rate in the sub- endocardium increased	- Irregular trends in remaining indexes of twisting function	- Marathon running induces sporadic changes in twisting function in the sub- endocardium and sub- epicardium

Author, Country, Study Design and Level of Evidence, Quality score	Population	Methods	Outcome	Additional Notes	Interpretation
Oxborough et al 2010 United Kingdom Pre-post = Level 4 D&B Score = 10/15	N = 17 (all males) Mean age: 33 ± 6 yrs Characteristics: Recreational runners	EI: Marathon (42.2km) MD: 209 ± 19 min MP: before, within 60 min, and after 6hrs of race completion OM: LV systolic apical and basal rotation, twist, diastolic apical and basal untwisting rate, untwisting rate MT: 2D Echo with STA	- LV diastolic apical and basal rotation rate, and untwisting rate decreased	 LV twist decreased slightly but not significantly Twist at aortic valve closure decreased Twist remained elevated during early diastole 	- Marathon running impairs diastolic twisting function and induces slight depressions in systolic function
Hanssen et al 2011 Germany Pre-post = Level 4 D&B Score = 11/15	N = 28 (all males) Mean age: 41 \pm 5 yrs Characteristics: Amateur marathon runners (completed \geq 1 marathon, mean training mileage 10 weeks prior to race: 43 \pm 17 km/week)	EI: Marathon (42.2km) MD: 245 ± 55 min MP: before, within 1hr of race completion, and 1 day after race completion OM: LV systolic apical and basal rotation, apical and basal rotation rate, twist, diastolic apical and basal rotation rate MT: cardiac MRI	- LV twist and twisting rate increased	- LV systolic apical rotation remained elevated during early diastole	- Marathon running enhances systolic twisting function but impairs diastolic twisting function

Author, Country, Study	Population	Methods	Outcome	Additional Notes	Interpretation
Design and Level of	L				*
Evidence, Quality score					
Nottin et al	N = 20 (all males)	EI: Continuous cycling	- Time to peak systolic	- Reduction in rapid LV	- Prolonged cycling
2011	Mean age: 25 ± 5 yrs	(cadence: 70-80 rpm,	apical rotation rate and	untwisting during early	impairs diastolic
France	Characteristics: healthy	heart rate: >150 bpm)	time to peak diastolic	diastole	twisting function and
Pre-post = Level 4		MD: 120 min	untwisting rate		slightly reduces systolic
D&B Score = $9/15$		MP: before, within 30-	increased		twisting function
		45 min after protocol			
		completion			
		OM: LV systolic apical			
		and basal rotation,			
		apical and basal rotation			
		rate, twist, twisting rate,			
		diastolic apical and			
		basal rotation rate,			
		untwisting rate			
		MT: 2D Echo with STA			

D&B = Down's and Black Quality Index Score, EI = exercise intervention, MD = mean exercise duration, MP = measurement period, OM = outcome measures, MT = measurement technique, STA = speckle tracking analysis

Author, Country, Study Design and Level of Evidence, Quality score	Population	Methods	Outcome	Additional Notes	Interpretation
Tischler and Niggel 2003 USA Pre-post = Level 4 D&B Score = 11/15	N = 25 (14 males) Mean age: 35.6 yrs Characteristics: 15 healthy volunteers, 10 referred for stress echocardiography	EI: Maximal exercise test – Bruce protocol MD: 14 ± 4min MP: before and immediately after exercise OM: LV twist MT: 2D echo with image angle calculations	- LV twist increased	- LV end-systolic volume decreased, ejection fraction increased	- Maximal exercise augments LV systolic function
Neilan et al 2006 USA Pre-post = Level 4 D&B Score = 11/15	N = 17 (12 males) Mean age: 37 yrs Characteristics: Elite rowers	EI: 2000m rowing sprint to exhaustion on ergometer MD: males: 6.6 ± 0.45 min, females: 7.2 ± 0.15 min MP: before and within 5- 10 minutes after exercise OM: LV systolic apical and basal rotation, LV twist MT: 2D echo with STA	- LV basal rotation and twist increased	 LV apical rotation increased but not significantly (p=0.07) Evidence of reversed diastolic filling (reduced early passive filling, and increased late active filling) 	- Maximal exercise augments LV systolic function but may impair LV diastolic function

Table 3.5: Effects of acute maximal exercise on systolic and diastolic LV twisting mechanics.

Author, Country, Study	Population	Methods	Outcome	Additional Notes	Interpretation
Design and Level of					
Evidence, Quality score					
Scott et al	N = 18 (all males), 9	EI: 15 1-min workloads	-NA: No change in	- ET: evidence of	- Maximal exercise
2010	endurance-trained	at 100% VO ₂ max power	twisting mechanics	impaired diastolic	impairs LV systolic and
Canada	(ET),	output, separated by 2-	- ET: LV systolic apical	function (reduced time	diastolic function in ET
Prospective controlled	9 normally active (NA)	min recoveries at 20%	rotation rate and	period between diastolic	but not NA individuals
trial = Level 2	Mean age: $ET= 29 \pm 6$	VO ₂ max power output	diastolic untwisting rate	untwisting and LV filling	
D&B Score = $10/15$	yrs	on a cycle ergometer	decreased. Time to	– in normal hearts there is	
	& N= 35 ±7 yrs	MD: 45 min approx.	peak twist and time to	distinct separation)	
	Characteristics:	MP: before, 6.2 ± 2.6	peak untwisting rate		
	ET=VO ₂ max>50ml/kg	min after, and 38.4 ± 3.8	increased.		
	/min, regular training	min after exercise			
	NA=VO ₂ max<50ml/k	OM: LV systolic apical			
	g/min, no regular	and basal rotation rates,			
	training	twist, time to peak twist,			
	-	diastolic untwisting rate,			
		time to peak untwisting			
		rate			
		MT: Cardiac MRI			

D&B = Down's and Black Quality Index Score, EI = exercise intervention, MD = mean exercise duration, MP = measurement period, OM = outcome measures, MT = measurement technique, STA = speckle tracking analysis, ET = endurance-trained individuals, NA = normally active individuals

