THE EFFECTS OF ENDURANCE TRAINING AND AGE ON LEFT VENTRICULAR ROTATION

by

BEN ESCH

M.Sc., The University of British Columbia, 2005
B.Sc., The University of Alberta, 2003

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

THE FACULTY OF GRADUATE STUDIES

(Human Kinetics)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

August 2009

Abstract

Recent advances in cardiac ultrasound allow for the effective assessment of left ventricular (LV) rotation. LV rotation makes systole more efficient, and significantly aids diastolic filling. To date little information exists on LV rotation in endurance-trained individuals across the lifespan. Therefore, the purpose of this series of investigations was to describe the effects of endurance training and age on LV rotation. In the first investigation, resting LV rotation was assessed with echocardiography and speckle-tracking analysis in 52 athletes ranging in age from 24-76. Athletes were divided into young (≤ 44 years) and older (> 45 years). Neither peak torsion (Old: 16.8±6.4°; Young: 15.0±4.4°) or peak recoil rate (Old: -127.8±48.2°/s; Young: -106.4±39.6°/s) were significantly different between young and old athletes, suggesting preservation of cardiac function with lifelong exercise training. In an attempt to discern the impact of aging on exercising LV rotation, speckle-tracking analysis was used to compare heart transplant recipients (HTR, age: 61 ± 9 years) with recipient (RM, age: 60 ± 12 years) and donor (DM, age: 35 ± 8 years) age-matched individuals. In response to exercise, DM significantly increased peak torsion and peak recoil rate, whereas RM could not. Despite having a heart 25 years younger, LV rotation in HTR was similar to RM, suggesting accelerated aging of the cardiac allograft. Considering pre-transplant etiology, surgery and medications, it is encouraging that HTR responded similarly to healthy RM. In the third experiment, the relationship between preload reduction with lower body negative pressure (LBNP) and LV recoil was compared in normally active and endurance-trained individuals. The major finding of this investigation was that in response to LBNP, normally active individuals were able to increase LV recoil rate; whereas LV recoil rate

slowed in endurance athletes during preload reduction. This training mediated LV rotational difference may be an additional mechanism which can help explain the higher incidence of orthostatic intolerance in athletes. Together, these findings add significantly to the small number of investigations examining LV rotation in endurance-athletes and contribute to the foundation for future experiments in this emerging area of research.

Table of Contents

List of Tables

List of Figures

List of Symbols, Nomenclature and Abbreviations

Symbol	Definition
β	Cardiac Beta Receptor
°	Degrees
A	Atrial Peak Mitral Filling Velocity
AC	Aortic Valve Closure
AO	Aortic Valve Opening
BSA	Body Surface Area
CRT	Cardiac Resynchronization Therapy
D	Diastole
DM	Donor Matched
E	Early Peak Mitral Filling Velocity
E’	Early Filling Annular Velocity
E/A	Ratio of Early to Atrial Mitral Filling Velocity
E/E’	Ratio of Early Mitral Filling to Early Myocardial Velocity
EDV	End Diastolic Volume
EF	Ejection Fraction
EJ	Time of Peak Ejection
ESV	End Systolic Volume
ET	Endurance-trained Athletes
HTR	Heart Transplant Recipient
IVPG	Intraventricular Pressure Gradient
LBNP	Lower Body Negative Pressure

LV	Left Ventricle
MC	Mitral Valve Closure
MRI	Magnetic Resonance Imaging
MVO	Mitral Valve Opening
N2B	Titin Isoform (N2B)
NA	Normally Active Individuals
pkE	Time of Peak Early Filling Velocity
QRS	QRS-wave from Electrocardiograph
rads	Radians
RM	Recipient Matched
S	Systole
SV	Stroke Volume
TPR	Total Peripheral Resistance
VO_2	Volume of Oxygen Consumption

Acknowledgements

I would like to start by acknowledging the help and guidance of my supervisor Dr. Darren Warburton. Darren welcomed me into both his home and his laboratory. His enthusiasm for research is infectious and his work ethic provides a great example for all his students. My time spent in his lab in Vancouver will remain with me for the rest of my life, and I thank him for that.

I would like to thank Dr. Mark Haykowsky for being an integral part of my thesis process. I appreciate Mark welcoming me into his laboratory and working tirelessly beside me on these projects. I will be forever grateful for his assistance.

The support provided by Dr. Don McKenzie was instrumental to my survival as a student and person throughout the thesis process. I sincerely appreciate his willingness to discuss science and life with me. Knowing his door was always open was a great comfort.

Dr. Richard Thompson provided hours upon hours of assistance with data collection, interpretation and presentation. I feel privileged to have been able to work with Rich during my PhD. I am grateful for all his help.

Many late nights were spent with Dr. Ian Paterson conducting data analysis, and I thank him for all his time, knowledge and willingness to teach. I feel extremely fortunate to have worked with Ian during my PhD projects.

I would like to thank Dr. Darlene Reid and Dr. Jack Taunton for acting as University Examiners for my thesis defense, as well as Dr. Patrick Neary for being the External Examiner. Your time and insights were greatly appreciated.

I would like to acknowledge and thank all the members of the CPR lab, as well as the graduate students in Human Kinetics for their support and encouragement over the years. You guys helped make research and life fun! Thank you!

I would like to thank great friends Dominik Zbogar, Andrew Coghlan, Michael Kennedy and Corey Tomczak (in no particular order) for being there for a brother in need. Without your laughter and strength I would not be where I am today.

And to the newly minted Dr. Jessica Scott I owe a million thanks! The entire process was made remarkably better in everyway by the fact that we shared the experiences we did. I can not imagine making it through all I did without you. I feel ridiculously fortunate that we met when we did and that we were able to be lab mates and partners through the highs and lows that are graduate school. A part of me will always belong to you. Thank you for everything.

I could write a book as long as this thesis and still not adequately express all that my family means to me. Jesse, Dylan and Evan, you give me more support, strength and perhaps most importantly laughter than any brother could ask for. You guys are the best and can do anything you wish! My parents, Hugh and Sherril, have done nothing but give me all the love and support that a son would ever need, and then they gave me more. I will never be able to repay you. I love you all with all my heart. You are the best!

Co-Authorship Statement

A version of Chapter Two from this dissertation has been published as: BT Esch and DER Warburton (2009). Left Ventricular Torsion and Recoil: Implications for Exercise Performance and Cardiovascular Disease. *Journal of Applied Physiology* 106: 362-369. I was responsible for literature research and manuscript preparation for this review of the literature. A version of Chapter Three will be submitted for publication as: BT Esch, JM Scott, R Shave, K George, D Oxborough, RB Thompson, MJ Haykowsky and DER Warburton. Left Ventricular Torsion and Recoil in Young and Old Endurance-Trained Athletes. I was responsible for completing the work described in this paper, including study design, data collection and analysis as well as manuscript preparation. A version of Chapter Four from this thesis has been previously published as: BT Esch, JM Scott, DER Warburton, R Thompson, D Taylor, J Cheng-Baron, I Paterson, MJ Haykowsky (2009). Left Ventricular Torsion and Untwisting during Exercise in Heart transplant Recipients. *The Journal of Physiology* 587 (10): 2375-2386. I was responsible for completing the work described in this paper, including study design, data collection, data analysis and preparation of the manuscript. A version of Chapter Five will be submitted for publication as: BT Esch, JM Scott, I Paterson, MJ Haykowsky, DER Warburton, K Chow, J Cheng-Baron, RB Thompson. A New Twist on Orthostatic Stress in Endurance Athletes. I was responsible for completing the work described in this paper, including data collection, data analysis and preparation of the manuscript. All co-authors reviewed and edited the published material.

CHAPTER ONE: Introduction

Due to myocardial fiber orientation, the human heart functions in three planes of motion: longitudinal, radial and circumferential (12, 13). All three motions are evident during systole and diastole, and are inextricably linked in their response to alterations in preload, afterload and heart rate (3, 14). This collection of experiments will support the notion that the proceeding systolic contraction plays a crucial role in subsequent diastolic events, particularly for circumferential function (9). As will be outlined, the early nature of left ventricular (LV) diastolic circumferential untwisting makes it unique compared to longitudinal or radial relaxation (2, 11). Rapid early untwisting begins during isovolumetric relaxation, suggesting a crucial role for LV circumferential rotation in the generation of early diastolic pressure gradients and ultimately LV filling (8, 9).

Until recently, cardiac imaging techniques have predominantly provided indices of longitudinal and radial function. Relatively new technological advances in cardiac ultrasound allow for the non-invasive assessment of LV rotation in humans at rest and during exercise (5, 7). Therefore, the following experiments were conducted in an attempt to better understand cardiac adaptations to endurance-training and aging with a particular focus on LV circumferential rotation.

1.1 Statement of the Problem

Years of exercise training results in numerous cardiac adaptations, with the most evident being larger end-diastolic volumes and stroke volumes at rest and during exercise (4, 6, 15, 16). A greater amount of LV filling at a similar heart rate is indicative of enhanced diastolic function, and is a prevalent finding amongst endurance-trained individuals (4, 16).

Diastolic filling may be reduced in healthy older individuals, but can be preserved with life-long aerobic exercise training (1, 10). Since LV circumferential untwisting has an influence on early diastolic filling, identifying alterations to untwisting are important in order to understand the cardiac adaptations which occur in response to endurance-training and aging. Accordingly, the primary objectives of this collection of experiments were to: 1) describe the influence of lifelong endurance-training on LV rotation; 2) identify resting and exercise LV rotational responses of a relatively young heart placed in an older body following heart transplantation; 3) investigate the role of LV untwisting in endurance-trained athletes as a mechanism contributing to orthostatic intolerance.

Chapter two presents the current literature pertaining to the study of LV circumferential rotation. Chapter three discusses the first experiment which involved an examination of the impact of ultra-marathon training on LV rotation in athletes ranging from age 24-76. Chapter four presents an investigation on LV rotation in heart transplant recipients. In this unique model of aging, resting and exercise LV rotational responses of heart transplant recipients were compared with those of individuals matched to the age of the transplant recipient, as well as those matched to the age of the donor heart. Chapter five discusses findings from the final investigation which compared LV rotational responses in endurance-trained individuals with normally active individuals during orthostatic stress in an attempt to better understand orthostatic intolerance in endurance athletes. Finally, chapter six provides an overview of the knowledge that was gained from this collection of experiments, as well as a discussion regarding the impact of this information for future investigations.

1.2 Chapter One References

1. **Arbab-Zadeh A, Dijk E, Prasad A, Fu Q, Torres P, Zhang R, Thomas JD, Palmer D, and Levine BD.** Effect of aging and physical activity on left ventricular compliance. *Circulation* 110: 1799-1805, 2004.
2. **Burns ATM, I.G. Thomas, J.D. MacIsaac, A. and Prior, D.** Doin' the twist: new tools for an old concept of myocardial function. *Heart* 94: 978-983, 2008.
3. **Dong SJ, Hees PS, Huang WM, Buffer SA, Jr., Weiss JL, and Shapiro EP.** Independent effects of preload, afterload, and contractility on left ventricular torsion. *Am J Physiol* 277: H1053-1060, 1999.
4. **Gledhill N, Cox D, and Jamnik R.** Endurance athletes' stroke volume does not plateau: major advantage is diastolic function. *Med Sci Sports Exerc* 26: 1116-1121, 1994.
5. **Helle-Valle T, Crosby J, Edvardsen T, Lyseggen E, Amundsen BH, Smith HJ, Rosen BD, Lima JA, Torp H, Ihlen H, and Smiseth OA.** New noninvasive method for assessment of left ventricular rotation: speckle tracking echocardiography. *Circulation* 112: 3149-3156, 2005.
6. **Levine BD, Lane LD, Buckey JC, Friedman DB, and Blomqvist CG.** Left ventricular pressure-volume and Frank-Starling relations in endurance athletes. Implications for orthostatic tolerance and exercise performance. *Circulation* 84: 1016-1023, 1991.
7. **Notomi Y, Lysyansky P, Setser RM, Shiota T, Popovic ZB, Martin-Miklovic MG, Weaver JA, Oryszak SJ, Greenberg NL, White RD, and Thomas JD.** Measurement of ventricular torsion by two-dimensional ultrasound speckle tracking imaging. *J Am Coll Cardiol* 45: 2034-2041, 2005.
8. **Notomi Y, Martin-Miklovic MG, Oryszak SJ, Shiota T, Deserranno D, Popovic ZB, Garcia MJ, Greenberg NL, and Thomas JD.** Enhanced ventricular untwisting during exercise: a mechanistic manifestation of elastic recoil described by Doppler tissue imaging. *Circulation* 113: 2524-2533, 2006.
9. **Notomi Y, Popovic ZB, Yamada H, Wallick DW, Martin MG, Oryszak SJ, Shiota T, Greenberg NL, and Thomas JD.** Ventricular untwisting: a temporal link between left ventricular relaxation and suction. *Am J Physiol Heart Circ Physiol* 294: H505-513, 2008.
10. **Prasad A, Popovic ZB, Arbab-Zadeh A, Fu Q, Palmer D, Dijk E, Greenberg NL, Garcia MJ, Thomas JD, and Levine BD.** The effects of aging and physical activity on Doppler measures of diastolic function. *Am J Cardiol* 99: 1629-1636, 2007.
11. **Sengupta PP, Khandheria BK, and Narula J.** Twist and untwist mechanics of the left ventricle. *Heart Fail Clin* 4: 315-324, 2008.
12. **Streeter DD, Jr., Spotnitz HM, Patel DP, Ross J, Jr., and Sonnenblick EH.** Fiber orientation in the canine left ventricle during diastole and systole. *Circ Res* 24: 339-347, 1969.
13. **Torrent-Guasp F, Ballester M, Buckberg GD, Carreras F, Flotats A, Carrio I, Ferreira A, Samuels LE, and Narula J.** Spatial orientation of the ventricular muscle band: physiologic contribution and surgical implications. *J Thorac Cardiovasc Surg* 122: 389-392, 2001.

14. **Tyberg JV, Keon WJ, Sonnenblick EH, and Urschel CW.** Mechanics of ventricular diastole. *Cardiovasc Res* 4: 423-428, 1970.
15. **Warburton DE, Gledhill N, Jamnik VK, Krip B, and Card N.** Induced hypervolemia, cardiac function, VO2max, and performance of elite cyclists. *Med Sci Sports Exerc* 31: 800-808, 1999.
16. **Warburton DE, Haykowsky MJ, Quinney HA, Blackmore D, Teo KK, and Humen DP.** Myocardial response to incremental exercise in endurance-trained athletes: influence of heart rate, contractility and the Frank-Starling effect. *Exp Physiol* 87: 613-622, 2002.

[1]CHAPTER TWO: Review of Literature

Recent technological advances in echocardiography provide the ability to quantify left ventricular (LV) function across its three planes of motion: longitudinal, radial and circumferential (61). Tissue Doppler along with speckle-tracking imaging and analysis allow for the assessment of myocardial shortening (strain), rates of shortening (strain rates) as well as tissue velocities, and tissue displacements (linear and angular) throughout the cardiac cycle. One of the most intriguing outcomes from these technological advancements is the ability to quantify LV rotation.

As will be discussed in this brief review, the importance of measuring LV rotation lies in its potential for early detection of pathology (25), the ability of torsion techniques to provide regional information, as well as the importance of LV rotation as an indicator of active diastolic relaxation (6). Torsion and diastolic recoil may be of particular importance when the cardiac cycle is abbreviated during exercise. Therefore, this review will consider the potential implications and uses for the study of LV circumferential rotation in health and disease.

[1] A version of this chapter has been published as: BT Esch and DER Warburton (2009). Left Ventricular Torsion and Recoil: Implications for Exercise Performance and Cardiovascular Disease. *Journal of Applied Physiology* 106: 362-369 used with permission.

2.1 Left Ventricular Torsion and Recoil

2.1.1 Mechanics of Torsion

Atrial-ventricular plane displacement has recently been shown to account for approximately 60% of stroke volume (8). The remaining contribution to stroke volume is from radial compression and LV circumferential twisting. Left ventricular twisting was first described by Harvey in 1628 (26). Looking from the ventricular apex, during systole the apex rotates counter-clockwise whereas the LV base rotates clockwise resulting in torsion (figure 2.1) (20, 40). Untwisting occurs in the opposite direction during early diastole resulting in diastolic recoil.