Table 3.6: Effects of chronic endurance	exercise on LV systolic and	diastolic twisting mechanics.
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Author, Country, Study Design and Level of Evidence Quality score	Population	Methods	Outcome	Additional Notes	Interpretation
Weiner et al 2010 USA Pre-post = Level 4 D&B Score = 12/15	N = 15 (all males) Mean age: 18.6 ± 0.5 yrs Characteristics: 1^{st} year university student members of the competitive rowing program	EI: 90 days of endurance exercise training (EET) MD: 13.6 ± 0.9 hrs/week of organized, primarily endurance oriented training (12.6 ± 0.7 vs. 1.0 ± 0.9 hrs/week EET and strength training respectively) MP: before and after 90 days of EET OM: LV systolic apical and basal rotation, twist, time to peak twist, diastolic apical and basal rotation rate, untwisting rate MT: 2D Echo with STA	- LV systolic apical rotation, twist, diastolic apical rotation rate, and untwisting rate increased	- Percentage of LV untwisting that occurred during isovolumic relaxation time increased	- EET results in improved systolic and diastolic twisting function

D&B = Down's and Black Quality Index Score, EI = exercise intervention, MP = measurement period, OM = outcome measures, MT = measurement technique, STA = speckle tracking analysis

Chapter IV: Thesis Investigation: The Influence of Aerobic Fitness and Venous Return on LV Twisting Mechanics During Incremental Exercise

The purpose of this chapter is to provide a brief introduction and rationale for the thesis investigation, as well as a detailed description of the methods and results. This chapter also contains a thorough discussion of the results and limitations of the methodology. A version of this chapter will be submitted for publication. This research was conducted under Human Ethics approval certificate number: H11-01893.

4.1 Introduction

The twisting and untwisting of the left ventricle (LV) and the associated rotational parameters are collectively known as LV twisting mechanics. These indices of systolic and diastolic function provide important insights into cardiac function beyond the traditional measures of ejection fraction and Doppler indicators of diastolic function. LV twist helps to optimize systolic function as it allows for maximal LV pressure generation with minimal myocardial shortening, while LV untwisting has been postulated to help augment ventricular filling via diastolic suction (Sengupta *et al.*, 2008a). Owing to recent improvements in cardiac imaging, the changes in LV twisting mechanics during conditions of physiological stress have become the focus of much research (Helle-Valle *et al.*, 2005). One physiological stressor of particular interest is exercise, as it results in increases in heart rate, myocardial contractility, systolic blood pressure (surrogate indicator of afterload), and preload (via the Frank-Starling mechanism) - four factors known to influence LV twisting mechanics (Dong *et al.*, 1999).

Regular aerobic exercise training is well known to be associated with a reduced risk of cardiovascular disease (Warburton *et al.*, 2006), and results in various cardiac morphological alterations (Morganroth *et al.*, 1975). Chronic aerobic exercise is also known to result in systolic and diastolic functional changes, which allow endurance-trained (ET) athletes to improve their aerobic performance (Warburton *et al.*, 1999a). These changes include the enhanced potential to continuously increase cardiac output (Q) and stroke volume (SV) throughout incremental exercise (Gledhill *et al.*, 1994). The mechanisms underpinning these exercise-induced changes are not clear. Recently, LV twisting mechanics have been proposed as a potential mechanism to explain these findings (Esch & Warburton, 2009). Endurance-training is known to produce increases in blood volume (and therefore preload) (Convertino *et al.*, 1980), as well as myocardial contractility (Warburton *et al.*, 2002); factors previously demonstrated to augment LV twisting mechanics in ET athletes in comparison to normally active (NA) individuals.

To help determine the role of LV twisting mechanics in the ability of ET individuals to continuously augment cardiac function during exercise, we aimed to assess LV twisting mechanics during exercise in both ET and NA populations. To further improve our understanding of LV twisting, we investigated the effects of exercising in different postural positions, so as to examine the effects of acute changes in venous return. We hypothesized that LV twisting mechanics during exercise would be increased as a result of chronic-endurance training, as well as under conditions of higher venous return.

4.2 Methods

4.2.1 Participants

Sixteen males between the ages of 18 and 39 were recruited to participate in this investigation. Participants included eight endurance-trained athletes, and eight normally active individuals whom were assigned to their respective groups based on their reported training history, which was verified through measurement of maximal aerobic power (VO₂max). All participants were required to commit to three separate testing days: one assessment day, and two experimental test days, all separated by a minimum of 48 hours. Participants were also required to be free of symptoms or diagnosis of a chronic condition, which was confirmed using the PAR-Q+ screening questionnaire (Warburton *et al.*, 2011). This study was approved by the University of British Columbia Clinical Research Ethics Board, and all participants provided written informed consent prior to the experiment.

4.2.2 Assessment Day

Upon arriving at the testing facility for the assessment day, participants' height and weight were measured. Each participant underwent a standard (upright body position) incremental exercise test on an electronically braked cycle ergometer (Ergometrics er800s; Ergoline, Blitz, Germany) in order to assess VO₂ max. The workload was increased by 25-30 W every minute until exhaustion while breath-by-breath expired gas and ventilatory parameters were acquired and averaged every 15 s using a calibrated metabolic cart (Ergocard; Medisoft, Dinant, Belgium). To ensure achievement of their VO₂max, following the incremental loading phase, participants rested for 5 min and then then performed a supra-maximal work load with a requirement of an increase of ~5 mL•kg⁻¹•min⁻¹ beyond their volitional peak work rate. Heart rate was monitored continuously with a 3-lead electrocardiogram.

4.2.3 Experimental Test Days

During each experimental test day participants performed incremental cycling on an electronically braked cycle ergometer at work rates that elicited steady-state heart rates of 110, 130, 150, and 170 beats•min⁻¹ in the supine and upright positions. The approximate work rates were determined from the VO_2 max test completed during the assessment day, and adjusted as necessary to maintain steady state during each stage. Participants were allowed to self-select their pedaling cadence, but participants generally chose a rate of 80-100 rpm. Each exercise stage was approximately 4 min in duration and at least 2 min of rest was provided between stages. Each participant underwent a cardiac ultrasound assessment at rest and during each exercise stage upon reaching the targeted steady state heart rate. A measure of brachial blood pressure was recorded by an experienced technician via manual sphygmomanometer at every stage. Expired gas and ventilatory parameters were measured continuously throughout exercise. The order of the supine and upright exercise was randomly assigned amongst participants to minimize the possibility of an order effect confounding the results of the investigation. The supine exercise test was performed on a specialized supine cycle ergometer (Lode, Angio 2003, Groningen, Netherlands) in the left lateral position tilted at a 45° angle for optimal sonographic imaging.

4.2.4 Experimental Test Day Measurement Techniques

4.2.4.1 Haemodynamic Measures

Heart rate, SV, and Q were measured using an impedance cardiography device (Physio Flow PF-05, Manatec Biomedical, Paris), which has previously been validated at rest and during mild to high intensity exercise against both the direct Fick (Charloux *et al.*, 2000; Richard *et al.*, 2001) and CO₂ rebreathing (Tordi *et al.*, 2004) methods of measuring Q. In brief, this relatively

new device differs from standard impedance cardiography because of its auto-calibration procedure, which is based on each participants age, height, weight, body mass, systolic/diastolic blood pressure, and resting impedance (a measure of resting impedance is taken before each trial with the participant lying still and relaxed) (Charloux *et al.*, 2000). In addition, the PhysioFlow does not require the calculation of basal thoracic impedance (Z_0), which can be difficult as Z_0 is affected by perspiration, adipose tissue, and poor electrical contact (Charloux *et al.*, 2000). These adaptations are thought to improve the accuracy of the technology in comparison to previous impedance cardiography systems that had questionable accuracy during exercise conditions (Warburton *et al.*, 1999c, b).

4.2.4.2 Echocardiography

Two-dimensional transthoracic images were acquired using the parasternal short axis view at the level of the base (mitral valve), and apex (distal to the papillary muscles) with a Vivid-I cardiac ultrasound (GE Medical Systems, Wauwatosa, WI, USA) at a constant high frame rate (67 Hz). Pulsed Doppler was recorded at the tips of the mitral leaflets to assess the timing of both the onset of early filling blood flow (mitral valve opening [MVO]), and peak early filling blood flow (peak-E). Aortic blood flow velocity was recorded in the ascending aorta with a 2.0 MHz transducer (GE Medical Systems, Wauwatosa, WI, USA) placed at the suprasternal notch to assess the timing of the onset of aortic blood flow (aortic valve opening [AO]), the peak of aortic blood flow (peak ejection [peak-EJ]), and the end of aortic blood flow (aortic valve closure [AVC]). Isovolumic relaxation time (IVRT) was calculated as MVO – AVC. All echocardiography was performed by a highly trained, board certified (American Registry of Diagnostic Medical Sonography, ARDMS) sonographer with over 10 years of experience in research.

4.2.4.3 Data Analysis

Two-dimensional and Doppler data were analyzed using EchoPAC software (GE Healthcare, USA) by a single, trained investigator. Speckle-tracking analysis was applied to the basal and apical short axis images in order to quantify rotation and rotation velocities. LV twist and the respective velocities were calculated as the instantaneous difference between apical and basal rotations/rotation velocities from which peak twist, peak twisting, and peak untwisting velocities were derived. From all speckle-tracking analysis, the raw data files were saved to an off-line computer where data were averaged over three cardiac cycles. In order to adjust for the slight differences in individual heart rates at rest and during each exercise stage, raw data was normalized to a percentage of systolic duration, with the onset of the QRS being 0% and aortic valve closure equivalent to 100%, while diastole was from 100% onward. Cubic spline interpolation was then used to determine data points at 2% increments of systolic and diastolic duration throughout the cardiac cycle in order to produce the data in Figures 4.6 and 4.7 (Esch et al., 2009). Speckle-tracking analysis for the 170 bpm exercise stage was not possible in four participants during upright exercise (1 ET, 3 NA), and in four participants during supine exercise (2 ET, 2 NA) because of poor image quality.

4.2.4.4 Statistics

A three-way mixed model ANOVA with repeated measures was used to compare differences in haemodynamic measures between training groups, between postures, and across the different exercise stages. LV twist mechanic measures were first assessed using three-way ANOVA in all participants (n = 16) up to 150 bpm, and then again in the participants who had echocardiographic images at 170 bpm in both postural positions (n = 9; 5 ET, 4 NA). Post-hoc comparisons were used to identify differences between means when main effects were observed,

as well as to compare group differences in baseline characteristics. Data are presented as means \pm standard deviation. Significance was set *a priori* at p < 0.05.

4.3 Results

4.3.1 Participants

Endurance-trained and normally active individuals did not differ in age, height, weight, maximum heart rate, and resting mean arterial pressure (Table 4.1). By design, the endurance-trained individuals had significantly higher relative and absolute VO_{2max} values (p < 0.0001). Endurance-trained individuals also had greater maximal power output (p < 0.0001), as well as lower BMI (p = 0.047).

4.3.2 Heart Rate and Oxygen Consumption

Heart rate increased significantly throughout incremental upright and supine exercise in both training groups (Table 4.2, p < 0.05). Heart rate was significantly higher at rest in the upright posture and in the NA group (p < 0.05). Oxygen consumption in both training groups increased significantly throughout incremental upright and supine exercise up to 170 bpm (Figure 4.1). There was a significant interaction effect between training status and exercise intensity (p < 0.0001), as VO₂ increased to a greater extent in the ET group. However, by design percentage of VO₂ max (relative exercise intensity) at each stage increased with exercise intensity, but did not differ between groups (p > 0.05, Table 4.2). There was also a significant interaction between posture and exercise intensity, such that VO₂ increased to a greater extent at 170 bpm during upright exercise (p < 0.0001, Figure 4.1).