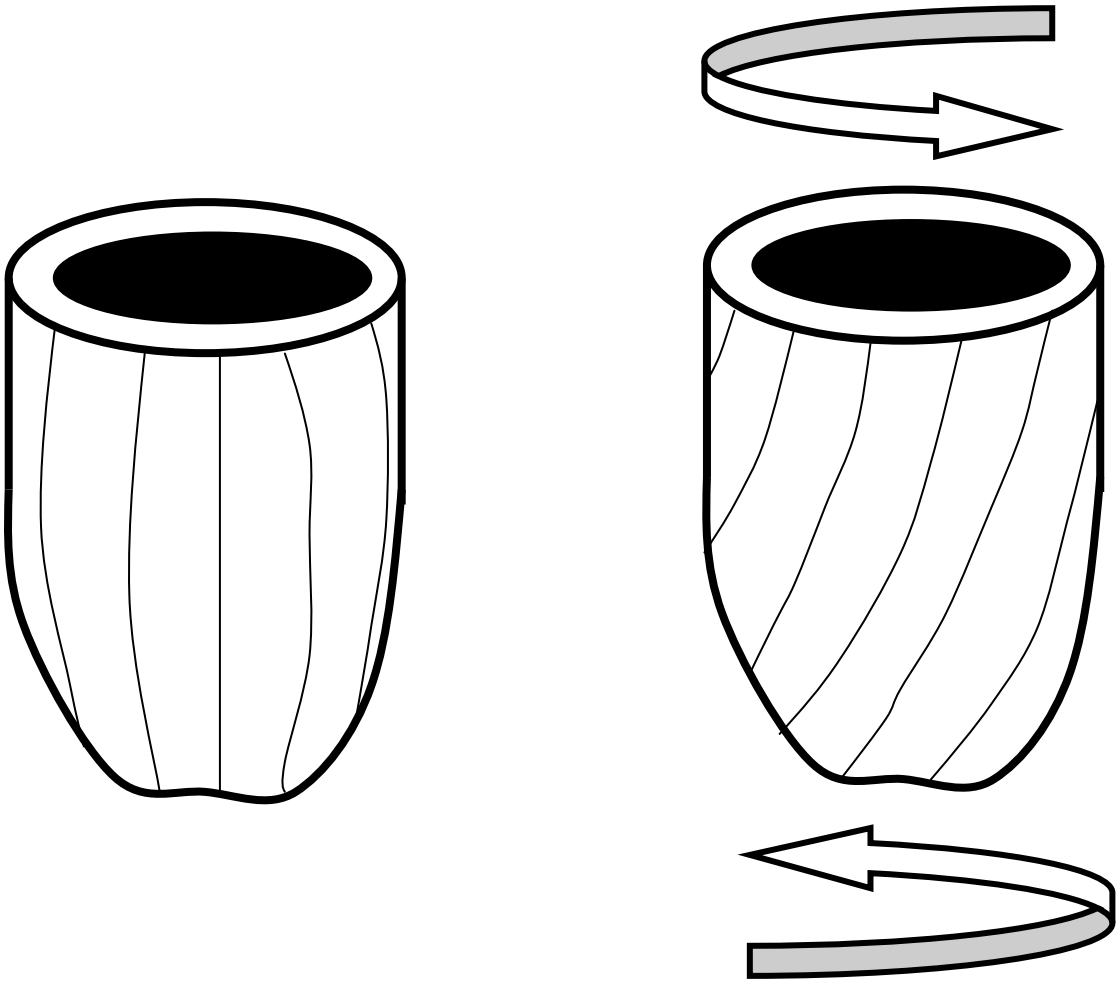


Figure 2.1. **Left ventricular torsion**.
The LV on the left is shown in diastole; the LV on the right depicts (viewed from the apex) the counterclockwise rotation of the apex, and clockwise rotation at the base during systole. Note: the vertical lines on the LV do not represent fiber orientation, but are to illustrate the direction of torsion.

For the purposes of this review, twisting and untwisting are the rotational deformations (measured in degrees) for either the apex or base of the heart, and torsion and recoil are the net difference between the apex and base. Rotation is used as a blanket term to include both systolic and diastolic indices of LV circumferential motion. Left ventricular torsion and recoil are a result of the dynamic interaction between obliquely oriented epicardial and endocardial fibers wound oppositely (56). Streeter et al. elegantly showed the transition in myocardial fiber orientation in stages from the endocardium to the (relatively) perpendicular mid-wall, and then to the opposite angles toward the epicardium (56). The left-handed helix of the epicardium dominates rotational motion due to its longer lever arm from the center of the LV. The endocardial layer, with a right-handed helix, moves together with the epicardium, though providing some opposition to epicardial motion (75). As a result of torsion, epicardial and endocardial sarcomere shortening in all directions tends to be equilibrated during ejection, resulting in reduced stress between myocardial fibers (2). Systolic twist acts to limit myocardial energy expenditure by creating high interventricular systolic pressures with minimal muscle shortening resulting in efficient LV contraction (3). The resultant recoil of the LV has important implications for diastolic filling. It should be duly noted that each systolic contraction has a significant impact on the following diastole (45). In fact, the elastic recoil which occurs during early diastole is thought to be a result of the vigorous contraction and compression of cardiac proteins such as titin (21, 31). The potential energy stored in the spring-like titin is unleashed during diastole; aiding myocardial relaxation and diastolic filling (21, 31). A portion of the energy released during recoil

may also be generated from the release of sheer strains built up between the endocardial and epicardial layers (33, 48).

The effective filling pressure of the LV is the difference between left atrial pressure and LV pressure; also known as the transmitral pressure gradient. During systole, LV pressures are high, and the mitral valve is closed. After systolic contraction, LV pressures begin to fall, the aortic valve closes and isovolumetric relaxation commences resulting in a further drop in LV pressure. Once left atrial pressure is greater than LV pressure the mitral valve opens and early diastolic filling occurs. The rate of blood flow into the LV during early diastole is directly proportional to the transmitral pressure gradient (12, 34). Early diastolic filling occurs until left atrial and LV pressures are approximately at equilibrium, then finally, atrial contraction occurs. During systole, the apex twists in a counterclockwise direction to aid with the ejection of blood. However, the rapid recoil (untwisting) of the myocardium, approximately 40% of which occurs during isovolumetric relaxation, has significant effects on both LV and transmitral pressures (44). Rapid untwisting during isovolumetric relaxation is crucial in the development of low LV pressures (44). Delayed or prolonged untwisting results in ineffective recoil, with little benefit to the transmitral pressure gradient (20, 44, 47). Rapid myocardial untwisting in early diastole has been shown to contribute to the occurrence of diastolic suction, whereby minimum LV pressure may become relatively negative (or increasing chamber dimension despite declining pressures) (64). A lower LV pressure (assuming a constant left atrial pressure) results in a greater transmitral filling gradient, and a higher rate of flow (12, 34). Therefore, any perturbation that could affect the rate of untwisting either acutely (e.g. reduced end-systolic volume) or chronically (e.g. endurance-training)

could significantly impact transmitral filling, end-diastolic volume (EDV), and ultimately stroke volume.

2.1.2 Diastolic Filling Rates, Transmitral Pressures and LV Rotation during Exercise

An elevated heart rate during exercise results in reduced diastolic filling time (23). Consequently, diastolic function (and diastolic filling rate) must be augmented during exercise in order to attain the same LV EDV in a shorter amount of time. Endurance-trained athletes have larger increases in LV EDV and stroke volume compared to untrained individuals and therefore, they must have a more dramatic increase in diastolic filling and function during exercise (23, 70). Doppler echocardiography has been used to show an increase in the early diastolic peak filling velocity with exercise, and a greater increase in endurance athletes compared to normal individuals (13, 59). These findings are all indicative of enhanced filling rates in endurance athletes during exercise. Numerous mechanisms could contribute to greater LV filling and EDV in endurance athletes including greater blood volumes (14, 68), increased LV compliance (38), reduced diastolic ventricular interactions (17), as well as potentially greater increases in the transmitral pressure gradient and LV rotation with exercise.

Increased early diastolic filling velocities during exercise suggest an increase in the transmitral pressure gradient. Numerous researchers have shown the transmitral pressure gradient (or the intraventricular pressure gradient measured from apex to base) to be increased during exercise (9, 44, 52). In the animal model, Cheng et al (1992) demonstrated an increase in the transmitral pressure gradient as a result of a reduced minimal LV pressure without a significant change in left atrial pressure (9). Due to the reductions in minimal LV pressure, there was a downward shift in the diastolic portion of

the pressure-volume relationship during exercise compared to rest. The net result was an increased LV EDV and stroke volume despite a shorter diastolic filling time (9). Similar increases in the transmitral pressure gradient as a result of reductions in minimal LV pressure have been shown in humans during dobutamine infusion (65).

Recently, Notomi et al. (2006) have demonstrated that ventricular torsion and recoil increase during submaximal exercise in healthy individuals (44). Interestingly, these authors demonstrated a sequential time course between peak diastolic untwisting rates, the peak intraventricular pressure gradient (an indicator of diastolic suction) (42), and peak early diastolic filling velocity (figures 2.2 and 2.3). The sequential nature of their findings suggests the important contribution of each phase on the following step; that is, untwisting aids in generating the pressure gradient, and the pressure gradient is essential for peak diastolic filling velocity.

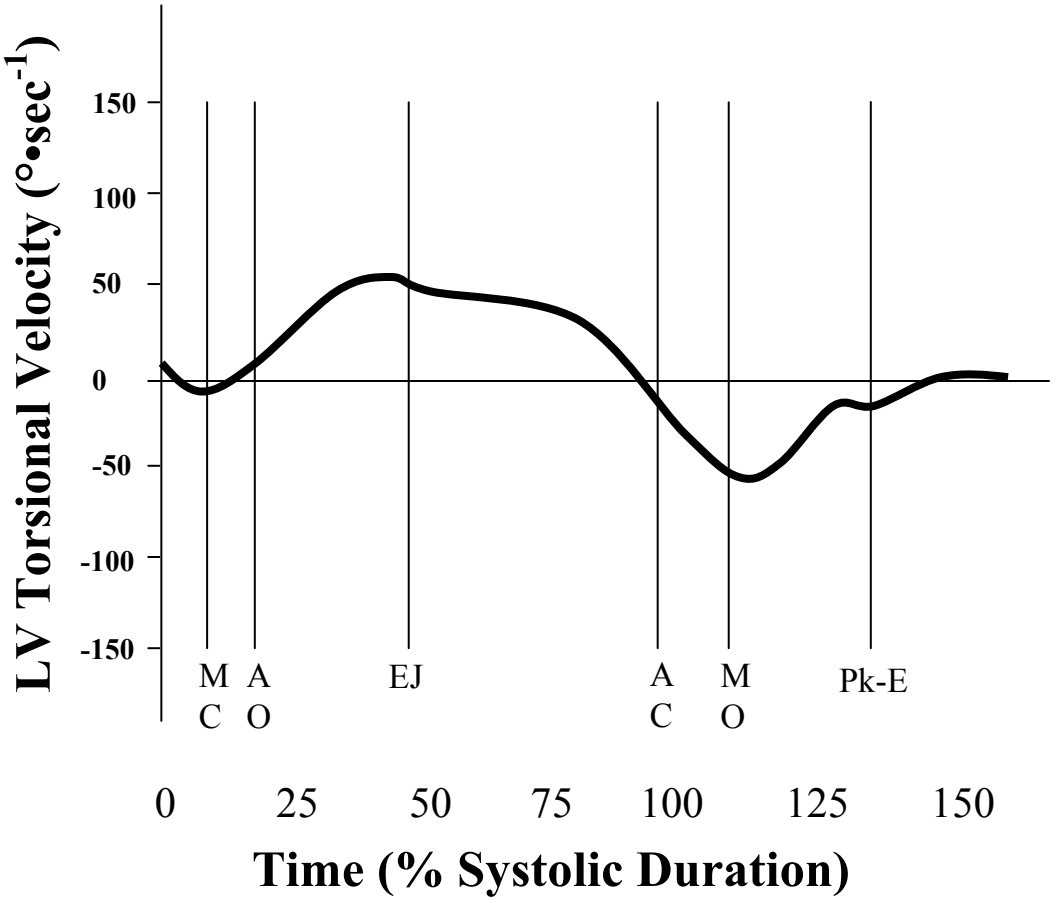


Figure 2.2. Mean left ventricular rotational velocity at rest in healthy individuals. The data is presented over time as a percentage of systolic duration, where 0% is end-diastole (onset of QRS interval) and 100% is aortic valve closure. The vertical lines signify valve timing (MC = mitral valve closure, AO = aortic valve opening, AC = aortic valve closure, MO = mitral valve opening) as well as aortic (EJ = peak aortic ejection velocity) and mitral (Pk-E = peak early mitral filling velocity) peak flow velocities. At rest and during exercise, the peak IVPG was found to occur between MO and Pk-E. Generally, positive values are indicative of systolic twisting and negative values are indicative of untwisting in diastole. This figure was adapted from Notomi et al. (2006) (44).

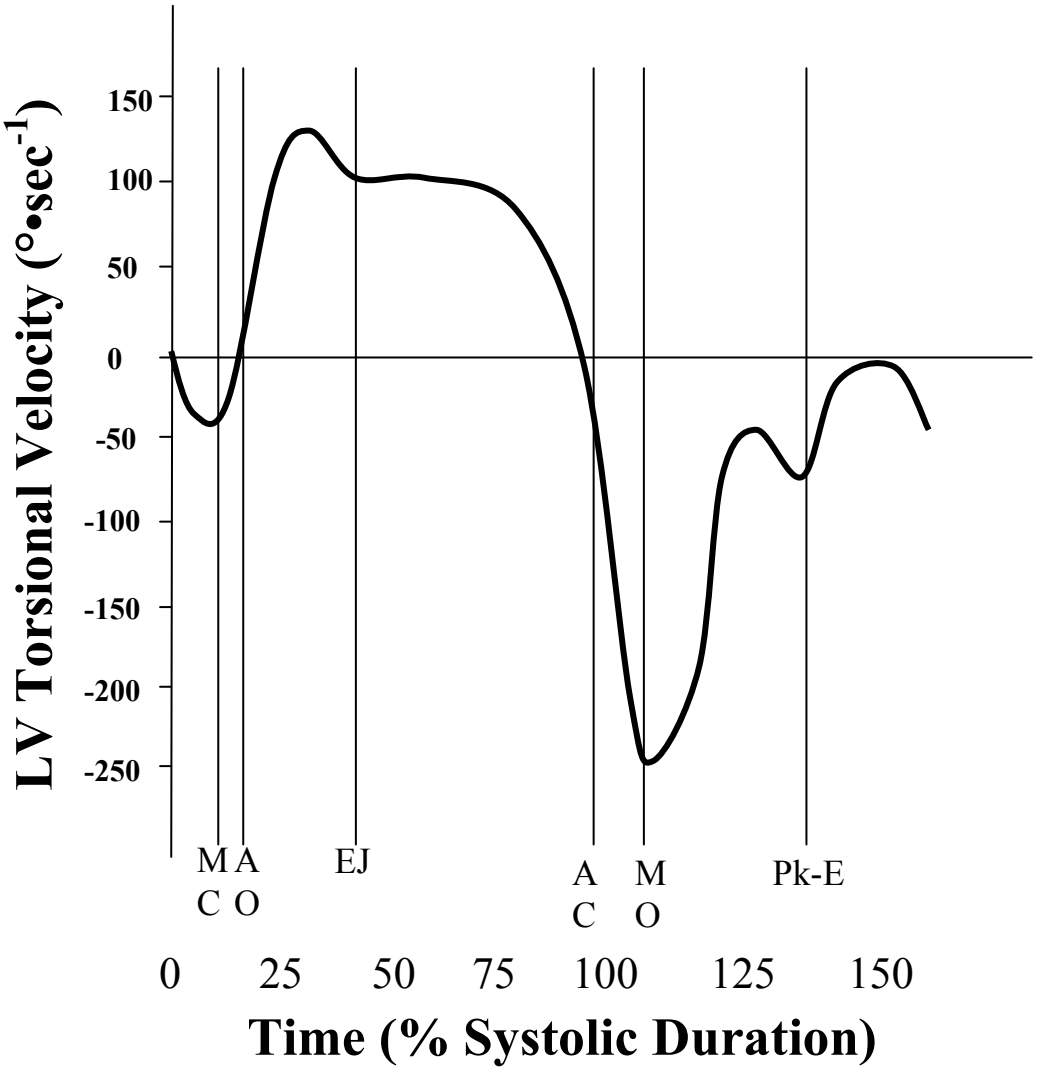


Figure 2.3. Mean LV rotational velocity during sub-maximal exercise in healthy individuals.
The symbols are the same as in figure 2.2

Notomi and colleagues (2006) also reported that during exercise the greatest relative increase in proportional contribution to stroke volume is from LV circumferential motion (44). It should be noted that the participants in the study by Notomi et al. (2006) were exercising at a relatively low intensity (heart rate of approximately 112 beats per minutes) for a short period of time. Others have also shown increases in torsion and recoil with low intensity acute exercise, or after exercise (41, 63). Stuber et al. (1999) found no differences in resting LV torsion and recoil between healthy normal individuals and competitive rowers, however, no exercise data was obtained (57). In contrast Nottin et al. (2008) found apical rotation and LV torsion to be reduced in elite cyclists (48). They suggest that there findings may be related to differences in heart rates between athletes and non-athletes, or to structural adaptations of the myocardium. Interestingly, Nottin et al. found differences between endocardial and epicardial torsion in their control group, but no such transmural differences in the athletes (48). They also suggested that a lower torsion at rest in the athletes may allow for a greater torsion reserve during exercise; however, exercise torsion was not measured in their investigation. Interestingly, Rovner et al. (2005) demonstrated that the presence of higher intraventricular pressure gradients (i.e., greater LV suction) was directly related to VO_2max (52). There has yet to be a systematic assessment of LV torsion and recoil during incremental or steady state prolonged exercise, and there have been no systematic comparisons between endurance-trained athletes, sedentary individuals, and cardiac patients. A partial explanation for the lack of rotational data during exercise is due to the technical difficulty of obtaining high quality ultrasound images during high ventilations and heart rates. However, the work of Cheng and colleagues (1992) as well as Notomi et al (2006), suggest that LV torsion and

recoil may play a significant role in the augmentation of diastolic function seen during exercise (9, 44).

2.2 Measurement of Ventricular Torsion

Quantification of LV torsion and recoil in humans has been conducted primarily with three methods: implanted myocardial markers, magnetic resonance image (MRI) tissue tagging, and echocardiography (tissue Doppler and speckle-tracking). Implanted radiopaque metallic markers or sonomicrometers in the myocardium can be established during clinically indicated cardiac surgery, but the invasive nature of this procedure makes them rare if not unnecessary in humans (considering the newer non-invasive technologies).

Magnetic resonance imaging is the current gold-standard for measuring LV rotation (46). To track the degrees of rotation throughout the cardiac cycle, the myocardium is "tagged" using a unique pulse sequence to manipulate the longitudinal magnetization of the myocardium (49, 76). Analyzing the movement of tissue tags provides quantification of the dynamic behavior of the myocardium. The technique of tagged MRI has been used in numerous investigations to assess torsion and recoil in a wide range of populations (20, 40, 46, 49). The assessment of LV torsion and recoil with MRI requires the acquisition of cross-sectional (short axis) images at both the LV apex and base (level of the mitral valve). The major advantages of MRI derived torsion measurements are the spatial resolution and precision of the tissue tagging. High quality MRI images with tissue tagging can also allow for separate assessments of the endocardium and epicardium (39). Conversely, the temporal resolution is relatively slow compared to echocardiographic methods. As with echocardiography, MRI techniques are still limited by a two

dimensional image. The spatial constraints of the magnet as well as the accessibility and affordability of MRI make it less practical than echocardiography for many researchers.

Recently, developments have been made to allow for the assessment of torsion and recoil using two-dimensional and Doppler echocardiography (for a review see (60)). Numerous recent publications have demonstrated the abilities of slightly different methods of analysis to arrive at a similar outcome (1, 43, 46). Myocardial tissue velocities can be tracked at the base and apex in the short-axis plane allowing for the determination of rotational velocities (46). The tissue Doppler technique of assessing torsion has been shown to correlate well with MRI ($r=0.84$ (46)); however, as with all Doppler recordings there is concern about angle dependency. Two-dimensional ultrasound speckle tracking has been proposed as a less angle and velocity dependent measure of LV torsion (29, 43). Structures smaller than the wavelength of the ultrasound beam cause constructive and destructive interference which results in speckle patterns within the tissue (43). Speckle motion is highly related to myocardial motion, particularly when small displacements are involved (as in circumferential rotation) (29, 43). The speckles are tracked throughout the cardiac cycle in order to quantify the rotational displacement of the myocardium (43). After manually tracing the endocardial boarder, computer software is used (for example EchoPAC, GE Healthcare) to automatically select "speckles" and then track them frame by frame using the sum of absolute difference algorithm (37). As with MRI, short axis, two-dimensional images are required at the apex and base (mitral valve level) (60). Circumferential motion (in degrees) and rates of rotation (degrees/second) are provided by the software for both a mean measure, and for six equidistant regions around the circumference. Recently, Hui et al. have shown

the ability of 2-D derived speckle-tracking to quantify transmural (endocardium and epicardium) torsions (33). Speckle tracking has been shown to correlate very well with MRI in humans (r=0.93) (43) and sonomicrometry in canines during both rest and dobutamine infusion (29). The advantages of tissue speckle tracking for the assessment of LV rotation include the relatively high temporal resolution, the possibility of acquiring images during exercise (with careful controls) and the general accessibility of echocardiography. With respect to temporal resolution, the frame rates chosen are important with a range of 50-90Hz generally suggested for resting humans (6). With low frame rates the myocardial motion is too large frame to frame, and with frame rates that are too high, the opposite occurs. In both cases, the automated software can not accurately track the myocardium (6). The disadvantages of speckle-tracking derived LV rotation include the reliance on adequate image quality, and the attempt to track a three-dimensional motion with a two-dimensional image. As opposed to MRI where slices of the LV can be chosen very precisely, a limitation exists with echocardiography derived torsion, particularly when measuring the apex. Data acquisition at the apex is generally guided by acquiring a sample "below the papillary muscles" which can cause measurements to be taken at varying proximities to the true apex.

Most studies reporting torsion and twist provide details regarding inter and intra-observer variability (which is normally between 5 and 10%), but little has been reported to date regarding the reproducibility of speckle-tracking or Doppler derived torsion at rest or exercise. Kim et al. (2007) reported that speckle-tracking was feasible in only 35% of volunteers tested, however, others have reported higher success rates (36). Speckle tracking derived torsion and twist depend on numerous factors which require technical

care making the acquisition of high quality images at the appropriate LV levels susceptible to error (or low feasibility).

2.3 Factors That Affect LV Rotation

Numerous factors have been implicated in altering LV rotation. Changes in preload, afterload, contractility, heart rate, and sympathetic activation have been shown to alter rotation. Dong et al (1999) manipulated preload, afterload, and contractile state (via dobutamine infusion) independently in an isolated canine heart preparation (15). The directly proportional relationship between torsion and LVEDV and the inversely proportional relationship between torsion and end-systolic volume in the study by Dong et al. (1999) exhibit the volume dependency of LV torsion (15). In fact, many others have shown a low end-systolic volume to be the strongest predictor of increases in untwisting rate and diastolic suction (45, 64, 67). In the same investigation, Dong et al. (1999) fixed LVEDV and end-systolic volume during dobutamine infusion. Dobutamine resulted in an elevated peak systolic pressure and an increase in LV torsion and recoil, demonstrating the force dependent nature of LV rotation (15). Although Cheng et al. (1992) did not measure torsion directly; they demonstrated that generation of a lower minimal LV pressure was affected by both heart rate and sympathetic stimulation (9). Conversely, Wang et al. found no relationship between heart rate and peak untwisting rates in heart failure patients (67).

2.3.1 Factors Affecting LV Torsion during Acute Exercise and Exercise Training

Given that the previously discussed factors have been shown to affect LV rotation and minimum LV pressure generation, let us consider the exercising human model. Heart

rate, venous return, contractility, and sympathetic stimulation all increase with the onset of exercise. Conversely, due to an elevation in cardiac output, systolic blood pressure (a commonly used surrogate for ventricular afterload) increases throughout exercise. As previously discussed, an elevation in afterload is detrimental to LV torsion. However, the adverse effects of an elevated afterload are likely offset by an increase in all of the other factors that affect torsion. Therefore, it is not surprising that numerous investigators have shown torsion to increase with exercise (41, 44, 63).

Examining the factors that affect LV rotation, and knowing that these factors generally increase during acute exercise, the question then becomes 'does chronic endurance training result in changes to these factors, ultimately increasing LV rotation during exercise?' It has been established that endurance exercise training results in an increased blood volume (11, 14, 71). Increased blood volume is one of the major adaptations to endurance training and it has a direct impact on LV EDV and stroke volume (69). Taken independently, due to higher LV EDV, endurance athletes would be expected to have greater LV rotation compared to untrained individuals during exercise (15). Using systolic blood pressure as a surrogate for afterload, Gledhill et al. (1994) demonstrated that at matched heart rates, endurance athletes have a significantly reduced systolic blood pressure (23). Based on differences in afterload alone, endurance-trained athletes would exhibit higher degrees of LV torsion and recoil during exercise. Thus, training induced changes in total blood volume and/or afterload may account for higher LV torsion and recoil during exercise.

Small increases in contractility have been shown to occur with exercise training (53, 70) which would influence the force dependency of torsion in endurance-trained athletes.

Altered LV torsion and recoil as a result of chronic exercise training may also be due to changes in heart rate. Intrinsic heart rate has been shown to be reduced in endurance athletes (35), and lower resting heart rates have been shown to be related to reduced resting torsion in athletes (48). As well, peak heart rates have been shown to be reduced in trained individuals (73). Despite potentially having lower resting and peak heart rates, the greater heart rate reserve found in athletes may prove to be beneficial for increasing torsion with exercise.

Concentric hypertrophy caused by pressure overload has been shown to have detrimental consequences for LV torsion (57). Resting LV torsion and recoil were found to be reduced in elite cyclist who exhibited an increase in end-diastolic diameter, wall thickness, and LV mass (48). It is possible that structural adaptations to the endocardium or epicardium may have resulted in these rotational changes in athletes. However, the effects of training induced LV eccentric hypertrophy on LV torsion and recoil during exercise have yet to be determined.

Interestingly, Dorfman and colleagues (2008) have shown that cardiac deconditioning induced by 18 days of head-down tilt resulted in reduced LV untwisting (16). However, individuals undergoing head-down tilt were able to increase LV untwisting rates by exercising in the supine position (16), emphasizing the important influence of exercise training on LV recoil.

2.3.2 Factors Affecting LV Torsion during Prolonged Exercise

To date, no studies have examined the effects of sustained (one or more hours) exercise on LV rotation. However, numerous investigations have shown alterations in parameters that affect LV rotation or could be a consequence of reductions in LV

rotation. It has been clearly established that reductions in ejection fraction and contractility can occur following prolonged exercise (generally longer than 4 hours) (55, 72) and both reductions in contractility and higher end-systolic volumes have been related to reductions in LV torsion and recoil (15, 64). As discussed above, sympathetic stimulation can directly influence LV rotation, and the cardiac response to sympathetic activation has been shown to be blunted after prolonged strenuous exercise (55, 72). In addition, indices of diastolic function such as Doppler tissue velocity and early diastolic filling velocity are often reduced following prolonged exercise which may also indicate reductions in the early transmitral filling gradient (22, 55, 72). Whether these factors contribute to reduced LV rotation or are a consequence of it, it seems highly plausible that LV torsion and recoil are altered following prolonged exercise. This remains an area which requires further research to confirm these hypotheses.

2.4 The Effects of Age and Gender on LV Torsion

2.4.1 Torsion across the Lifespan

Important functional changes occur in the myocardium from infancy to late adulthood. Some of these alterations are directly related to LV rotation. Notomi and colleagues (2006) assessed LV torsion and twisting velocities in individuals from nine months to 49 years and found that with advancing age there was an increase in LV torsion and untwisting velocity (47). However, when torsion was normalized for LV length, there was a decline in torsion and untwisting velocity during childhood (3-10 year olds) with an increase to above infant levels in middle aged adults (35-49 years old) (47). Interestingly, Notomi et al. (2006) found that in infancy, both basal and apical rotation were counterclockwise during systole, but throughout childhood and adolescents basal

systolic rotation gradually became more clockwise resulting in ventricular torsion (47). As well, the timing of LV untwisting in infancy was less effective than in adults since the majority of untwisting in infants occurs in conjunction with or after mitral valve opening. A delay which prevents a larger contribution of LV untwisting to reduced transmitral gradients (47). Several other investigations examining older individuals have shown LV torsion to be maintained or increased compared to younger adults (5, 28, 50). However, others have shown intraventricular pressure gradients to be reduced in the elderly (51). Indeed, Burns et al. (2007) found LV torsion to be elevated in older males at rest, yet the augmentation (or reserve) of torsion during exercise was shown to be significantly less in the older cohort (5). Lumens et al. found reduced endocardial circumferential shortening in elderly individuals (39). They suggested that reduced endocardial function would result in less opposition to the dominant epicardium ultimately causing elevated rotation. It has been proposed that endocardial function is more likely to reduce with age due to the sub-endocardium's greater susceptibility to fibrosis and/or subclinical reductions in perfusion (7, 66). The finding of reduced sub-endocardial function and increased torsion in older individuals occurred despite no abnormalities in ejection fraction or LV mass, indicating measurements of torsion may be important for the early detection of cardiovascular dysfunction (39). Further details examining the effects of exercise on LV torsion in individuals of all ages warrants further investigation.

2.4.2 Sex Differences

Numerous investigations examining LV rotation have included both male and female participants (29, 44, 47, 50). However, because the data was pooled, any potential sex differences remain unknown. Differences in sympathetic activity, systolic function, LV

chamber compliance and blood volume between females and males may result in some disparities in LV rotation (18, 27, 32, 54, 74). If the assessment of torsion is to become an important clinical and research tool, normative data in a wide range of populations, including females, must be identified.

2.5 LV Rotation and Cardiac Dysfunction

The importance of quantifying LV rotation lies in its potential for guiding clinical treatment. Measurements of peak torsion, the time of peak torsion as well as the rate and time of peak untwisting provide further insight into pathology beyond traditional clinical measures such as ejection fraction and Doppler indices of diastolic function. Numerous explanations for alterations in LV torsion in cardiac patients have been proposed, including: 1) remodeling of the myocardium causing less mechanically advantageous orientation for contraction; 2) degradation of the extracellular matrix which aids in the storing of potential energy during systolic contraction to be released during early diastole (4, 62). It is also possible that alterations in regional myocardial blood flow (e.g. the endocardium) or electrical activation may result in altered patterns of LV rotation in cardiac patients. Therefore, the ability to easily quantify and track changes in LV rotation may provide further insights into cardiac structure and function beyond traditional measures. As an example, Hansen et al. (1987) have shown that despite no change in ejection fraction, reductions in torsion and torsion rate were found in patients undergoing acute cardiac allograft rejection (25). As the patients recovered, torsion returned to pre-rejection levels. In addition, LV torsion has been shown to be increased in diabetics (Type 1 and 2) (10, 19), and it is suggested that this may be a precursor to the myocardial alterations found in diabetic cardiomyopathy (10).

Reductions in peak and peak rates of torsion and recoil have been shown to be reduced in heart failure patients with a reduced ejection fraction (20). In dilated cardiomyopathy, alterations of the timing of diastolic untwist have been shown to occur, whereby less rotation occurs in the isovolumetric phase of diastole, resulting in less effective untwisting (62). Conversely, Wang et al. (2007) have shown that heart failure with preserved ejection fraction have normal LV twist and untwist (67). The differences observed between patients with systolic and diastolic heart failure may lie in differences in chamber geometry or in the inability of patients with systolic heart failure to reduce their end-systolic volume (48).

Patients with systolic heart failure and non-uniform electromechanical contraction are candidates for cardiac resynchronization therapy (CRT) (24). Recent investigations have shown the ability of speckle-tracking derived strain in different regions (circumferentially) to aid in the placement of pacing leads, that is, target the area of greatest delay in contraction (58). Investigators have shown that the degree to which circumferential shortening is synchronized can be used to predict which patients will respond to CRT (30), while others have shown no change in LV torsion following CRT despite improvements in ejection fraction (77). There is no doubt that the multidimensional (longitudinal, radial, and circumferential) and regional (around the circumference of a 2-D image) information provided by tissue Doppler and speckle-tracking analysis is of great benefit for the advancement of CRT treatment and outcomes. More research is required in this emerging area of research to help identify the predictive and evaluative powers of assessing LV rotation in patients undergoing CRT.

Individuals with chronic aortic stenosis have been shown to display elevated peak LV torsion compared to healthy controls (57). Numerous investigations have demonstrated increased LV torsion in the face of chronically increased afterload, which has been attributed largely to wall thickening and altered fiber orientation (40, 57). However, those with aortic stenosis exhibit delayed diastolic untwisting, where a greater proportion of untwisting occurs after mitral valve opening, indicating less effective diastolic recoil and reduced early diastolic filling (40, 57).

The above discussion provides a few examples of how measures of LV rotation can be used to provide additional insights into myocardial structure and function which go beyond basic traditional imaging measures. The further potential of LV rotational analysis may be seen during physiological stress as the heart may adequately compensate for dysfunction at rest, yet be limited and exposed during exercise. As an example, Notomi et al. (2006) found elevated resting torsion in patients with hypertrophic cardiomyopathy compared to healthy individuals, but the patients were unable to augment torsion and untwisting with exercise (44). Therefore, the importance of incorporating measures of LV rotation into standard stress-echocardiography may provide clinicians with further insight into cardiac dysfunction.

2.6 Scaling of LV Rotation

An important issue in the assessment of LV rotation, particularly when comparing different populations, is the normalization of data. Be it athletes, children, or cardiac patients, heart size will have an impact on LV rotation. Normalizing torsion to LV length has been proposed as a method for comparing different groups (47). As well, others have shown torsion to be related to the ratio of LV wall thickness to LV radius, a measure

which could potentially be incorporated into a normalization of torsion allowing comparisons across groups (39).

2.7 Conclusions

Left ventricular rotation has important implications for diastolic function both at rest and during exercise. The timing and magnitude of rotation have direct influences on the development of transmitral pressure gradients and ultimately LV filling. Recently advances in technology have made the quantification of LV rotation more available as both a research and clinical tool. The importance of assessing LV torsion lies in the ability to quantify ventricular function more accurately spatially (over different planes of motion and regions of the heart) and temporally (e.g. for mechanical synchrony or for examining myocardial motion in comparison to valve events). Measuring LV rotation may become an important clinical tool as it appears to be more sensitive to dysfunction than some of the traditional echocardiography measures.

2.8 Chapter Two References

1. **Akagawa E, Murata K, Tanaka N, Yamada H, Miura T, Kunichika H, Wada Y, Hadano Y, Tanaka T, Nose Y, Yasumoto K, Kono M, and Matsuzaki M.** Augmentation of left ventricular apical endocardial rotation with inotropic stimulation contributes to increased left ventricular torsion and radial strain in normal subjects: quantitative assessment utilizing a novel automated tissue tracking technique. *Circ J* 71: 661-668, 2007.
2. **Arts T and Reneman RS.** Dynamics of left ventricular wall and mitral valve mechanics--a model study. *J Biomech* 22: 261-271, 1989.
3. **Beyar R and Sideman S.** Effect of the twisting motion on the nonuniformities of transmyocardial fiber mechanics and energy demand--a theoretical study. *IEEE Trans Biomed Eng* 32: 764-769, 1985.
4. **Beyar R, Yin FC, Hausknecht M, Weisfeldt ML, and Kass DA.** Dependence of left ventricular twist-radial shortening relations on cardiac cycle phase. *Am J Physiol* 257: H1119-1126, 1989.
5. **Burns AT, La Gerche A, Macisaac AI, and Prior DL.** Augmentation of Left Ventricular Torsion with Exercise is Attenuated with Age. *J Am Soc Echocardiogr*, 2007.
6. **Burns ATM, I.G. Thomas, J.D. MacIsaac, A. and Prior, D.** Doin' the twist: new tools for an old concept of myocardial function. *Heart* 94: 978-983, 2008.
7. **Capasso JM, Palackal T, Olivetti G, and Anversa P.** Severe myocardial dysfunction induced by ventricular remodeling in aging rat hearts. *Am J Physiol* 259: H1086-1096, 1990.
8. **Carlsson M, Ugander M, Mosen H, Buhre T, and Arheden H.** Atrioventricular plane displacement is the major contributor to left ventricular pumping in healthy adults, athletes, and patients with dilated cardiomyopathy. *Am J Physiol Heart Circ Physiol* 292: H1452-1459, 2007.
9. **Cheng CP, Igarashi Y, and Little WC.** Mechanism of augmented rate of left ventricular filling during exercise. *Circ Res* 70: 9-19, 1992.
10. **Chung J, Abraszewski P, Yu X, Liu W, Krainik AJ, Ashford M, Caruthers SD, McGill JB, and Wickline SA.** Paradoxical increase in ventricular torsion and systolic torsion rate in type I diabetic patients under tight glycemic control. *J Am Coll Cardiol* 47: 384-390, 2006.
11. **Convertino VA, Brock PJ, Keil LC, Bernauer EM, and Greenleaf JE.** Exercise training-induced hypervolemia: role of plasma albumin, renin, and vasopressin. *J Appl Physiol* 48: 665-669, 1980.
12. **Courtois M, Vered Z, Barzilai B, Ricciotti NA, Perez JE, and Ludbrook PA.** The transmitral pressure-flow velocity relation. Effect of abrupt preload reduction. *Circulation* 78: 1459-1468, 1988.
13. **Di Bello V, Santoro G, Talarico L, Di Muro C, Caputo MT, Giorgi D, Bertini A, Bianchi M, and Giusti C.** Left ventricular function during exercise in athletes and in sedentary men. *Med Sci Sports Exerc* 28: 190-196, 1996.
14. **Dill DB, Braithwaite K, Adams WC, and Bernauer EM.** Blood volume of middle-distance runners: effect of 2,300-m altitude and comparison with non-athletes. *Med Sci Sports* 6: 1-7, 1974.