Table 4.1: Participant characteristics

_	ET (n =	8)	_	NA	(n =	8)	p-value
Age (yr)	28.3	±	4.3	-	25.1	±	2.5	NS
Height (cm)	182.8	\pm	7.2		179.5	±	3.9	NS
Mass (kg)	74.7	±	7.0		78.8	±	3.3	NS
BMI $(kg \cdot m^{-2})$	22.4	±	2.3		24.5	±	1.4	0.047
VO ₂ max (mL•kg ⁻¹ •min ⁻¹)	68.1	±	5.6		50.1	±	5.0	< 0.0001
$VO_2 max (L \bullet min^{-1})$	5.1	±	0.5		4.0	±	0.3	< 0.0001
HR _{max} (bpm)	186.4	±	6.3		191.9	±	12.9	NS
Power Output (W)	386.9	±	37.5		284.4	±	18.6	< 0.0001
Resting MAP (mmHg)	93.8	±	4.9		89.3	±	7.3	NS

NS, not significant (p > 0.05)

Table 4.2: Responses of heart rate and oxygen consumption to incremental exercise

								Heart	rate	, bpm							_
		Rest		1	110			130			150			170			
HR, bpm																	_
ET																	
	Upright	60	±	7	110	±	1	130	±	2	150	±	1	170	\pm	1	*
	Supine	54	±	8	110	\pm	2	130	±	0.5	150	±	1	170	±	3	
NA																	
	Upright	74	±	5	111	±	1	131	±	1	151	±	1	172	±	1	*
	Supine	60	±	5	110	±	1	131	±	1	151	±	1	169	±	2	
% VO ₂ ma	X																
ET																	
	Upright	6.9	±	1.6	41.9	\pm	4.7	56.3	\pm	5.0	71.9	\pm	4.9	87.7	±	5.4	*,‡
	Supine	7.3	±	1.9	43.4	±	5.5	58.9	±	8.0	70.6	±	7.8	80.7	±	5.8	ß
NA																	
	Upright	8.6	±	1.1	41.6	±	7.8	55.4	±	7.4	68.9	±	6.0	81.4	\pm	8.7	* *
	Supine	9.1	±	1.8	43.7	±	5.1	58.5	±	6.9	69.7	±	7.9	80.3	±	7.1	*,]

*, p < 0.05, significant increase with exercise intensity; \ddagger , p < 0.05, significant interaction between posture and exercise intensity





* p < 0.05, significant interaction effect between training status and exercise intensity; $\ddagger p < 0.05$, significant interaction between posture and exercise intensity. Data points are means, horizontal and vertical error bars are standard deviations.

4.3.3 Haemodynamic Measures

Stroke Volume (SV): There was a significant interaction effect between training status and exercise intensity, as SV increased to a greater extent in the ET group during exercise (p < 0.05; Figure 4.2). In the upright position, SV was the highest at 170 bpm, while in the supine position, SV reached a maximum at 150 bpm (Figure 4.2). There was no significant difference in resting SV between training groups in either posture. Supine exercise resulted in greater SV than upright exercise in both groups (p < 0.05).

Cardiac Output (Q): Q at rest was not different between training groups in either posture. During incremental exercise, Q increased continuously up to 170 bpm in both training groups and postures (p < 0.05; Figure 4.3). Similar to the SV response, there was a significant interaction effect for Q between training status and exercise intensity, as Q increased with incremental exercise, but to a greater extent in the ET group (p < 0.05). A significant interaction was also found between posture and exercise intensity, as Q was both significantly greater at maximum and increased to a greater extent during supine exercise (p < 0.05). The between group differences in Q during exercise became greater at the higher levels of exercise intensity.

End-Diastolic Volume (EDV): Significant interaction effects between training status and exercise intensity (p < 0.05; Figure 4.4), and between posture and exercise intensity (p < 0.05) were found, as both ET and supine exercise yielded greater increases in EDV. No difference in resting EDV was found between training groups in either posture. In ET, EDV in the upright and supine position increased to its highest level at 170 bpm, while in NA, EDV plateaued around 150 bpm.

Ejection Fraction: Ejection fraction at rest was not significantly different between training groups in either posture. Incremental upright and supine exercise resulted in increased ejection

fraction up to 150 bpm (p < 0.05; Figure 4.5). No significant interaction effects were found. The upright posture resulted in a borderline significant increase in ejection fraction as compared to the supine posture (p = 0.055).

Systolic Blood Pressure (SBP): No difference in resting SBP was found between training groups in either posture. During incremental exercise, SBP increased continuously (p < 0.05; Figure 4.6). There was a significant interaction between exercise intensity and training status, as SBP increased to a greater extent in ET individuals during exercise (p < 0.05). There was no influence of posture on SBP at rest or during exercise.





* p<0.05, significant interaction effect between training status and exercise intensity. Data points are means, horizontal and vertical error bars are standard deviations.





* p<0.05, significant interaction effect between training status and exercise intensity; $\ddagger p < 0.05$, significant interaction between posture and exercise intensity. Data points are means, horizontal and vertical error bars are standard deviations.





* p<0.05, significant interaction effect between training status and exercise intensity; $\ddagger p < 0.05$, significant interaction between posture and exercise intensity. Data points are means, vertical and horizontal error bars are standard deviations





No significant interactions. Data points are means, horizontal and vertical error bars are standard deviations.



Figure 4.6: Response of systolic blood pressure during incremental upright (A) and supine (B) exercise in endurance-trained (ET) and normally active (NA) groups. * p<0.05, significant interaction effect between training status and exercise intensity. Data points are means, vertical and horizontal error bars are standard deviations

4.3.4 LV Twist Mechanics

At rest, there were no significant differences in any LV twisting mechanics between the ET and NA groups. With the exception of apical rotation, all LV twisting mechanics increased from rest to exercise (all p < 0.05; Figures 4.7-4.8). In the supine position, all LV systolic and diastolic twisting mechanics plateaued at sub-maximal exercise intensities (110 -150 bpm) (Figures 4.9 - 4.10, Table 4.3). LV diastolic twisting mechanics in the upright position also reached a plateau at sub-maximal exercise intensities (around 110 bpm) (Figure 4.10, Table 4.3). In the upright position, LV twist initially reached a plateau around 110 bpm in both training groups. However, the sub-group (participants who were able to complete the 170 bpm stage in both postural positions (n = 9: 5 ET, 4 NA)), displayed a further increase in LV twist, though to a much larger extent in the ET group. This pattern resulted in a significant three-way interaction between exercise intensity, posture, and training status (Figure 4.9; p < 0.05). The secondary increase in LV twist was potentially driven by changes in basal rotation. Basal rotation in both training groups achieved highest levels at 170 bpm after an initial plateau at sub-maximal exercise intensities. This pattern resulted in a significant interaction between exercise intensity and posture (Figure 4.9; p < 0.05). There was also a significant interaction between exercise intensity and posture for LV systolic twisting velocity as both training groups achieved the greatest LV twisting velocity during upright exercise at 170 bpm (Figure 4.10; p < 0.05). The same interaction was also observed for LV systolic apical rotation velocity, in which both training groups achieved the greatest systolic apical rotation velocity during upright exercise at 170 bpm (Table 4.3; p < 0.05). Both training groups were also able to achieve the highest LV systolic basal rotation velocity during upright exercise at 170 bpm; however, there was no significant interaction between exercise intensity and posture (p > 0.05). LV systolic basal