15. **Dong SJ, Hees PS, Huang WM, Buffer SA, Jr., Weiss JL, and Shapiro EP.** Independent effects of preload, afterload, and contractility on left ventricular torsion. *Am J Physiol* 277: H1053-1060, 1999.
16. **Dorfman TA, Rosen BD, Perhonen MA, Tillery T, McColl R, Peshock RM, and Levine BD.** Diastolic Suction is Impaired by Bed Rest: MRI Tagging Studies of Diastolic Untwisting. *J Appl Physiol*, 2008.
17. **Esch BT, Scott JM, Haykowsky MJ, McKenzie DC, and Warburton DE.** Diastolic ventricular interactions in endurance-trained athletes during orthostatic stress. *Am J Physiol Heart Circ Physiol* 293: H409-415, 2007.
18. **Evans JM, Ziegler MG, Patwardhan AR, Ott JB, Kim CS, Leonelli FM, and Knapp CF.** Gender differences in autonomic cardiovascular regulation: spectral, hormonal, and hemodynamic indexes. *J Appl Physiol* 91: 2611-2618, 2001.
19. **Fonseca CG, Dissanayake AM, Doughty RN, Whalley GA, Gamble GD, Cowan BR, Occleshaw CJ, and Young AA.** Three-dimensional assessment of left ventricular systolic strain in patients with type 2 diabetes mellitus, diastolic dysfunction, and normal ejection fraction. *Am J Cardiol* 94: 1391-1395, 2004.
20. **Fuchs E, Muller MF, Oswald H, Thony H, Mohacsi P, and Hess OM.** Cardiac rotation and relaxation in patients with chronic heart failure. *Eur J Heart Fail* 6: 715-722, 2004.
21. **Fukuda N, Sasaki D, Ishiwata S, and Kurihara S.** Length dependence of tension generation in rat skinned cardiac muscle: role of titin in the Frank-Starling mechanism of the heart. *Circulation* 104: 1639-1645, 2001.
22. **George K, Oxborough D, Forster J, Whyte G, Shave R, Dawson E, Stephenson C, Dugdill L, Edwards B, and Gaze D.** Mitral annular myocardial velocity assessment of segmental left ventricular diastolic function after prolonged exercise in humans. *J Physiol* 569: 305-313, 2005.
23. **Gledhill N, Cox D, and Jamnik R.** Endurance athletes' stroke volume does not plateau: major advantage is diastolic function. *Med Sci Sports Exerc* 26: 1116-1121, 1994.
24. **Gorcsan J, 3rd, Tanabe M, Bleeker GB, Suffoletto MS, Thomas NC, Saba S, Tops LF, Schalij MJ, and Bax JJ.** Combined longitudinal and radial dyssynchrony predicts ventricular response after resynchronization therapy. *J Am Coll Cardiol* 50: 1476-1483, 2007.
25. **Hansen DE, Daughters GT, 2nd, Alderman EL, Stinson EB, Baldwin JC, and Miller DC.** Effect of acute human cardiac allograft rejection on left ventricular systolic torsion and diastolic recoil measured by intramyocardial markers. *Circulation* 76: 998-1008, 1987.
26. **Harvey W.** *Cardiac Classics*. London, England: Henry Kimpton, 1941.
27. **Hayward CS, Kalnins WV, and Kelly RP.** Gender-related differences in left ventricular chamber function. *Cardiovasc Res* 49: 340-350, 2001.
28. **Hees PS, Fleg JL, Dong SJ, and Shapiro EP.** MRI and echocardiographic assessment of the diastolic dysfunction of normal aging: altered LV pressure decline or load? *Am J Physiol Heart Circ Physiol* 286: H782-788, 2004.
29. **Helle-Valle T, Crosby J, Edvardsen T, Lyseggen E, Amundsen BH, Smith HJ, Rosen BD, Lima JA, Torp H, Ihlen H, and Smiseth OA.** New noninvasive method

for assessment of left ventricular rotation: speckle tracking echocardiography. *Circulation* 112: 3149-3156, 2005.
30. **Helm RH, Leclercq C, Faris OP, Ozturk C, McVeigh E, Lardo AC, and Kass DA.** Cardiac dyssynchrony analysis using circumferential versus longitudinal strain: implications for assessing cardiac resynchronization. *Circulation* 111: 2760-2767, 2005.
31. **Helmes M, Lim CC, Liao R, Bharti A, Cui L, and Sawyer DB.** Titin determines the Frank-Starling relation in early diastole. *J Gen Physiol* 121: 97-110, 2003.
32. **Higginbotham MB, Morris KG, Coleman RE, and Cobb FR.** Sex-related differences in the normal cardiac response to upright exercise. *Circulation* 70: 357-366, 1984.
33. **Hui L, Pemberton J, Hickey E, Li XK, Lysyansky P, Ashraf M, Niemann PS, and Sahn DJ.** The contribution of left ventricular muscle bands to left ventricular rotation: assessment by a 2-dimensional speckle tracking method. *J Am Soc Echocardiogr* 20: 486-491, 2007.
34. **Ishida Y, Meisner JS, Tsujioka K, Gallo JI, Yoran C, Frater RW, and Yellin EL.** Left ventricular filling dynamics: influence of left ventricular relaxation and left atrial pressure. *Circulation* 74: 187-196, 1986.
35. **Katona PG, McLean M, Dighton DH, and Guz A.** Sympathetic and parasympathetic cardiac control in athletes and nonathletes at rest. *J Appl Physiol* 52: 1652-1657, 1982.
36. **Kim HK, Sohn DW, Lee SE, Choi SY, Park JS, Kim YJ, Oh BH, Park YB, and Choi YS.** Assessment of left ventricular rotation and torsion with two-dimensional speckle tracking echocardiography. *J Am Soc Echocardiogr* 20: 45-53, 2007.
37. **Leitman M, Lysyansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, Kaluski E, Krakover R, and Vered Z.** Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. *J Am Soc Echocardiogr* 17: 1021-1029, 2004.
38. **Levine BD, Lane LD, Buckey JC, Friedman DB, and Blomqvist CG.** Left ventricular pressure-volume and Frank-Starling relations in endurance athletes. Implications for orthostatic tolerance and exercise performance. *Circulation* 84: 1016-1023, 1991.
39. **Lumens J, Delhaas T, Arts T, Cowan BR, and Young AA.** Impaired subendocardial contractile myofiber function in asymptomatic aged humans, as detected using MRI. *Am J Physiol Heart Circ Physiol* 291: H1573-1579, 2006.
40. **Nagel E, Stuber M, Burkhard B, Fischer SE, Scheidegger MB, Boesiger P, and Hess OM.** Cardiac rotation and relaxation in patients with aortic valve stenosis. *Eur Heart J* 21: 582-589, 2000.
41. **Neilan TG, Ton-Nu TT, Jassal DS, Popovic ZB, Douglas PS, Halpern EF, Marshall JE, Thomas JD, Picard MH, Yoerger DM, and Wood MJ.** Myocardial adaptation to short-term high-intensity exercise in highly trained athletes. *J Am Soc Echocardiogr* 19: 1280-1285, 2006.
42. **Nikolic SD, Feneley MP, Pajaro OE, Rankin JS, and Yellin EL.** Origin of regional pressure gradients in the left ventricle during early diastole. *Am J Physiol* 268: H550-557, 1995.
43. **Notomi Y, Lysyansky P, Setser RM, Shiota T, Popovic ZB, Martin-Miklovic MG, Weaver JA, Oryszak SJ, Greenberg NL, White RD, and Thomas JD.**

Measurement of ventricular torsion by two-dimensional ultrasound speckle tracking imaging. *J Am Coll Cardiol* 45: 2034-2041, 2005.
44. **Notomi Y, Martin-Miklovic MG, Oryszak SJ, Shiota T, Deserranno D, Popovic ZB, Garcia MJ, Greenberg NL, and Thomas JD.** Enhanced ventricular untwisting during exercise: a mechanistic manifestation of elastic recoil described by Doppler tissue imaging. *Circulation* 113: 2524-2533, 2006.
45. **Notomi Y, Popovic ZB, Yamada H, Wallick DW, Martin MG, Oryszak SJ, Shiota T, Greenberg NL, and Thomas JD.** Ventricular untwisting: a temporal link between left ventricular relaxation and suction. *Am J Physiol Heart Circ Physiol* 294: H505-513, 2008.
46. **Notomi Y, Setser RM, Shiota T, Martin-Miklovic MG, Weaver JA, Popovic ZB, Yamada H, Greenberg NL, White RD, and Thomas JD.** Assessment of left ventricular torsional deformation by Doppler tissue imaging: validation study with tagged magnetic resonance imaging. *Circulation* 111: 1141-1147, 2005.
47. **Notomi Y, Srinath G, Shiota T, Martin-Miklovic MG, Beachler L, Howell K, Oryszak SJ, Deserranno DG, Freed AD, Greenberg NL, Younoszai A, and Thomas JD.** Maturational and adaptive modulation of left ventricular torsional biomechanics: Doppler tissue imaging observation from infancy to adulthood. *Circulation* 113: 2534-2541, 2006.
48. **Nottin S, Doucende G, Schuster-Beck I, Dauzat M, and Obert P.** Alteration in left ventricular normal and shear strains evaluated by 2D-strain echocardiography in the athlete's heart. *J Physiol* 586: 4721-4733, 2008.
49. **Osman NF, Kerwin WS, McVeigh ER, and Prince JL.** Cardiac motion tracking using CINE harmonic phase (HARP) magnetic resonance imaging. *Magn Reson Med* 42: 1048-1060, 1999.
50. **Oxenham HC, Young AA, Cowan BR, Gentles TL, Occleshaw CJ, Fonseca CG, Doughty RN, and Sharpe N.** Age-related changes in myocardial relaxation using three-dimensional tagged magnetic resonance imaging. *J Cardiovasc Magn Reson* 5: 421-430, 2003.
51. **Popovic ZB, Prasad A, Garcia MJ, Arbab-Zadeh A, Borowski A, Dijk E, Greenberg NL, Levine BD, and Thomas JD.** Relationship among diastolic intraventricular pressure gradients, relaxation, and preload: impact of age and fitness. *Am J Physiol Heart Circ Physiol* 290: H1454-1459, 2006.
52. **Rovner A, Greenberg NL, Thomas JD, and Garcia MJ.** Relationship of diastolic intraventricular pressure gradients and aerobic capacity in patients with diastolic heart failure. *Am J Physiol Heart Circ Physiol* 289: H2081-2088, 2005.
53. **Rushmer RF, Smith O, and Franklin D.** Mechanisms of cardiac control in exercise. *Circ Res* 7: 602-627, 1959.
54. **Schwertz DW, Vizgirda V, Solaro RJ, Piano MR, and Ryjewski C.** Sexual dimorphism in rat left atrial function and response to adrenergic stimulation. *Mol Cell Biochem* 200: 143-153, 1999.
55. **Scott JM, Esch BT, Haykowsky MJ, Isserow S, Koehle MS, Hughes BG, Zbogar D, Bredin SS, McKenzie DC, and Warburton DE.** Sex differences in left ventricular function and beta-receptor responsiveness following prolonged strenuous exercise. *J Appl Physiol* 102: 681-687, 2007.

56. **Streeter DD, Jr., Spotnitz HM, Patel DP, Ross J, Jr., and Sonnenblick EH.** Fiber orientation in the canine left ventricle during diastole and systole. *Circ Res* 24: 339-347, 1969.
57. **Stuber M, Scheidegger MB, Fischer SE, Nagel E, Steinemann F, Hess OM, and Boesiger P.** Alterations in the local myocardial motion pattern in patients suffering from pressure overload due to aortic stenosis. *Circulation* 100: 361-368, 1999.
58. **Suffoletto MS, Dohi K, Cannesson M, Saba S, and Gorcsan J, 3rd.** Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. *Circulation* 113: 960-968, 2006.
59. **Sundstedt M, Hedberg P, Jonason T, Ringqvist I, and Henriksen E.** Echocardiographic Doppler assessments of left ventricular filling and ejection during upright exercise in endurance athletes. *Clin Physiol Funct Imaging* 27: 36-41, 2007.
60. **Teske AJ, De Boeck BW, Melman PG, Sieswerda GT, Doevendans PA, and Cramer MJ.** Echocardiographic quantification of myocardial function using tissue deformation imaging, a guide to image acquisition and analysis using tissue Doppler and speckle tracking. *Cardiovasc Ultrasound* 5: 27, 2007.
61. **Thomas JD and Popovic ZB.** Assessment of left ventricular function by cardiac ultrasound. *J Am Coll Cardiol* 48: 2012-2025, 2006.
62. **Tibayan FA, Lai DT, Timek TA, Dagum P, Liang D, Daughters GT, Ingels NB, and Miller DC.** Alterations in left ventricular torsion in tachycardia-induced dilated cardiomyopathy. *J Thorac Cardiovasc Surg* 124: 43-49, 2002.
63. **Tischler M and Niggel J.** Left ventricular systolic torsion and exercise in normal hearts. *J Am Soc Echocardiogr* 16: 670-674, 2003.
64. **Tyberg JV, Keon WJ, Sonnenblick EH, and Urschel CW.** Mechanics of ventricular diastole. *Cardiovasc Res* 4: 423-428, 1970.
65. **Udelson JE, Bacharach SL, Cannon RO, 3rd, and Bonow RO.** Minimum left ventricular pressure during beta-adrenergic stimulation in human subjects. Evidence for elastic recoil and diastolic "suction" in the normal heart. *Circulation* 82: 1174-1182, 1990.
66. **Van Der Toorn A, Barenbrug P, Snoep G, Van Der Veen FH, Delhaas T, Prinzen FW, Maessen J, and Arts T.** Transmural gradients of cardiac myofiber shortening in aortic valve stenosis patients using MRI tagging. *Am J Physiol Heart Circ Physiol* 283: H1609-1615, 2002.
67. **Wang J, Khoury DS, Yue Y, Torre-Amione G, and Nagueh SF.** Left Ventricular Untwisting Rate by Speckle Tracking Echocardiography. *Circulation*, 2007.
68. **Warburton DE, Gledhill N, Jamnik VK, Krip B, and Card N.** Induced hypervolemia, cardiac function, VO2max, and performance of elite cyclists. *Med Sci Sports Exerc* 31: 800-808, 1999.
69. **Warburton DE, Gledhill N, and Quinney HA.** Blood volume, aerobic power, and endurance performance: potential ergogenic effect of volume loading. *Clin J Sport Med* 10: 59-66, 2000.
70. **Warburton DE, Haykowsky MJ, Quinney HA, Blackmore D, Teo KK, and Humen DP.** Myocardial response to incremental exercise in endurance-trained athletes: influence of heart rate, contractility and the Frank-Starling effect. *Exp Physiol* 87: 613-622, 2002.

71. **Warburton DE, Haykowsky MJ, Quinney HA, Blackmore D, Teo KK, Taylor DA, McGavock J, and Humen DP.** Blood volume expansion and cardiorespiratory function: effects of training modality. *Med Sci Sports Exerc* 36: 991-1000, 2004.
72. **Welsh RC, Warburton DE, Humen DP, Taylor DA, McGavock J, and Haykowsky MJ.** Prolonged strenuous exercise alters the cardiovascular response to dobutamine stimulation in male athletes. *J Physiol* 569: 325-330, 2005.
73. **Whyte GP, George K, Shave R, Middleton N, and Nevill AM.** Training induced changes in maximum heart rate. *Int J Sports Med* 29: 129-133, 2008.
74. **Wiebe CG, Gledhill N, Warburton DE, Jamnik VK, and Ferguson S.** Exercise cardiac function in endurance-trained males versus females. *Clin J Sport Med* 8: 272-279, 1998.
75. **Wu MT, Tseng WY, Su MY, Liu CP, Chiou KR, Wedeen VJ, Reese TG, and Yang CF.** Diffusion tensor magnetic resonance imaging mapping the fiber architecture remodeling in human myocardium after infarction: correlation with viability and wall motion. *Circulation* 114: 1036-1045, 2006.
76. **Zerhouni EA, Parish DM, Rogers WJ, Yang A, and Shapiro EP.** Human heart: tagging with MR imaging--a method for noninvasive assessment of myocardial motion. *Radiology* 169: 59-63, 1988.
77. **Zhang Q, Fung JW, Yip GW, Chan JY, Lee AP, Lam YY, Wu LW, Wu EB, and Yu CM.** Improvement of Left Ventricular Myocardial Short-axis, but not Long-axis Function or Torsion after Cardiac Resynchronization Therapy-An Assessment by Two-Dimensional Speckle Tracking. *Heart*, 2008.

[1]CHAPTER THREE: Left Ventricular Torsion and Recoil in Young and Old Endurance-Trained Athletes

3.1 Introduction

Healthy aging is generally associated with preserved left ventricular (LV) systolic function and reduced diastolic function (27, 28). In older individuals, relaxation is prolonged, peak early mitral filling velocities (E) are reduced, and the LV is less compliant compared to younger individuals (1, 24, 26, 28).