rotation and basal rotation velocity, however, were significantly higher in the upright position across all intensities (Figure 4.9, Table 4.3; p < 0.05). Times to peak LV twisting mechanics all decreased with exercise (all p < 0.05; Table 4.4).





LV twist/twisting velocity is represented by the solid line green line, apical rotation/rotation velocity by the dashed blue line, and basal rotation/rotation velocity by the dotted red line. All LV twisting mechanics except apical rotation increased with the onset of upright exercise. Vertical lines represent cardiac cycle events. AO, aortic opening; Peak-EJ, peak aortic blood flow; AVC, aortic valve closure (end-systole); MVO, mitral valve opening; Peak-E, peak early diastolic filling blood flow. Note, 170 bpm stage from sub-set of participants with adequate echocardiographic images (5 ET, 4 NA). Error bars have been excluded for the purpose of clarity, but can be found in Figures 4.9-4.10 and Table 4.3.




LV twist/twisting velocity is represented by the solid line green line, apical rotation/rotation velocity by the dashed blue line, and basal rotation/rotation velocity by the dotted red line. All LV twisting mechanics except apical rotation increased with the onset of supine exercise. Vertical lines represent cardiac cycle events. AO, aortic opening; Peak-EJ, peak aortic blood flow; AVC, aortic valve closure (end-systole); MVO, mitral valve opening; Peak-E, peak early diastolic filling blood flow. Note, 170 bpm stage from sub-set of participants with adequate echocardiographic images (5 ET, 4 NA). Error bars have been excluded for the purpose of clarity, but can be found in Figures 4.9-4.10 and Table 4.3.



Figure 4.9: Response of peak LV apical and basal rotation and LV twist during upright (A) and supine (B) incremental exercise in endurance-trained (ET) and normally active (NA) individuals.

Note, 170 bpm stage in each series is from sub-set of participants with adequate echocardiographic images in both postural positions (5 ET, 4 NA). * p < 0.05, significant interaction effect between exercise intensity and posture; † p < 0.05, significant interaction between exercise intensity, posture, and training status. Data points are means, vertical and horizontal error bars are standard deviations.



Figure 4.10: Response of peak LV twisting and untwisting velocity during upright (A) and supine (B) incremental exercise in endurance-trained (ET) and normally active (NA) individuals.

Note, 170 bpm stage in each series is from sub-set of participants with adequate echocardiographic images (5 ET, 4 NA). * p < 0.05, significant interaction effect between exercise intensity and posture. Data points are means, vertical and horizontal error bars are standard deviations.

							Heart	rate,	bpm							-	
-	Rest]	110			130			150				170		
-								(sysi	tole)							-	
Apical rot vel, o	apical rot vel, deg/s																
ET																	
Upright	63.7	±	29.5	93.9	±	24.9	97.7	±	37.0	83.8	±	47.2	126.2	±	17.9	*	
Supine	69.5	±	18.0	93.8	±	39.1	113.7	±	43.7	106.1	±	37.9	88.5	±	20.9		
NA																	
Upright	87.0	±	28.0	96.0	±	27.3	81.1	±	22.7	101.3	±	36.1	131.4	±	12.4	*	
Supine	87.9	±	35.5	98.2	±	16.4	100.9	±	27.0	119.8	±	69.3	124.2	±	47.2		
Basal rot vel, de	eg/s																
ET																	
Upright	-47.4	±	13.1	-77.1	±	28.4	-101.2	±	35.1	-117.7	±	40.2	-142.9	±	37.1		
Supine	-56.7	±	19.3	-59.4	±	9.0	-76.3	±	18.0	-95.6	±	26.4	-99.5	±	46.7		
NA																	
Upright	-46.6	±	11.6	-70.7	±	28.6	-77.8	±	14.4	-114.0	±	15.6	-140.0	±	81.7		
Supine	-44.9	±	23.1	-77.4	±	30.9	-63.8	±	22.0	-86.7	±	18.8	-89.7	±	13.3		
							Peak (dias	tole)								
Apical rot vel, o	deg/s																
ET																	
Upright	-59.5	±	18.0	-94.8	±	34.1	-122.1	±	23.5	-135.3	±	66.6	-128.7	±	36.9		
Supine	-55.5	±	45.2	-101.3	±	38.8	-97.8	±	52.5	-115.6	±	34.1	-118.7	±	40.2		
NA																	
Upright	-66.1	±	32.4	-136.9	±	57.5	-124.5	±	20.9	-125.2	±	90.2	-124.4	±	26.6		
Supine	-83.7	±	26.9	-111.4	±	32.0	-124.1	±	74.9	-81.8	±	32.4	-138.2	±	44.6		
Basal rot vel, de	eg/s																
ET																	
Upright	35.7	±	19.6	41.5	±	24.6	66.9	±	60.1	70.1	±	16.6	37.6	±	53.7		
Supine	47.9	±	23.2	42.9	±	31.6	46.4	±	18.3	56.3	±	31.1	60.9	±	46.2		
NA																	
Upright	30.9	±	21.9	55.7	±	41.7	36.2	±	27.7	15.7	±	40.5	71.2	±	40.4		
Supine	32.3	±	21.2	44.0	±	30.3	39.0	<u>+</u>	19.1	50.2	±	38.0	37.4	±	28.2		

 Table 4.3: Responses of peak LV systolic and diastolic apical and basal rotation velocity during upright and supine incremental exercise in endurance-trained (ET) and normally active (NA) individuals

Rot, rotation; vel, velocity; deg/s, degrees per second. *, p < 0.05, significant interaction effect between exercise intensity and posture. Note, 170 bpm stage in each series is from sub-set of participants with adequate echocardiographic images (5 ET, 4 NA). Data are meants \pm standard deviations

		Heart rate, bpm																	
		Rest			110			130				150				170			
TTP Twist (ms)						_				-				_					
ET																			
Uprig	nt 0.32	±	0.04	0.24	±	0.03		0.20	±	0.03		0.19	\pm	0.01		0.17	±	0.02	
Supin	e 0.34	±	0.02	0.26	±	0.03		0.20	±	0.04		0.18	±	0.03		0.18	±	0.01	
NA																			
Uprig	nt 0.30	±	0.03	0.23	±	0.03		0.19	\pm	0.05		0.19	\pm	0.05		0.19	\pm	0.02	
Supin	e 0.32	±	0.02	0.24	±	0.04		0.20	±	0.04		0.18	±	0.04		0.17	±	0.02	
TTP Twisting Velocity (ms)																			
ET	, 0100105	(,																
Uprig	nt 0.15	±	0.06	0.15	±	0.08		0.13	±	0.04		0.13	<u>+</u>	0.04		0.09	±	0.03	
Supin	e 0.17	±	0.04	0.13	±	0.07		0.07	±	0.02		0.10	±	0.04		0.06	±	0.03	
NA	0117		0.0.	0110		0107		0107		0.02		0110		0101		0.00		0.00	
Uprig	nt 0.14	±	0.07	0.15	±	0.06		0.10	±	0.03		0.10	±	0.04		0.05	±	0.02	
Supin	e 0.12	±	0.07	0.12	±	0.06		0.09	±	0.05		0.08	±	0.04		0.10	±	0.04	
TTP Untwisting Velocity (ms)																			
ET																			
Uprig	nt 0.39	±	0.03	0.31	±	0.03		0.27	±	0.01		0.25	±	0.03		0.21	±	0.03	
Supin	e 0.42	±	0.03	0.33	±	0.02		0.27	±	0.02		0.26	±	0.01		0.22	±	0.01	
NA																			
Uprig	nt 0.39	±	0.06	0.31	±	0.03		0.26	±	0.02		0.23	±	0.03		0.23	±	0.03	
Supin	e 0.39	\pm	0.02	0.30	±	0.03		0.27	±	0.02		0.24	±	0.04		0.23	±	0.02	

Table 4.4: Changes in times to peak LV twisting mechanics during upright and supine incremental exercise in endurance-trained (ET) and normally active (NA) individuals

TTP, time to peak. Note, 170 bpm stage in each series is from sub-set of participants with adequate echocardiographic images (5 ET, 4 NA). Data are meants \pm standard deviations

4.4 Discussion

This was the first study to investigate the role of LV twisting mechanics in the SV response to incremental exercise in ET and NA individuals under conditions of differing venous return. The haemodynamic responses to incremental upright and supine exercise have been previously investigated in ET athletes (Warburton et al., 2002) and NA individuals (Poliner et al., 1980), and the changes in LV twisting mechanics during supine incremental exercise in NA individuals have been characterized (Stöhr et al., 2011c); however, to the best of our knowledge, no study has examined the influence of aerobic fitness and venous return on the changes in haemodynamics and LV twisting mechanics during incremental exercise. The participants involved in this investigation represented different ends of the aerobic fitness spectrum, and our investigation therefore provides unique insight into the role of LV twisting mechanics during exercise across the continuum of aerobic fitness in young healthy males. There were three novel findings: 1) High aerobic fitness has minimal influence on the response of LV twisting mechanics to incremental upright and supine exercise, despite resulting in significantly altered haemodynamic responses, 2) LV twisting mechanics plateau during incremental supine exercise at sub-maximal intensities in both NA and ET, and 3) Incremental upright exercise results in an uncoupling of LV systolic and diastolic twisting mechanics, as LV systolic twisting mechanics increase with exercise intensity, while LV diastolic twisting mechanics plateau at sub-maximal intensities.

4.4.1 LV Twisting Mechanics and Aerobic Fitness

The haemodynamic responses to incremental upright and supine exercise in ET and NA present in this study are consistent with previous research (Gledhill *et al.*, 1994; Krip *et al.*, 1997; Warburton *et al.*, 1999a). Our data demonstrates that endurance-training results in

significantly larger increases in CO, SV, EDV, and SBP during incremental exercise compared to NA. Yet the augmented haemodynamic responses that accompany endurance-training were not reflected in the rotational properties of the LV, as ET and NA individuals had similar changes in LV twisting mechanics during incremental exercise in both postural positions.

In the supine position, the changes in SV and LV systolic and diastolic twisting mechanics in NA during incremental exercise demonstrated a plateau at moderate intensity exercise (110 – 150 bpm), a finding consistent with previous research in healthy humans (Stöhr et al., 2011c). The present investigation also advances our understanding by extending this relationship between SV and LV twisting mechanics during exercise to ET athletes, and suggests that the structural and functional adaptations in the heart that occur as a result of chronic endurance training do not necessarily influence LV twisting mechanics. Contrary to the present study, Stohr and colleagues (2012) reported that ET had reduced LV twisting mechanics in comparison to NA, in the form of lower apical rotation (but not LV twist) at rest and during supine exercise at 40% peak-exercise capacity. While the exact mechanisms for this disagreement remains to be elucidated, our results indicate that basal rotation during both upright and supine incremental exercise appears to be greater at 110 bpm in NA than ET (Figure 4.9). This potentially reflects a similar reduction in LV twisting mechanics in ET at sub-maximal exercise intensities. Conversely, although Stohr and colleagues (2012) reported reduced apical rotation in ET, they found no significant differences between their training groups at rest or during moderate exercise in any other LV twist parameter, a finding more similar to the results of the present study. It is also important to note that SBP increased to a greater extent in ET than NA during both supine and upright incremental exercise. While the influence of changes in preload on LV twisting mechanics have shown inconsistent results (Weiner et al., 2010b; Nelson *et al.*, 2011), increases in afterload have consistently resulted in reduced LV twisting mechanics (Gibbons Kroeker *et al.*, 1995; MacGowan *et al.*, 1996; Dong *et al.*, 1999). Given that SBP is a commonly used surrogate for afterload, it is therefore possible that the similar changes in LV twisting mechanics in ET and NA during exercise is a result of diverging blood pressure responses, and that at matched blood pressures ET would exhibit lower LV twisting mechanics than NA. In support of this theory, Stohr and colleagues (2012) found no significant difference in SBP between their high and low aerobic fitness groups.