Endurance training improves diastolic function in athletes as demonstrated by larger E, higher mitral annular velocities in early diastole (E') and greater ventricular compliance (18, 25). Controversy exists regarding changes in diastolic function in older athletes. Some investigators have shown that years of training cannot offset age associated reductions in diastolic function (2, 12). However, others have shown the ability of lifelong endurance training to mitigate the deleterious effects of age on diastolic function, whereby senior athletes exhibit similar diastolic function to sedentary individuals four decades younger (1, 25, 26).

LV torsion is the result of counter-clockwise circumferential rotation at the apex and clockwise rotation at the base when viewed from the apex (5, 31). Torsion allows for optimal myocardial shortening and the efficient ejection of blood (3). In diastole, the potential energy stored during myocardial shortening is rapidly unleashed in the form of diastolic recoil (combined ventricular untwisting at the apex and base) (13, 15).

[1] A version of this chapter will be submitted for publication as: BT Esch, JM Scott, R Shave, K George, D Oxborough, RB Thompson, MJ Haykowsky and DER Warburton. Left Ventricular Torsion and Recoil in Young and Old Endurance-Trained Athletes.

Approximately 40% of LV recoil occurs during the isovolumic phase, making recoil crucial to the development of low LV pressures, and ultimately early LV filling (22).

LV torsion is elevated with increasing age, leaving little torsion reserve for exercise (4, 23, 24). Conversely, sedentary older individuals exhibit reduced rates of recoil as well as prolonged, less effective recoil (23, 24, 33). However, the effect of years of endurance training on LV torsion and recoil in older individuals is unknown. Therefore, we examined the impact of prolonged endurance training on LV torsion and recoil in older athletes. We hypothesized that endurance training would preserve LV torsion and recoil in older athletes so that it is similar to younger athletes.

3.2 Methods

3.2.1 Participants

We recruited 66 athletes between the ages of 24 and 76 to undergo resting two-dimensional echocardiography. All athletes were ultra-marathon runners and were participating in the 2008 Western States Endurance Run in California, USA (160km). Athletes were examined at the race site over two days prior to competition. Institutional ethics were obtained from the University of British Columbia (appendix A) as well as the Western States medical committee. All participants provided written informed consent prior to participation. Individuals with inadequate image quality or known cardiovascular disease were excluded from analysis.

3.2.2 Protocol

Each participant underwent M-mode, two dimensional and Doppler echocardiography (Vivid-i, GE Healthcare) while in the left lateral decubitus position. Limb-lead

electrocardiography and automated blood pressure were recorded during echocardiographic evaluation. Conventional parasternal long axis M-mode recordings of the LV as well as the aortic and mitral valves were obtained. Parasternal short axis images of the LV were acquired at the mitral valve level (base) and distal to the papillary muscles (apex). An apical four chamber view was also acquired in order to quantify LV end-diastolic volume, end-systolic volume and ejection fraction (30). Internal LV length was measured in the four chamber view, from the apex to the level of the mitral annulus. Pulsed Doppler recordings were made with the cursor placed at the tips of the mitral leaflets in order to quantify E and atrial (A) filling velocity. Septal E' was recorded using tissue Doppler imaging. The echocardiography data was acquired in the order listed above.

Height and mass were measured for each participant and body surface area was calculated (10). The athletes also completed a training history questionnaire documenting their training habits.

3.2.3 Data Analysis

In order to quantify aortic valve closure and mitral valve opening time, the temporal relationship between the onset of the QRS complex and valve opening and closure was measured. The M-mode recordings of the LV were also used to measure posterior wall thickness and internal cavity dimension in systole. Using EchoPAC software (GE Healthcare, USA), speckle-tracking analysis was applied to the short axis basal and apical images in order to quantify rotation, rotation rates, as well as circumferential and radial strain and strain rates (appendix B). Speckle-tracking analysis was conducted on the entire width of the myocardium, and separately on the endocardial (inner most

myocardium) and epicardial (outermost myocardium) layers. To calculate peak torsion and recoil as well as the rates of each, instantaneous rotations and rotation rates at the base were subtracted from apical values. The ratio of peak recoil rate/peak torsion was calculated for each individual in order to quantify the amount of recoil that occurred for a given amount of torsion. The absolute time difference between peak basal and peak apical rotation was calculated for each participant. Apical 4-chamber images were also analyzed with speckle-tracking in order to quantify longitudinal strain and strain rates. To allow group comparisons and averaging between data collected at different heart rates and frame rates, all data was normalized to a percentage of systole by cubic spline interpolation (Matlab, Mathworks,USA). All data began from the onset of the QRS (0%), with aortic valve closure equivalent to 100% and diastole occurring from 100% onwards. This normalization of event timings allowed for the quantification of the time peak rotation and rotation rates occurred, as well as the differences in the timings of apical and basal peak rotations. EchoPAC software automatically provides a tracking quality score between one (ideal) and three (non-tracking). Only images with a score of two or less were included in the analysis. All two dimensional and speckle-tracking data were averaged over three cardiac cycles and analyzed by a single technician.

From the mitral and tissue Doppler data, E/A and E/E' were calculated. LV mass (8) and LV mass index (calculated as LV mass/$BSA^{1.5}$) were also determined for each participant. Total systolic duration was calculated as the time in milliseconds (ms) from the onset of the QRS complex to aortic valve closure, while total diastolic duration was considered to be the remaining time from aortic valve closure to the onset of the next QRS. To provide an index of afterload, wall stress was calculated as: 0.334 x systolic

blood pressure x LV internal systolic dimension /posterior systolic wall thickness (1 + posterior systolic wall thickness/LV internal systolic dimension) (29).

3.2.4 Statistics

An independent t-test was used to compare differences between older and younger athletes. Linear regressions were applied to identify the relatedness of a given two variables. All statistics were completed using Statistica 6.0 and significance was set at $p<0.05$.

3.3 Results

3.3.1 Group Characteristics

Due to poor quality echocardiographic images we were able to successfully complete speckle-tracking analysis in 52 of 66 athletes (78.8%). Therefore, the data presented includes information from the 52 athletes with speckle-tracking analysis. To determine the influences of age on LV torsion and recoil, the athletes were divided into two groups (older athletes and younger athletes) based on the median age (44 years). The physical characteristics and training history of the two groups are displayed in table 3.1. The groups were well matched for the number of females per group, height, mass, and hours of running per week. By design the older athlete group was significantly older, and they had been running for a greater number of years compared to the young athletes ($p<0.05$). However, the distance ran per week was significantly higher in the young group ($p<0.05$).

	Older Athletes (n=25)	Young Athletes (n=27)
Males / Females	18 / 7	20 / 7
Age (years)	53.3 ± 8.3 *	37.6 ± 5.5
Height (cm)	173.8 ± 9.2	175.5 ± 11.2
Mass (kg)	69.3 ± 13.0	69.6 ± 14.4
Years Running (years)	18.9 ± 10.9*	12.9 ± 8.3
Distance Run/Week (km)	82.5 ± 33.6*	105.7 ± 34.2
Hours of Running/Week (hrs)	12.3 ± 4.7	11.9 ± 4.9

Table 3.1: Participant physical characteristics and training history
* indicates significantly different from young athletes ($p<0.05$)

Table 3.2 displays basic hemodynamic and cardiac characteristics of the two groups. There were no group differences in blood pressure, LV mass index, end-systolic volume, or ejection fraction. The groups did not differ in heart rate, or systolic (older: 376 ± 33ms; younger: 373 ± 30ms) and diastolic duration (older: 683 ± 191ms; younger: 727 ± 187ms). Younger athletes had a slightly higher LV mass, end-diastolic volume and wall stress; however, these differences did not reach statistical significance. Due to a lower E, older athletes had a significantly lower E/A ($p<0.05$). In addition, older athletes demonstrated a lower septal E' ($p<0.05$). The groups did not differ with respect to E/E'. LV length was not different between young and old athletes.

	Older Athletes	Young Athletes
Heart Rate (beats/min)	56 ± 8	56 ± 10
Systolic Blood Pressure (mmHg)	122 ± 16	116 ± 12
Diastolic Blood Pressure (mmHg)	79 ± 11	78 ± 8
LV Mass (g)	189 ± 49	196 ± 50
LV Mass Index (g/m^3)	77 ± 13	78 ± 13
End Diastolic Volume (mL)	138 ± 28	148 ± 44
End Systolic Volume (mL)	63 ± 18	65 ± 18
Ejection Fraction (%)	55 ± 6	56 ± 5
Wall Stress (10^3 dynes/cm^2)	52 ± 14	55 ± 18
Mitral E (m/s)	0.68 ± 0.18	0.77 ± 0.14
Mitral A (m/s)	0.56 ± 0.12	0.52 ± 0.11
E/A	1.23 ± 0.18*	1.53 ± 0.42
Septal E' (m/sec)	0.10 ± 0.02*	0.12 ± 0.02
E/E'	7.0 ± 1.9	6.7 ± 1.4

Table 3.2: Hemodynamic and cardiac characteristics
* indicates significantly different from young athletes ($p<0.05$)

3.3.2 LV Rotation and Rotation Rates

Peak basal rotation and the time at which peak basal rotation occurred were not different between groups. Peak apical rotation was significantly higher in older athletes compared to younger athletes ($p<0.05$); however, the time of peak apical rotation did not differ. Although there was a trend towards higher peak torsion in the older group, peak torsion and the time of peak torsion did not differ between groups (figure 3.1). The time difference between the occurrence of peak apical and peak basal rotation was not different between groups (older: 25.2 ± 21.7ms, younger: 27.2 ± 19.8ms). Older athletes completed a significantly greater percentage of their recoil at the time of mitral valve opening (51.0 ± 28.1%) compared to younger athletes (37.6 ± 16.7%, $p<0.05$).

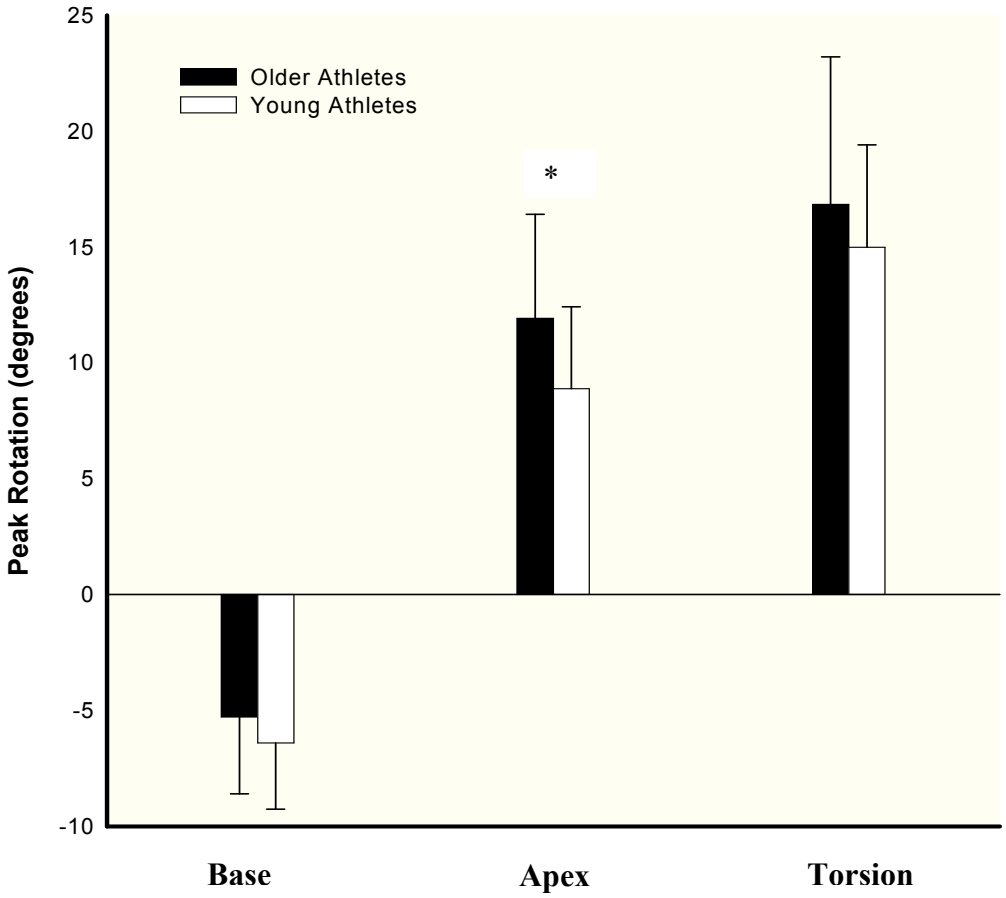


Figure 3.1. Peak LV rotation at the base, apex, as well as peak torsion in older athletes (black bars) and young athletes (white bars).
Values are group means ± standard deviation. * indicates groups are significantly different ($p<0.05$).

There were no group differences for peak basal rotation rate in either systole or diastole; however, peak apical rotation velocity was higher in older athletes in both systole and diastole. The groups' mean timings of peak basal and apical rotation rates did not differ during systole or diastole. Peak torsion and recoil velocities did not differ between groups (figures 3.2 and 3.3). Peak torsion velocity occurred earlier in older athletes ($p<0.05$), whereas there was no group difference in the time of peak recoil velocity. The groups did not differ in the ratio of peak recoil rate/peak torsion.

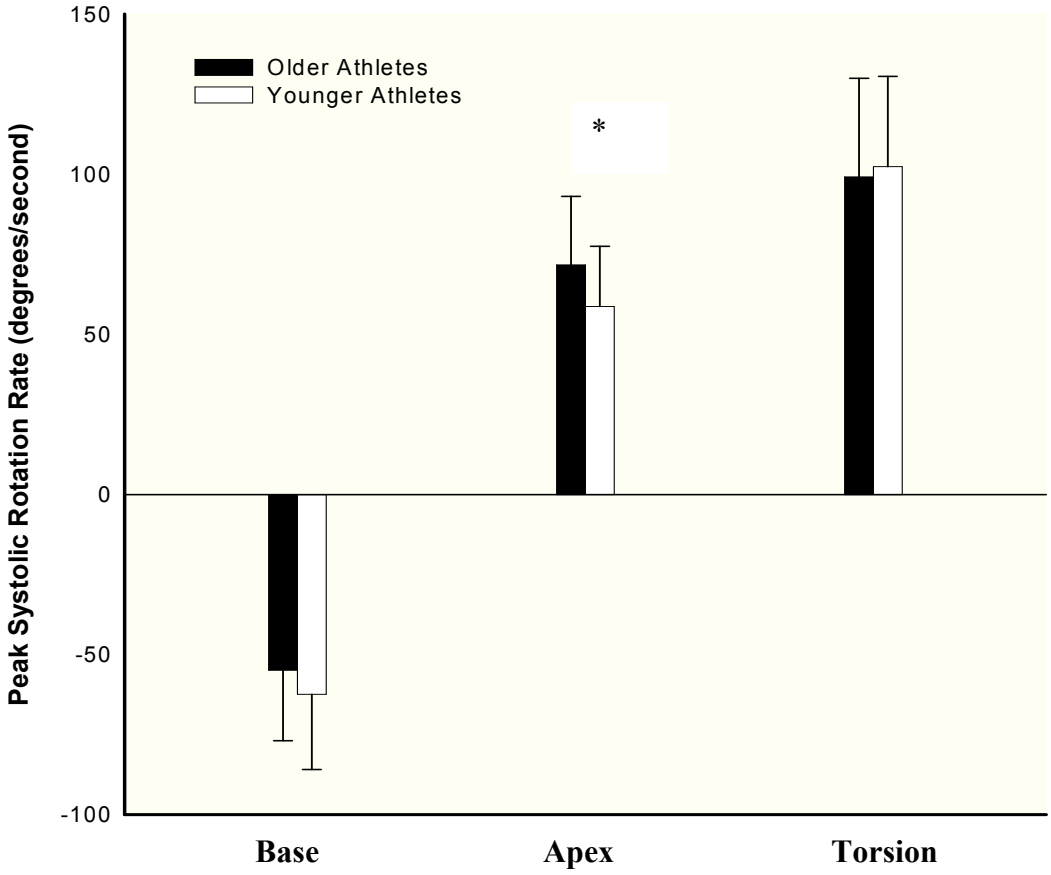


Figure 3.2. Peak LV systolic rotation rates at the base, apex, as well as peak systolic torsion velocity in the older athletes (black bars) and young athletes (white bars). Values are group means ± standard deviation. * indicates groups are significantly different ($p<0.05$).

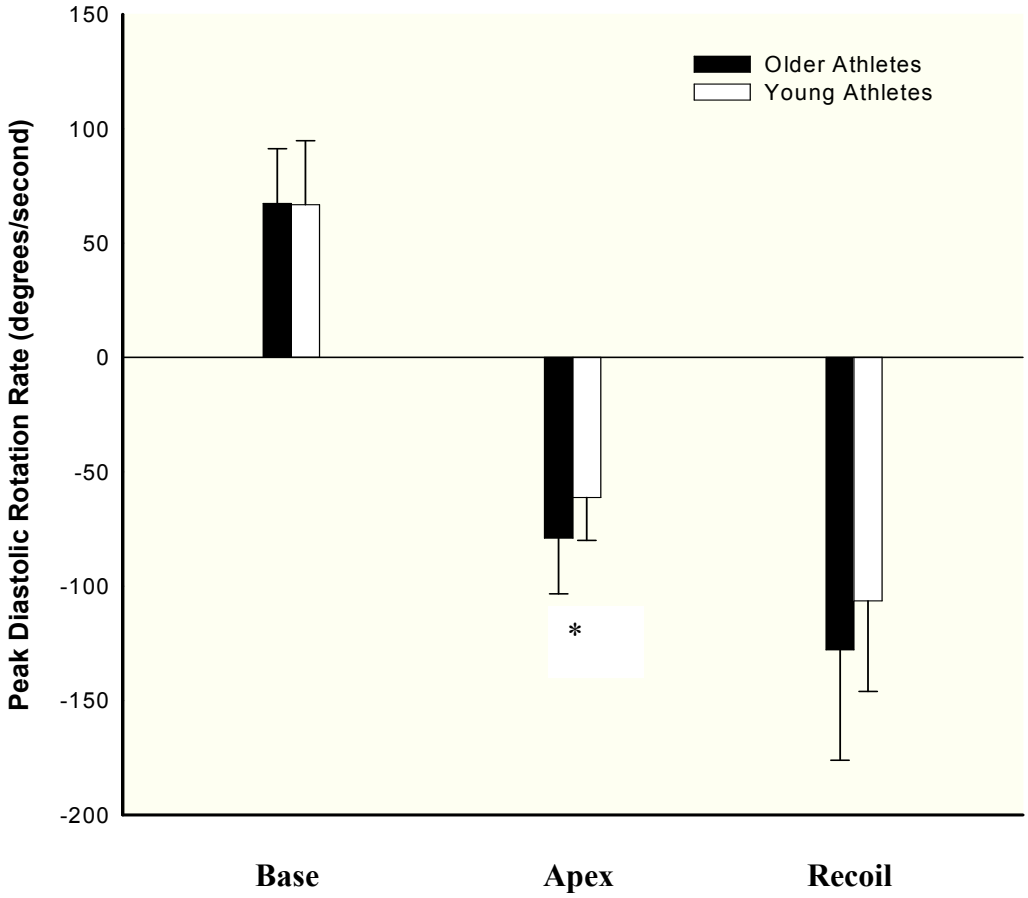


Figure 3.3. Peak LV diastolic rotation rates at the base, apex, as well as peak diastolic recoil velocity in the older athletes (black bars) and young athletes (white bars). Values are group means ± standard deviation. * indicates groups are significantly different ($p<0.05$).

3.3.3 Endocardial and Epicardial Rotation

Successful speckle-tracking analysis was completed on both the endocardium and epicardium in 32 of 52 athletes (12 older athletes, 20 younger athletes). The rotation and rotation rate results, as well as circumferential strain for the endocardium and epicardium are shown in table 3.3. Peak apical rotation and peak apical circumferential strain were higher in the endocardium of older athletes compared to younger athletes ($p<0.05$). Endocardial basal rotation and strain were not different between groups. Apical epicardial rotation was also higher in the older athletes; however, there were no group differences for epicardial basal rotation, or circumferential strain at the apex or base.

	Older Athletes	Young Athletes
Endocardium		
Base Rotation (degrees)	-8.2 ± 2.9	-7.0 ± 2.6
Apex Rotation (degrees)	17.1± 6.2*	10.5 ± 3.8
Base Circumferential Strain (%)	-23.9 ± 4.6	-21.9 ± 3.1
Apex Circumferential Strain (%)	-38.1 ± 4.6*	-30.8 ± 3.8
Epicardium		
Base Rotation (degrees)	-5.2 ± 2.4	-4.8 ± 2.4
Apex Rotation (degrees)	9.9 ± 3.7*	6.4 ± 3.2
Base Circumferential Strain (%)	-14.2 ± 2.5	-13.4 ± 2.2
Apex Circumferential Strain (%)	-18.7 ± 3.2	-16.6 ± 3.6

Table 3.3: Endocardial and epicardial rotation and circumferential strain
* indicates significantly different from young athletes ($p<0.05$)

3.3.4 Myocardial Strain and Strain Rates

Circumferential and radial strain, as well as strain rate analysis, was completed in all 52 athletes. The image quality of one older athlete was insufficient to analyze for longitudinal strain. Strain and strain rate data are summarized in table 3.4. There were no group differences in either basal or apical circumferential or radial peak strain. There were also no group differences for longitudinal strain.

Basal circumferential and radial peak strain rates in systole and diastole were not different between groups. Apical circumferential systolic and diastolic strain rates were not statistically different, nor was apical radial strain rate in diastole. Apical radial peak systolic strain rate was significantly higher in older athletes. Longitudinal strain rate was not different between groups in systole or diastole, although there was a trend towards the younger athletes having a higher peak diastolic strain rate ($p=0.051$).

	Older Athletes	Young Athletes
Circumferential Strain (%)		
Base	-19.3±3.9	-18.9±3.7
Apex	-29.0±5.9	-26.7±4.8
Radial Strain (%)		
Base	46.9±14.0	45.7±13.4
Apex	28.6±18.7	24.8±18.5
Longitudinal Strain (%)	-18.61±2.4	-18.4±2.7
Circumferential Strain Rate S (%•s^{-1})		
Base	-1.1±0.2	-1.1±0.2
Apex	-1.7±0.5	-2.0±0.3
Circumferential Strain Rate D (%•s^{-1})		
Base	1.5±0.5	1.4±0.4
Apex	2.3±0.8	2.4±0.8
Radial Strain Rate S (%•s^{-1})		
Base	1.7±0.3	1.7±0.3
Apex	1.5±0.6*	1.1±0.4
Radial Strain Rate D (%•s^{-1})		
Base	-1.4±0.5	-1.4±0.4
Apex	-1.6±0.6	-1.5±0.7
Longitudinal Strain Rate S (%•s^{-1})	-0.9±0.2	-0.9±0.2
Longitudinal Strain Rate D (%•s^{-1})	1.1±0.3	1.3±0.3

Table 3.4: Left ventricular strain and strain rates
* indicates significantly different from young athletes ($p<0.05$). S: systole; D: diastole

3.3.5 Correlations

The correlations include data for all the athletes combined. Age was not significantly related to peak torsion (figure 3.4, r: 0.28) or the ratio of peak recoil rate/peak torsion. Additionally, age was not correlated with peak recoil rate (r: -0.25, $p=0.08$). Peak recoil rate was strongly related to peak torsion (r: -0.70, $p<0.05$). Systolic circumferential strain rate at the apex and base were related to peak untwisting rates at the apex (r: 0.45, $p<0.05$) and base (r: -0.49, $p<0.05$) respectively.

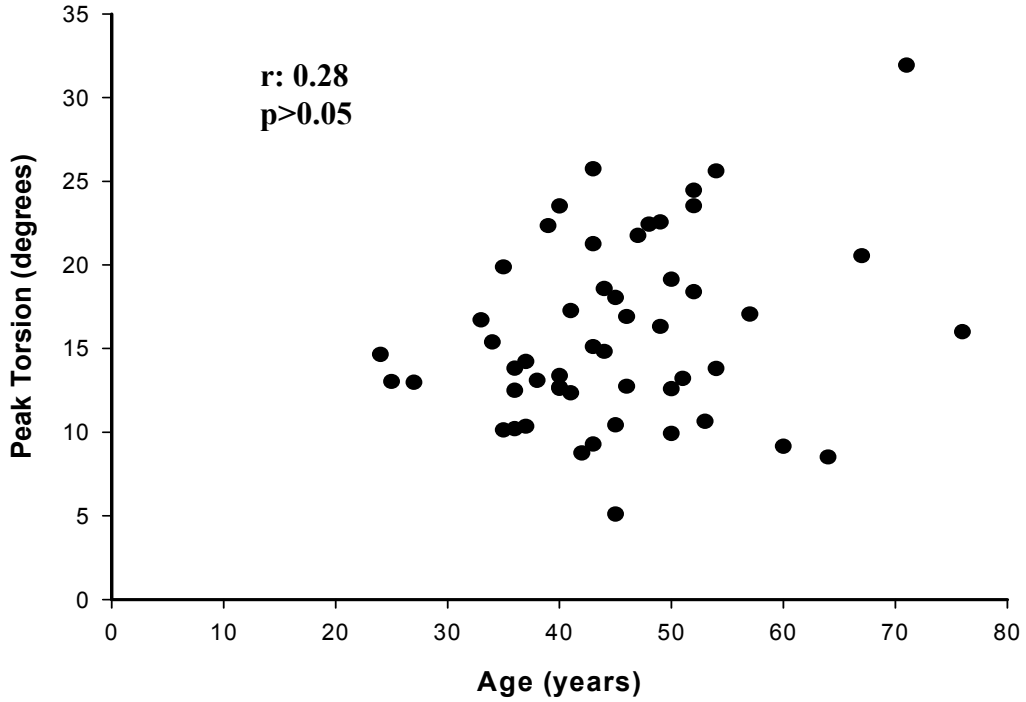


Figure 3.4. Relationship between age and peak torsion for all athletes.
Age and peak torsion were not significantly related.

3.4 Discussion

Our main finding was that peak torsion was not increased in older athletes, nor was it correlated with age. Secondly, peak untwisting rate was not slower in older athletes. Taken together, these findings suggest that long term endurance training can preserve LV rotation such that older athletes' hearts function similarly to those of younger athletes.

3.4.1 Endurance Training, Aging and Peak Torsion

Previous investigations in sedentary individuals have consistently shown that advancing age is related to increased LV torsion and slower, prolonged untwisting rates (4, 19, 24, 35, 38). Previous studies on torsion and aging have found an increase in apical rotation to be primarily responsible for the observed increased torsion. To date, two primary mechanisms have been proposed to explain why LV torsion is elevated in older individuals: 1) more synchronous timing of peak apical and basal rotation; 2) a change in the relative proportion of endocardial and epicardial shortening.

Van Dalen (2008) and colleagues have recently demonstrated that in older individuals, peak basal and apical rotation occur much closer temporally compared to younger individuals (35). Since peak torsion is calculated as the highest instantaneous difference between the apex and base, if the peak values of each component are closer together, the resulting peak torsion will be higher. Generally, with advancing age, the time of peak apical rotation is delayed so that it overlaps more closely with peak basal rotation, ultimately resulting in higher torsion (35). The underlying mechanisms of delayed apical rotation remain unknown, although it has been proposed that it may be related to the prolonged duration of contraction observed in older myocardium (17, 35). Our data

showed nearly identical group time differences in the duration between peak basal and apical rotation. The fact that apical rotation was not prolonged in our older athletes likely contributed to the non-significant group difference for peak torsion. Systolic duration was not prolonged in the older athletes, perhaps as a result of similar group afterload (as indicated by wall stress). Previous aging and torsion studies have reported potentially higher afterload (using systolic blood pressure as a surrogate), which may result in prolonged contraction, delayed peak apical rotation, and ultimately more simultaneous apical and basal rotation causing higher peak torsion (19, 35). The fact that our older athletes had significantly higher apical rotation which did not translate to higher overall torsion, suggests that the maintained basal and apical timing delay may be partially responsible for this finding.

The second proposed mechanism contributing to elevated torsion in older sedentary individuals involves an alteration in the interaction between the endocardial and epicardial layers. The muscle fibers of the endocardium and epicardium are wound oppositely and obliquely, making them responsible for generating LV rotation (32, 34). Epicardial shortening dominates myocardial rotation due to its longer distance from the centre of the LV, and overcomes the oppositional forces applied by the endocardium (31). Lumens et al. (2006) showed that endocardial function deteriorates with age, resulting in less opposition of the epicardium, and ultimately higher torsion (19). The endocardium appears to be more susceptible to ischemic episodes and increased collagen deposits, which may be the mechanism for reduced endocardial function in the elderly (6, 36). Similar to our findings of preserved rotational timings, we found no reduction in endocardial strain in older athletes. In fact, older athletes had higher endocardial

circumferential strain at the apex. In addition to preserved timing of apical rotation, it is likely that maintained endocardial function will better oppose epicardial dominated torsional motion, and result in lower peak torsion in older athletes compared to older sedentary individuals. Preserved endocardial function in older athletes may be explained by the finding in isolated myocardium that the contractile properties of the endocardium may be more responsive to exercise training compared to the epicardium (7, 9, 20, 21). This may benefit older individuals by reducing the likelihood of ischemia or collagen infiltration which could alter endocardial function.

3.4.2 Endurance Training, Aging and Recoil Rate

Previous experiments have documented slower peak rates of recoil as well as delayed recoil in older individuals (4, 19, 24, 38). The peak rate of LV recoil was not reduced in the older athletes in this investigation, nor was the time of peak recoil. We also found that the recoil rate for a given amount of torsion (as quantified by the peak recoil rate/peak torsion) did not differ between groups, suggesting a preservation of the link that rotation provides between systole and diastole (22). The spring-like protein titin, appears to play an important role in transferring energy stored during systole to diastolic relaxation (15). Sedentary aging results in increased myocardial fibrosis and stiffening (1, 14, 16) which may be related to an increased expression of the stiffer N2B titin isoform (37). A greater proportion of N2B titin may reduce the active recoil properties of the myocardium by reducing the amount of energy transferred from systole (15). However, older individuals in this investigation had preserved diastolic recoil, suggesting that endurance training may help maintain the properties of a younger myocardium (including titin isoform ratio)

in older athletes. The strong correlation between recoil rate and peak torsion also suggests that the link between systolic and diastolic rotation is preserved in all athletes.

The fact that the percentage of recoil which occurred by mitral valve opening was higher in older athletes is further evidence to support the notion that endurance training has helped to preserve myocardial function in older athletes. We have previously reported similar results for older and younger individuals (11); however, in response to exercise, the older individuals drastically reduced the amount of recoil which occurred prior to mitral valve opening, whereas younger individuals maintained approximately the same amount of recoil as during rest. Only resting measures were taken in this investigation, so we can only speculate about what would occur during exercise. Young individuals increase LV peak torsion and recoil rate during exercise, whereas older individuals cannot (4, 11, 22). We reason that older endurance-trained individuals would likely be able to augment LV torsion and recoil during exercise to a greater extent than sedentary age-matched individuals, but still not to the same degree as young individuals. However, future investigations are needed to clarify the LV rotational response in older endurance trained athletes.

3.4.3 Global LV Function and Myocardial Strains

Similar to previous investigations, we found ejection fraction, as well as circumferential and longitudinal strains to be similar in older and younger individuals (24). Although many systolic parameters were similar (including peak torsion) between groups, the diastolic indices of septal E' and E/A were reduced in older athletes. Diastolic indices appear to be more commonly reduced with age, and this investigation would support the notion that not all of the deleterious effects of age can be completely offset by

endurance training (2, 12). It is also possible that the differences in E/A and E' are simply related to lower preload in the older athletes.

3.4.4 Limitations and Future Directions

The findings of this investigation should be considered with some limitations in mind. First, our information regarding training history was based on self-report, although all individuals were scheduled to run a 160km race. A more quantitative assessment of aerobic fitness, such as VO_2 max may have been beneficial. Since our aim was to examine the effects of endurance-training on age related changes in LV rotation, we used a young athletic group to act as a comparison. The inclusion of sedentary individuals (both young and old) would have allowed us to contrast our findings with the effects of sedentary aging; however, numerous investigations have previously demonstrated the influence of age on LV rotation (4, 19, 22, 24, 35). Our group disparities in age were not as large as in many previous investigations examining aging effects on cardiac function (19, 24), yet we feel that since LV torsion was not significantly related to age, our results would have been similar had we examined more disparate groups.

3.5 Conclusions

The major findings of this investigation suggest that prolonged endurance-training can help mitigate the adverse effects of age on LV peak torsion and recoil rate. These results add to the body of literature suggesting that endurance exercise training can preserve myocardial function in older athletes so that it is similar to younger individuals.

3.6 Chapter Three References

1. **Arbab-Zadeh A, Dijk E, Prasad A, Fu Q, Torres P, Zhang R, Thomas JD, Palmer D, and Levine BD.** Effect of aging and physical activity on left ventricular compliance. *Circulation* 110: 1799-1805, 2004.
2. **Baldi JC, McFarlane K, Oxenham HC, Whalley GA, Walsh HJ, and Doughty RN.** Left ventricular diastolic filling and systolic function of young and older trained and untrained men. *J Appl Physiol* 95: 2570-2575, 2003.
3. **Beyar R and Sideman S.** Effect of the twisting motion on the nonuniformities of transmyocardial fiber mechanics and energy demand--a theoretical study. *IEEE Trans Biomed Eng* 32: 764-769, 1985.
4. **Burns AT, La Gerche A, Macisaac AI, and Prior DL.** Augmentation of Left Ventricular Torsion with Exercise is Attenuated with Age. *J Am Soc Echocardiogr*, 2007.
5. **Burns ATM, I.G. Thomas, J.D. MacIsaac, A. and Prior, D.** Doin' the twist: new tools for an old concept of myocardial function. *Heart* 94: 978-983, 2008.
6. **Capasso JM, Palackal T, Olivetti G, and Anversa P.** Severe myocardial dysfunction induced by ventricular remodeling in aging rat hearts. *Am J Physiol* 259: H1086-1096, 1990.
7. **Cazorla O, Ait Mou Y, Goret L, Vassort G, Dauzat M, Lacampagne A, Tanguy S, and Obert P.** Effects of high-altitude exercise training on contractile function of rat skinned cardiomyocyte. *Cardiovasc Res* 71: 652-660, 2006.
8. **Devereux RB and Reichek N.** Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. *Circulation* 55: 613-618, 1977.
9. **Diffee GM and Nagle DF.** Regional differences in effects of exercise training on contractile and biochemical properties of rat cardiac myocytes. *J Appl Physiol* 95: 35-42, 2003.
10. **DuBois D DE.** A formula to estimate the approximate surface area if height and weight be known. *Arch Int Med* 17: 863-871, 1916.
11. **Esch BT, Scott JM, Warburton DE, Thompson R, Taylor D, Cheng Baron J, Paterson I, and Haykowsky MJ.** Left ventricular torsion and untwisting during exercise in heart transplant recipients. *J Physiol* 587(10): 2375-2386, 2009.
12. **Fleg JL, Shapiro EP, O'Connor F, Taube J, Goldberg AP, and Lakatta EG.** Left ventricular diastolic filling performance in older male athletes. *Jama* 273: 1371-1375, 1995.
13. **Fukuda N, Sasaki D, Ishiwata S, and Kurihara S.** Length dependence of tension generation in rat skinned cardiac muscle: role of titin in the Frank-Starling mechanism of the heart. *Circulation* 104: 1639-1645, 2001.
14. **Harris TS, Baicu CF, Conrad CH, Koide M, Buckley JM, Barnes M, Cooper Gt, and Zile MR.** Constitutive properties of hypertrophied myocardium: cellular contribution to changes in myocardial stiffness. *Am J Physiol Heart Circ Physiol* 282: H2173-2182, 2002.
15. **Helmes M, Lim CC, Liao R, Bharti A, Cui L, and Sawyer DB.** Titin determines the Frank-Starling relation in early diastole. *J Gen Physiol* 121: 97-110, 2003.