4.4.2 LV Twisting Mechanics and Posture

In accordance with previous research, the haemodynamic results of the present investigation demonstrate that, in comparison to the upright position, CO, SV and EDV were consistently greater in the supine position throughout incremental exercise (Poliner et al., 1980; Warburton et al., 2002). The present data also demonstrate that during supine exercise, SV reached a plateau at moderate intensity exercise, consistent with previous investigations (Poliner et al., 1980; Warburton et al., 2002). The observed plateau in LV systolic and diastolic twisting mechanics at sub-maximal intensities during supine exercise is, as discussed above, in accordance with prior investigations in healthy males (Stöhr et al., 2011c). In response to upright exercise, however, our data demonstrate that LV systolic twisting mechanics increase with exercise intensity, while LV diastolic twisting mechanics plateau at moderate intensity exercise – a novel finding. The diverging responses in LV twisting mechanics to upright and supine exercise are independent of training status, and likely reflect the changes in cardiac loading conditions induced by the change in posture. Movement from the upright position to the supine position causes the movement of blood into the ventricles and serves to mimic an acute change in blood volume, evident in our results as greater resting SV and EDV in the supine position.

During supine incremental exercise, our data demonstrate that SV and EDV fail to increase beyond 130 - 150 bpm, indicating that the myocardial limits for ventricular filling may have been reached (Warburton et al., 2002). Similarly, the plateau in LV twisting mechanics may also indicate a mechanical limitation during supine exercise. In addition, pericardial constraint may also play a role in limiting LV twisting mechanics during supine exercise as a result of the increased myocardial volumes (Esch et al., 2007). Patients with constrictive pericarditis have been shown to have lower LV twisting mechanics (Warburton et al., 2007; Sengupta et al., 2008b; Phillips et al., 2012). In contrast, during upright incremental exercise, the reduced SV and EDV suggest that no myocardial volume limitation was reached, and potentially explains why LV systolic twisting mechanics continually increased with exercise intensity. Furthermore, the reduced pericardial constraint during upright exercise may also have allowed LV systolic twisting mechanics to increase at high exercise intensities. However, the mechanism responsible for the uncoupling of LV systolic and diastolic twisting mechanics remains unknown. A similar uncoupling was found during a dehydration and mild exercise protocol in healthy males, and the authors proposed that concurrent changes in afterload and preload as a result of simultaneous changes in blood pressure and volume were the cause (Stöhr et al., 2011b). In the present study, however, preload was higher during supine exercise, yet there was no effect of posture on the SBP response to exercise. It is possible that a limit in the amount of elastic potential energy that can be stored in myocardial proteins during systolic contractions was reached (Granzier & Labeit, 2004). Diastolic untwisting is thought to result from the rapid release of this stored potential energy (Fukuda et al., 2001). If the increasingly vigorous systolic contractions present at high intensity exercise did not result in more potential energy storage, then it follows that a limit in LV diastolic twisting mechanics would be reached. Therefore, this suggests that although

diastolic untwisting has been previously demonstrated to play a large role in diastolic function during low intensity exercise through its contributions to diastolic suction (Notomi *et al.*, 2006a), the role of diastolic untwisting in diastolic suction during high intensity exercise is greatly diminished.

4.4.3 Study Limitations and Methodological Considerations

All investigations utilizing 2D echocardiography to examine LV twisting mechanics suffer from the same inherent methodological limitations of image quality and through-plane myocardial tissue motion. In particular, these limitations become increasingly important under exercise conditions when higher respiratory rates and body movement are common (Drury *et al.*, 2012). To minimize this risk, our investigation employed a board-certified (ARDMS) sonographer with over 10 years of research experience who was blinded to the purposes of the study. While echocardiography suffers from lower spatial resolution and precision in comparison to MRI, the higher temporal resolution that accompanies echocardiography likely produced the most accurate results possible. However, it must still be noted that image collection at near-maximal exercise intensities was exceptionally difficult, and of the images collected at the 170 bpm stage, not all were suitable for image analysis. In addition, we used cubic spline interpolation to further ensure that LV twisting mechanics were accurately compared across exercising heart rates.

4.5 Conclusion

Our results indicate that, contrary to our hypothesis, high aerobic fitness has no influence on the response of LV twisting mechanics to incremental exercise in either the upright or supine position. Incremental supine exercise was shown to result in a plateau at sub-maximal intensities of both haemodynamic and twisting mechanic measures, in which myocardial mechanical

limitations and pericardial constraint may play a role. Incremental upright exercise was demonstrated to result in an uncoupling of LV systolic and diastolic twisting mechanics, indicating that LV twisting mechanics are sensitive to changes in posture. These observations help further our understanding of LV twisting mechanics under conditions of physiological stress, and improve our knowledge concerning the implications of chronic endurance training.

Chapter V: General Discussion, Future Directions, and Conclusions

The purpose of this chapter is to present the overall conclusions from the thesis investigation. This chapter also discusses some remaining limitations and findings, as well as outlines future directions for this field of research.