16. **Lakatta EG.** Cardiovascular aging research: the next horizons. *J Am Geriatr Soc* 47: 613-625, 1999.
17. **Lakatta EG, Gerstenblith G, Angell CS, Shock NW, and Weisfeldt ML.** Prolonged contraction duration in aged myocardium. *J Clin Invest* 55: 61-68, 1975.
18. **Levine BD, Lane LD, Buckey JC, Friedman DB, and Blomqvist CG.** Left ventricular pressure-volume and Frank-Starling relations in endurance athletes. Implications for orthostatic tolerance and exercise performance. *Circulation* 84: 1016-1023, 1991.
19. **Lumens J, Delhaas T, Arts T, Cowan BR, and Young AA.** Impaired subendocardial contractile myofiber function in asymptomatic aged humans, as detected using MRI. *Am J Physiol Heart Circ Physiol* 291: H1573-1579, 2006.
20. **Natali AJ, Turner DL, Harrison SM, and White E.** Regional effects of voluntary exercise on cell size and contraction-frequency responses in rat cardiac myocytes. *J Exp Biol* 204: 1191-1199, 2001.
21. **Natali AJ, Wilson LA, Peckham M, Turner DL, Harrison SM, and White E.** Different regional effects of voluntary exercise on the mechanical and electrical properties of rat ventricular myocytes. *J Physiol* 541: 863-875, 2002.
22. **Notomi Y, Martin-Miklovic MG, Oryszak SJ, Shiota T, Deserranno D, Popovic ZB, Garcia MJ, Greenberg NL, and Thomas JD.** Enhanced ventricular untwisting during exercise: a mechanistic manifestation of elastic recoil described by Doppler tissue imaging. *Circulation* 113: 2524-2533, 2006.
23. **Notomi Y, Srinath G, Shiota T, Martin-Miklovic MG, Beachler L, Howell K, Oryszak SJ, Deserranno DG, Freed AD, Greenberg NL, Younoszai A, and Thomas JD.** Maturational and adaptive modulation of left ventricular torsional biomechanics: Doppler tissue imaging observation from infancy to adulthood. *Circulation* 113: 2534-2541, 2006.
24. **Oxenham HC, Young AA, Cowan BR, Gentles TL, Occleshaw CJ, Fonseca CG, Doughty RN, and Sharpe N.** Age-related changes in myocardial relaxation using three-dimensional tagged magnetic resonance imaging. *J Cardiovasc Magn Reson* 5: 421-430, 2003.
25. **Palka P, Lange A, and Nihoyannopoulos P.** The effect of long-term training on age-related left ventricular changes by Doppler myocardial velocity gradient. *Am J Cardiol* 84: 1061-1067, 1999.
26. **Popovic ZB, Prasad A, Garcia MJ, Arbab-Zadeh A, Borowski A, Dijk E, Greenberg NL, Levine BD, and Thomas JD.** Relationship among diastolic intraventricular pressure gradients, relaxation, and preload: impact of age and fitness. *Am J Physiol Heart Circ Physiol* 290: H1454-1459, 2006.
27. **Port S, Cobb FR, Coleman RE, and Jones RH.** Effect of age on the response of the left ventricular ejection fraction to exercise. *N Engl J Med* 303: 1133-1137, 1980.
28. **Prasad A, Popovic ZB, Arbab-Zadeh A, Fu Q, Palmer D, Dijk E, Greenberg NL, Garcia MJ, Thomas JD, and Levine BD.** The effects of aging and physical activity on Doppler measures of diastolic function. *Am J Cardiol* 99: 1629-1636, 2007.
29. **Reichek N, Wilson J, St John Sutton M, Plappert TA, Goldberg S, and Hirshfeld JW.** Noninvasive determination of left ventricular end-systolic stress: validation of the method and initial application. *Circulation* 65: 99-108, 1982.

30. **Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I, and et al.** Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 2: 358-367, 1989.
31. **Sengupta PP, Khandheria BK, and Narula J.** Twist and untwist mechanics of the left ventricle. *Heart Fail Clin* 4: 315-324, 2008.
32. **Streeter DD, Jr., Spotnitz HM, Patel DP, Ross J, Jr., and Sonnenblick EH.** Fiber orientation in the canine left ventricle during diastole and systole. *Circ Res* 24: 339-347, 1969.
33. **Takeuchi M, Nakai H, Kokumai M, Nishikage T, Otani S, and Lang RM.** Age-related changes in left ventricular twist assessed by two-dimensional speckle-tracking imaging. *J Am Soc Echocardiogr* 19: 1077-1084, 2006.
34. **Torrent-Guasp F, Ballester M, Buckberg GD, Carreras F, Flotats A, Carrio I, Ferreira A, Samuels LE, and Narula J.** Spatial orientation of the ventricular muscle band: physiologic contribution and surgical implications. *J Thorac Cardiovasc Surg* 122: 389-392, 2001.
35. **van Dalen BM, Soliman OI, Vletter WB, ten Cate FJ, and Geleijnse ML.** Age-related changes in the biomechanics of left ventricular twist measured by speckle tracking echocardiography. *Am J Physiol Heart Circ Physiol* 295: H1705-1711, 2008.
36. **Van Der Toorn A, Barenbrug P, Snoep G, Van Der Veen FH, Delhaas T, Prinzen FW, Maessen J, and Arts T.** Transmural gradients of cardiac myofiber shortening in aortic valve stenosis patients using MRI tagging. *Am J Physiol Heart Circ Physiol* 283: H1609-1615, 2002.
37. **Wu Y, Bell SP, Trombitas K, Witt CC, Labeit S, LeWinter MM, and Granzier H.** Changes in titin isoform expression in pacing-induced cardiac failure give rise to increased passive muscle stiffness. *Circulation* 106: 1384-1389, 2002.
38. **Zhang L, Xie M, and Fu M.** Assessment of age-related changes in left ventricular twist by two-dimensional ultrasound speckle tracking imaging. *J Huazhong Univ Sci Technolog Med Sci* 27: 691-695, 2007.

[1]CHAPTER FOUR: Left Ventricular Torsion and Untwisting during Exercise in Heart transplant Recipients

4.1 Introduction

During systole, opposite circumferential rotation of the base (clockwise) and apex (counter-clockwise) results in left ventricular (LV) torsional deformation which assists the ejection of blood (7). Conversely, in early diastole the release of stored elastic energy is strongly associated with the reversal of torsion (untwisting) and rapid reductions in LV pressure (16, 33). Rapid, early untwisting ultimately allows the LV to fill at relatively low left atrial pressures (32, 42). Since almost half of ventricular untwisting occurs prior to mitral valve opening (32), the quantification of LV untwisting is an important measure of early, active relaxation (10). Rapid LV untwisting has been shown to be associated with the generation of intraventricular pressure gradients (IVPG), which provide an index of diastolic suction (31, 32). The ability to augment LV untwisting during exercise, given its relation to diastolic suction, is an important factor for increasing the rate of LV filling when diastolic time is reduced (11, 32).

A slow rate of ventricular untwisting may contribute to the impaired diastolic function observed in heart transplant recipients (HTR). The typical hemodynamic response to exercise in HTR includes a blunted increase in end-diastolic volume despite high LV filling pressures (25). The likely causes for this sub-optimal pattern of LV filling are cardiac denervation, immunosuppressive therapy, and a stiff vasculature (38). Ineffective

[1] A version of this chapter has been previously published as: BT Esch, JM Scott, DER Warburton, R Thompson, D Taylor, J Cheng-Baron, I Paterson, MJ Haykowsky (2009). Left Ventricular Torsion and Untwisting during Exercise in Heart transplant Recipients. *The Journal of Physiology* 587 (10): 2375-2386.

LV untwisting may also contribute to the reduced diastolic function commonly observed in HTR.

In response to exercise, young healthy individuals can increase LV torsion, twisting, and untwisting velocities (32); however, with exercise healthy older individuals (> 60 years) generally demonstrate attenuated peak torsion, and peak untwisting rates (9). In HTR the donor heart is, on average, nearly two-decades younger than the recipient age (48); therefore, how exercise will affect LV torsion and untwisting rate in HTR is uncertain. We sought to compare LV torsion, untwisting rates and IVPG during sub-maximal exercise in HTR with both young and old healthy individuals in an attempt to better understand the impaired diastolic function in HTR. In addition, we examined myocardial strain (percent shortening) and strain rates in the longitudinal, radial and circumferential planes in order to provide indices of cardiac function across all three planes of motion in addition to rotational measures. We hypothesized that, similar to healthy older individuals, HTR would be unable to increase peak torsion, circumferential strain and the peak rate of LV untwisting, and would also have lower peak IVPG than young individuals in response to exercise.

4.2 Methods

4.2.1 Ethical Approval

This study was approved by the University of Alberta Health Research Ethics Board (Biomedical Panel), and all participants provided written informed consent prior to the experiment. This investigation was conducted in accordance with the declaration of Helsinki.

4.2.2 Participants

Twenty males were recruited to complete resting and sub-maximal exercise echocardiographic examinations. One individual was excluded from the study due to poor echocardiography image quality. The participants included eight clinically stable HTR, and eleven healthy, activity matched controls (six matched for the recipient age (RM), and five matched for the donor age (DM)).

4.2.3 Protocol

Each participant underwent resting and exercise cardiac ultrasound assessment while seated on a modified cycle ergometer (back supported at 105°). Heart rate (electrocardiography) and blood pressure (cuff sphygmomanometer) were recorded concurrently at rest and during exercise. Following resting evaluations, participants cycled at a power output equivalent to 80% of their ventilatory threshold. As part of a larger investigation, participants completed an assessment of VO_{2peak} and ventilatory threshold on a separate day (43). The workload equivalent to the power output at 80% of ventilatory threshold allowed us to make group comparisons at the same relative intensity while maximizing exercise image quality. Participants cycled continuously at the set power output for 20 minutes, while echocardiography began after five minutes of cycling and lasted approximately 15 minutes.

4.2.4 Echocardiography

M-mode recordings were made at both the aortic and mitral valves to quantify valve opening and closure times with respect to the onset of the QRS complex. Two-dimensional transthoracic images were acquired using the parasternal short axis view at

the level of the base (mitral valve), mid-ventricle (papillary muscles) and apex (distal to the papillary muscles) with a Vivid-i cardiac ultrasound (GE Medical Systems, Wauwatosa, Wisconsin, USA) at high frame rates (60-90 Hz). Apical 4-chamber images were also obtained in each participant. Pulsed Doppler was recorded at the tips of the mitral leaflets to assess peak early mitral inflow velocity (E). Peak lateral mitral annular velocity during early diastole ($E^{'}$) was recorded at rest and during exercise. Color M-mode images of mitral inflow (apical 4-chamber) were also recorded for each participant. The data was acquired in the order listed above at a stable heart rate throughout (±2 beats/min).

4.2.5 Data Analysis

Two-dimensional and Doppler data were analyzed using EchoPAC software (GE Healthcare, USA). Speckle-tracking analysis was applied to the basal and apical short axis images in order to quantify circumferential rotation and strain as well as radial displacement, radial strain and the rates of change in these parameters (appendix B). Speckle-tracking analysis requires the manual tracing of the endocardium, and an adjustment of the "tracking area" to fit the width of the myocardium. Each image is automatically tracked from the onset of the QRS complex for one cardiac cycle and is scored between 1.0 (optimal) and 3.0 (non-tracking) based on tracking quality. Only images with a tracking score of 2.0 or less were included in the analysis.

Left ventricular torsion was calculated as the difference between the apical and basal rotations from which peak torsion, peak twisting and peak untwisting rates were derived (44). Radial displacements, circumferential and radial strain as well as strain rate data were averaged between the basal and apical slices. The rate of radial displacement,

towards the centre of the LV (systole) or in diastole (radial expansion), were also quantified. In addition, the apical 4-chamber data were analyzed with speckle-tracking to quantify longitudinal strain and strain rate. From the 4-chamber speckle-data, longitudinal contraction (systole) and lengthening (diastole) were quantified. From all speckle-tracking analysis, the raw data files were saved to a personal computer where data was averaged over 3 heart beats to produce the data in figures 1-3. Event timing was calculated as a percentage of systole, with the onset of QRS being 0% and aortic valve closure equivalent to 100%. For each participant systole occurred from 0 to 100%, whereas diastole was from 100% onward. Due to data being acquired at different frame rates and different heart rates, cubic spline interpolation (Matlab, Mathworks,USA) was used to determine data points at 2% increments of systolic duration throughout the cardiac cycle.

Pulsed Doppler was used to quantify E, as well as the time of E. Tissue Doppler data were used to assess E', and E/E' was calculated. E/E' has previously been shown to be related to pulmonary capillary wedge pressure (47). All Doppler and two-dimensional (speckle-tracking included) data were analyzed and averaged over three cardiac cycles. IVPG were calculated with custom software using Euler's equation with input velocity data from color M-mode images, as previously described (19). Briefly, the color M-mode image, which is composed of mitral inflow color-coded velocity data from the mitral leaflets to the apex, is read into a custom software program which extracts the spatial and temporal velocity map. Once the velocities are obtained, Euler's equation is applied to calculate instantaneous pressure gradients. To provide an index of afterload, systolic wall stress was calculated as: (1.33 x systolic blood pressure) x (end-systolic cavity area /

myocardial area) (20). Mean arterial pressure, LV mass and LV volumes were calculated using standard formulas (13, 49).

4.2.6 Statistics

A repeated measures ANOVA was applied to identify differences across intensity with Tukey's post hoc comparisons (Statistica 6.0, USA). Independent t-tests were used to identify group differences including changes from rest to exercise. Data are presented as mean ± standard deviation, and significance was set at $p<0.05$.

4.3 Results

4.3.1 Participants

Participant characteristics are described in table 4.1. By design HTR (61 ± 9 years) and RM (60 ± 12 years) were significantly older than DM (35 ± 8 years). HTR were 7.4 ± 6.2 (range 2.5-21.3) years post transplant. All HTR were on standard immunosuppressive therapy (43). Participants successfully completed the exercise session at a similar relative percentage of ventilatory threshold heart rate (HTR: 86 ± 7%; RM: 82 ± 7%; DM: 80 ± 8%).

Table 4.1: Participant characteristics. * indicates different from DM ($p<0.05$).

	HTR (n=8)	**RM** (n=6)	**DM** (n=5)
Height (cm)	173 ± 8	174 ± 10	177 ± 11
Mass (kg)	78 ± 12	79 ± 7	78 ± 4
Left Ventricular Mass (g)	182 ± 43	172 ± 27	204 ± 60
$V0_2$ max (mL/kg/min)	24.2 ± 10.9*	36.3 ± 10.7	51.1 ± 10.4

4.3.2 Hemodynamics

There was no significant difference in resting or exercise heart rate between groups; however DM exhibited a greater heart rate increase with exercise compared to HTR and RM ($p<0.05$, table 4.2). There were no group differences at rest or during exercise in ejection fraction; however, all three groups increased ejection fraction in response to exercise with DM (13.2 ± 4.0 %) having greater increases than HTR (5.3 ± 4.4 %) and RM (7.5 ± 3.2 %, $p<0.05$). Neither end-diastolic nor end-systolic volumes were different between groups at rest; however, DM had a significantly greater increase in exercising end-diastolic volume compared to HTR ($p<0.05$, table 4.2). In addition, DM (-8.5 ± 4.0 mL) reduced end-systolic volume more during exercise compared to HTR (0.5 ± 5.4 mL) and RM (-1.6 ± 3.4 mL, $p<0.05$). Rest and exercise data for peak E, E', E/E' and IVPG are shown in table 4.2. The change in peak IVPG from rest to exercise was 1.3-fold higher in DM versus HTR or RM ($p>0.05$, table 4.2). Mean arterial pressure was not different between groups at rest (HTR: 89.6 ± 7.2 mmHg; RM: 88.8 ± 6.1 mmHg; DM: 83.5 ± 4.3 mmHg) or in response to exercise (HTR: 97.2 ± 10.0 mmHg; RM: 97.2 ± 5.4 mmHg; DM: 98.2 ± 3.8 mmHg). Systolic wall stress was not different between groups at rest (HTR: 67.7 ± 12.5 dynes/cm^2; RM: 60.6 ± 10.8 dynes/cm^2; DM: 58.8 ± 15.2 dynes/cm^2) or during sub-maximal exercise (HTR: 75.0 ± 19.2 dynes/cm^2; RM: 59.3 ± 10.1 dynes/cm^2; DM: 56.1 ± 20.1 dynes/cm^2); however, it should be noted that wall stress was reduced in response to exercise in RM and DM, but increased in HTR.