5.1 General Discussion and Future Directions

The recent technological improvements in cardiac imaging have allowed LV twisting mechanics to be measured in a variety of physiological and pathological conditions. As outlined in Chapters II and III, during low to moderate exercise, LV twisting mechanics appear to play an important role in augmenting cardiac output (Q), due to their ability to optimize systolic and diastolic efficiency while minimizing myocardial oxygen demand. Indeed, under mild exercising conditions and other physiological conditions such as heat stress, LV twisting mechanics seem to be an influential aspect of cardiac function. However, the results from this thesis investigation, coupled with recent research (Stöhr et al., 2011c), would indicate that their importance during conditions of moderate to high exercise intensity is limited. Once the human body's oxygen demand reaches a certain threshold and the cardiovascular system is forced to significantly increase Q, it appears that other cardiovascular factors play a larger role in maintaining or augmenting cardiac function than LV twisting mechanics. Diastolic suction driven by the rapid untwisting of the LV during diastole has previously been proposed to significantly improve diastolic function at rest and during mild exercise (Notomi et al., 2006a). However, our data and those of other recently published investigations (Stöhr et al., 2011c), demonstrate that LV diastolic twisting mechanics plateau at moderate intensity exercise, therefore limiting the contribution of diastolic untwisting to the generation of diastolic suction during exercise. This is an interesting finding especially given that diastolic function has been proposed as the

mechanism behind the ability of endurance athletes to continually increase stroke volume (SV) up to maximal intensity during upright exercise (Gledhill *et al.*, 1994). Taken together, it would appear that the twisting and untwisting of the LV during high intensity exercise is not a primary determinant of cardiac function. It may be that despite the ability of LV twisting mechanics to optimize LV systolic and diastolic efficiency at rest, this cardiac efficiency may be of lesser importance for increasing Q at high intensity exercise.

However, it must be stressed that the measurement of LV twisting mechanics at moderate to high exercise intensities is exceptionally difficult. It may be the case that despite ours, and others attempts at minimizing methodological errors that the measurement of LV twisting mechanics at higher exercise intensities is flawed and due to technical limitations, should not be continued. The significant variability in the existing literature surrounding exercise of all intensities is evidence to support such a claim (see Chapter III). In fact, much of the discrepancies present in the existing literature on LV twisting mechanics during exercise could be attributed to methodology and not necessarily physiology. It is therefore our recommendation that while LV twisting mechanics undoubtedly play an important role in cardiac function at rest and low intensity exercise, their measurement during moderate to high intensity exercise is cautioned unless strong controls are applied. Given the aforementioned significant influence of the point of apical image collection on the calculation of LV twist (van Dalen et al., 2008) (see Chapters II and III), stringent guidelines need to be applied at all times in the collection of the required short axis apical and basal echocardiographic images. Recently, Weiner and colleagues (2010a) introduced the idea of defining apical images as "the imaging plane with no visible papillary muscles and an end-diastolic ratio of LV cavity diameter to total LV diameter of 0.5." While this guideline has reportedly been used at rest (Weiner et al., 2010a; Weiner et al., 2010b) and during low intensity exercise (Stöhr *et al.*, 2012), the ability to apply such stringent image collection protocols during moderate to high intensity exercise remains questionable (Phillips & Warburton, 2012).

A similar methodological issue surrounds the debate concerning the response to incremental exercise, and the relationship between SV and LV twisting mechanics during exercise therefore hinges quite significantly on experimental protocols. It has been previously noted that differences in participant sample populations, measurement techniques, testing procedures, and postural positions can influence the SV response to exercise (Warburton et al., 2002) – all confounding factors that influence the changes in LV twisting mechanics during exercise as well (see Chapter III). In addition, it has recently been demonstrated that even inter-individual variances in cardiovascular factors such as effective arterial elastance, an index of arterial load on the heart, can differentially influence the SV response to exercise in participants of similar aerobic fitness (Chantler et al., 2012). Specifically they demonstrated three SV responses to exercise as previously shown by Janicki et al., (1990) in heart disease patients and by Warburton et al., (2007; 2008) in health individuals. This particular investigation involved a sample size of 352 healthy subjects and its findings are therefore quite compelling. Perhaps a similarly large, comprehensive investigation is required in order to determine if the observed plateau in LV twisting mechanics during moderate to high intensity exercise is the result of methodology or underlying physiology.

Future research in this field should focus on the changes in LV twisting mechanics in response to smaller physiological stressors, where LV twisting mechanics are more likely to have a larger role in cardiac function. It must also be noted that LV twisting mechanics are important cardiac function indicators in various cardiovascular pathologies, and that their measurement has

led to a better understanding of certain diseases (Sengupta *et al.*, 2008c). This area of research also deserves greater attention. Ideally, the measure of LV twisting mechanics would become part of the standard clinical echocardiographic workup, although based on the time consuming nature of their analysis, this does not appear possible unless substantial technological improvements are made.

5.2 Conclusions

In order to summarize the outcomes of this thesis investigation, each of the four original hypotheses of this study will be considered in turn. The first hypothesis stated that endurancetraining would result in greater LV twisting mechanics during exercise conditions. This hypothesis was rejected, as our data demonstrated no difference in LV twisting mechanics during incremental exercise between training groups in either posture. The second hypothesis stated that increasing exercise intensity would result in greater LV twisting mechanics in NA and ET. This hypothesis cannot be fully accepted or rejected and is dependent on postural position. Our data demonstrated that during supine incremental exercise, LV systolic and diastolic twisting mechanics increased from rest to exercise, but then reached a plateau at moderate intensity exercise. During upright incremental exercise, LV systolic twisting mechanics continued to increase with exercise intensity, while LV diastolic twisting mechanics again reached a plateau at moderate intensity exercise. The third hypothesis stated that conditions of higher venous return (supine vs. upright) would result in greater LV twisting mechanics. This hypothesis must be rejected. Our data did not demonstrate that supine exercise resulted in greater LV twisting mechanics than upright exercise. We found significant interaction effects between posture and exercise intensity, indicating that the change in postural position influenced LV twisting mechanics during exercise, but no evidence to indicate that the increased venous return in the

supine position resulted in greater LV twisting mechanics. The fourth and final hypothesis stated that the SV response to exercise would depend on fitness level and would be related to changes in LV twisting mechanics. The initial clause of this hypothesis must be accepted, as we found a significant interaction effect between training status and exercise intensity for the SV response to exercise. ET athletes were able to increase their SV to a greater extent than their NA counterparts. The second clause of this hypothesis can be partially accepted as well, as both SV and LV twisting mechanics plateaued at sub-maximal intensities during supine incremental exercise. This relationship did not hold true for upright exercise, and serves as the reason this clause of the hypothesis cannot be fully accepted.

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