	HTR (n=8)	**RM** (n=6)	**DM** (n=5)
Heart Rate (beats/min)			
Rest	89±9.4	67±13.1	65±9.9
Exercise	118±12.2*	110±11.2*	125±6.9*
Change	29±15.4†	43±12.5†	60±10.2
End-diastolic Volume (mL)			
Rest	88.9±23.0	97.5±2.6	110.1±20.1
Exercise	103.4±27.0*	119.8±5.0*	135.8±24.2*
Change	14.5±7.3†	22.3±3.4	25.7±6.2
Mitral E (cm/sec)			
Rest	61.7±9.3	47.6±4.9	64.0 ± 14.1
Exercise	96.9±22.2*	87.3±20.2*	106.0 ± 18.6*
Change	35.2±20.6	39.7±17.2	42.0±9.7
Lateral E' (cm/sec)			
Rest	9.7±3.2	8.9±1.7	10.6±1.4
Exercise	16.2±3.4*	13.7±2.3*	18.6±3.5*
Change	6.5±2.5	4.8±2.1†	8.0±2.3
E/E'			
Rest	7.1±3.2	5.5±1.3	6.0±0.9
Exercise	6.3±2.0	6.4±0.9	5.7±0.5
Change	-0.8±2.0	0.9±0.9 †	-0.3±0.6
Peak IVPG (mmHg)			
Rest	2.0±0.5	1.7±0.5	2.2±0.8
Exercise	4.7±2.1*	4.4±1.3*	5.8±1.6*
Change	2.7±1.8	2.7±1.0	3.6±1.7
% Untwisted at MVO			
Rest	45.1±10.8	52.9±4.1	38.3±11.5
Exercise	28.8±22.8	27.2±19.7	39.7±12.5
Change	-16.3±24.8	-25.7±22.7†	1.4±13.4
Peak Untwisting Rate (rads/sec)			
Rest	-2.1±0.7	-2.3±0.9	-1.6±0.6
Exercise	-2.3±0.7	-3.0±1.3	-3.7±0.8*
Change	-0.2±0.9†	-0.7±1.3	-2.1±0.5
Peak Torsion (degrees)			
Rest	15.6±6.0	19.1±6.0	14.9±2.4
Exercise	14.7±3.4	16.5±5.0	21.5±5.5
Change	-0.9±4.4†	-2.6±7.0†	6.5±5.6

Table 4.2: LV torsion and indices of diastolic function at rest and during exercise.
* indicates different from rest ($p<0.05$), † indicates different from DM ($p<0.05$).

4.3.3 Event Timing and Speckle-tracking

Peak torsion in DM was significantly elevated with exercise compared to HTR and RM (Figure 4.1). With exercise, HTR and RM decreased peak torsion despite increased radial shortening (Figure 4.2). Mean torsion-displacement loops at rest and exercise revealed a linear systolic portion, and a non-linear diastolic portion in all groups (Figure 4.2).

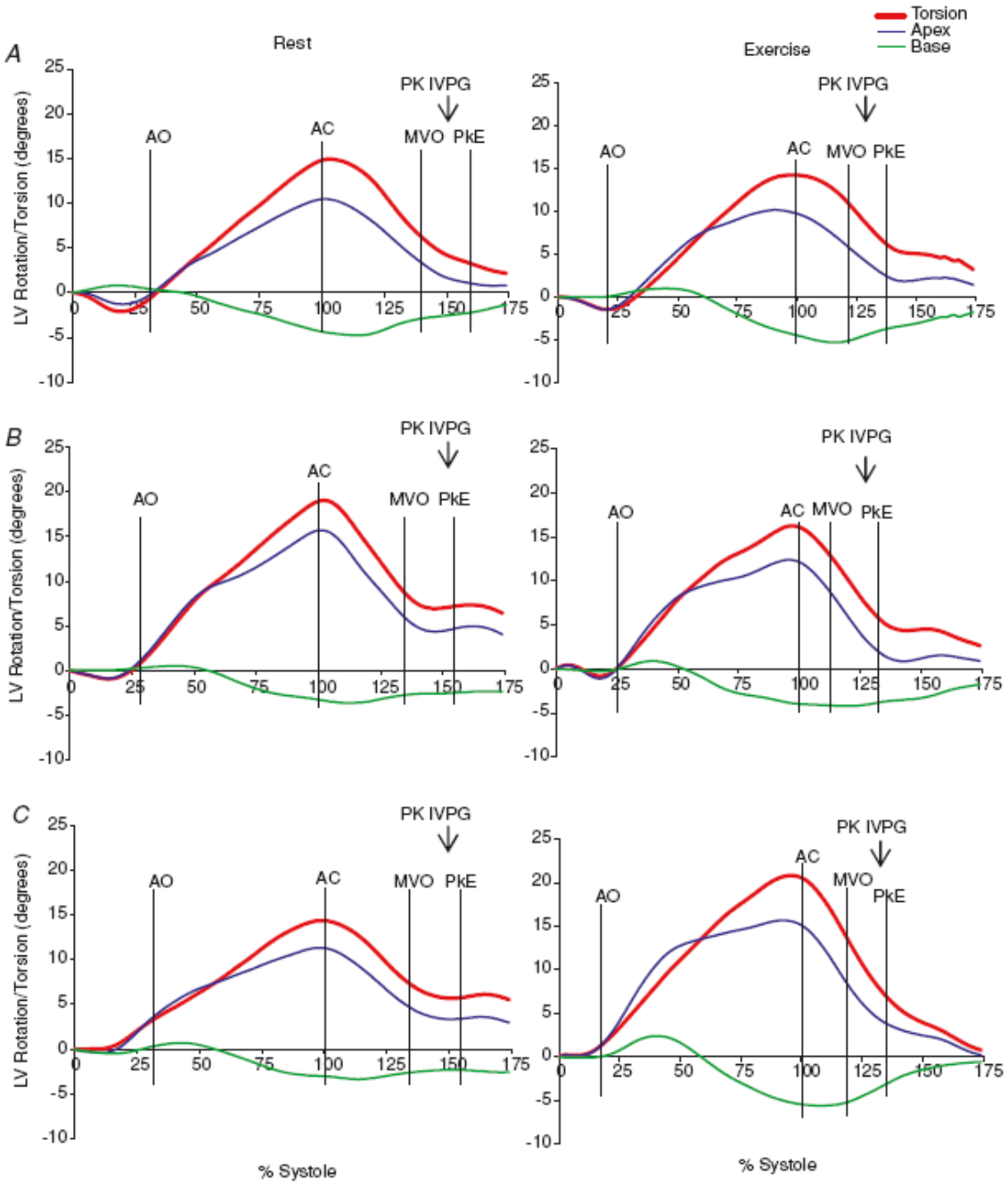


Figure 4.1. Left ventricular torsion at rest and exercise.
LV torsion at rest (left) and during exercise (right) for (A) HTR, (B) RM and (C) DM. Torsion is represented by the red line, apical twist/untwist by the blue, and basal twist/untwist by the green. The change in peak torsion from rest to exercise was significantly greater in DM compared to RM and HTR. The black lines indicate event timing: AO: aortic valve opening, AC: aortic valve closure, MVO: mitral valve opening, PK IVPG: peak intraventricular pressure gradient, PKE: peak early filling velocity.

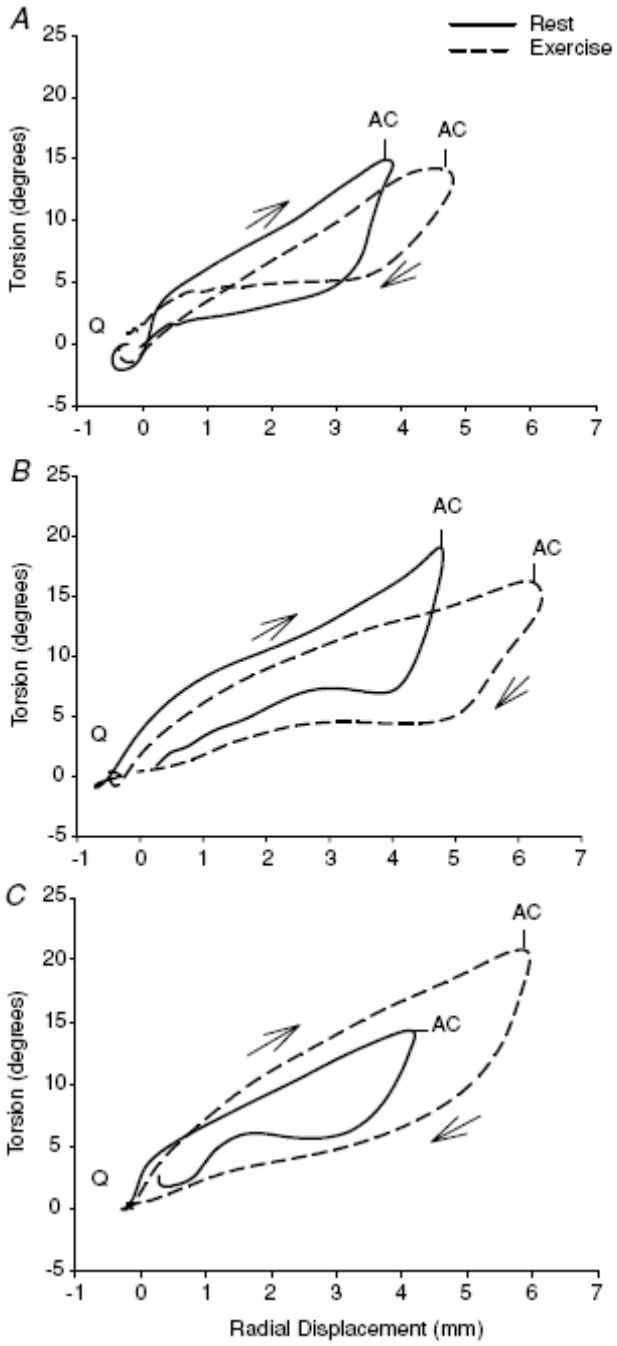


Figure 4.2. Torsion-radial displacement loops.
Torsion-Radial Displacement Loops for (A) HTR, (B) RM and (C) DM during rest (solid line) and exercise (dashed line). Note the reductions in peak torsion in response to exercise in HTR (A) and RM (B), despite the increased radial displacement. Data begins and ends at the onset of the QRS complex (Q). End-systole is at aortic valve closure (AC).

The peak rate of LV untwisting occurred prior to mitral valve opening, which preceded peak IVPG, and was followed by E (Figure 4.3). There were no group differences in the timing of peak LV untwisting, mitral valve opening or peak IVPG. The percentage of LV untwisting that occurred prior to mitral valve opening was similar at rest and exercise in DM, yet declined dramatically from rest to exercise in RM and HTR (table 4.2).

There were no group differences for the peak rate of twisting at rest and sub-maximal exercise; however, DM had a greater change in peak twisting velocity compared to RM. DM also exhibited a significantly greater increase from rest to exercise in the peak rate of untwisting compared to HTR and RM ($p<0.05$, Figure 4.3). There were no group differences in the rates of longitudinal or radial contraction at rest or exercise, but the diastolic peak rates of radial expansion and lengthening changed from rest to exercise to a greater extent in DM compared to HTR and RM ($p<0.05$, Figure 4.3).

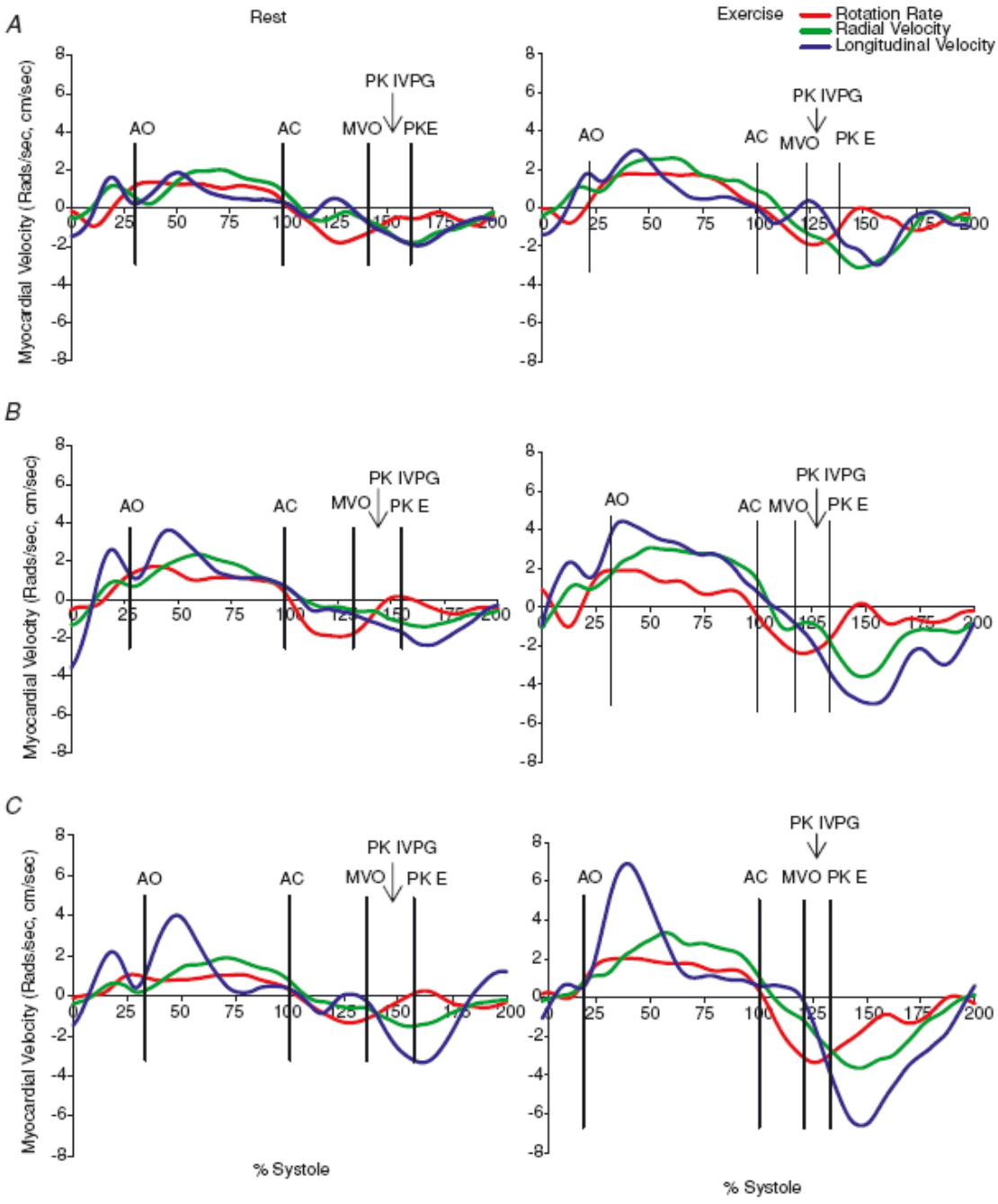


Figure 4.3. Ventricular velocity curves
Average cardiac cycles for rotational rate, radial velocity and longitudinal myocardial velocities at rest (left) and exercise (right) for (A) HTR, (B) RM, and (C) DM. The red line represents the circumferential rotation rate (rads•sec^{-1}), the green line is radial velocity (cm•sec^{-1}) and the blue line is longitudinal velocity (cm•sec^{-1}). Note the increase in peak untwisting rate in DM compared to HTR and RM. The black lines indicate event timing; abbreviations are the same as for figure 1.

Longitudinal and radial strains were similar between groups; however, DM had a significantly greater increase in systolic circumferential strain rate compared to HTR ($p<0.05$). Additionally, the diastolic circumferential strain rate increased twice as much in DM compared to HTR in response to exercise; but this was not statistically significant. For complete circumferential, longitudinal, and radial strain and strain rate data see table 4.3.

Table 4.3: Systolic (S) and diastolic (D) strains. (*) different from rest, (†) different from DM ($p<0.05$).

	HTR (n=8)	**RM** (n=6)	**DM** (n=5)
Circumferential Strain (%)			
Rest	-14.9±3.5	-19.3±3.1	-15.9±2.7
Exercise	-17.0±3.1	-22.7±5.1	-21.8±2.9
Change	-2.1±4.2	-3.4±6.4	-5.9±1.7
Longitudinal Strain (%)			
Rest	-10.1±3.9	-14.2±3.8	-11.8±2.1
Exercise	-13.4±4.5	-17.7±5.0	-16.9±3.2*
Change	-3.3±1.6	-3.5±5.3	-5.1±3.1
Radial Strain (%)			
Rest	25.5±8.6	26.9±8.8	23.2±0.4
Exercise	27.9±8.2	32.0±5.9	36.0±6.4
Change	2.4±10.3	5.1±8.4	12.8±6.7
Circumferential Strain Rate S (%•s^{-1})			
Rest	-1.2±0.2	-1.5±0.5	-1.1±0.1
Exercise	-1.5±0.4	-2.0±0.3	-1.9±0.3*
Change	-0.3±0.4†	-0.5±0.4	-0.8±0.2
Circumferential Strain Rate D (%•s^{-1})			
Rest	1.3±0.5	1.4±0.4	1.2±0.2
Exercise	1.9±0.5*	2.3±0.5*	2.4±0.2*
Change	0.6±0.5	0.9±0.5	1.2±0.3
Longitudinal Strain Rate S (%•s^{-1})			
Rest	-0.8±0.2	-1.0±0.3	-0.8±0.2
Exercise	-1.1±0.4	-1.3±0.3	-1.4±0.3*
Change	-0.3±0.3	-0.3±0.4	-0.7±0.3
Longitudinal Strain Rate D (%•s^{-1})			
Rest	0.8±0.2	0.9±0.3	0.8±0.2
Exercise	1.6±0.6*	1.4±0.3	1.6±0.2*
Change	0.8±0.4	0.5±0.4	0.8±0.2
Radial Strain Rate S (%•s^{-1})			
Rest	2.0±0.4	1.8±0.4	1.2±0.2
Exercise	2.7±0.7*	2.9±0.5*	2.4±0.5*
Change	0.7±0.7	1.1±0.2	1.2±0.4
Radial Strain Rate D (%•s^{-1})			
Rest	-2.0±0.5	-1.6±0.3	-1.5±0.3
Exercise	-2.6±0.8	-2.7±0.4*	-3.0±0.6*
Change	-0.6±1.0	-1.1±0.5	-1.5±0.6

There was a significant correlation for all groups (data combined) between the change in end-systolic volume from rest to exercise with the change in peak rate of untwisting ($r=0.52$, $p<0.05$) and change in IVPG ($r=-0.58$, $p<0.05$). However, the strongest predictor of the ability to augment peak untwisting rate with exercise was the change in circumferential systolic strain rate ($r=0.68$, $p<0.05$, Figure 4.4).

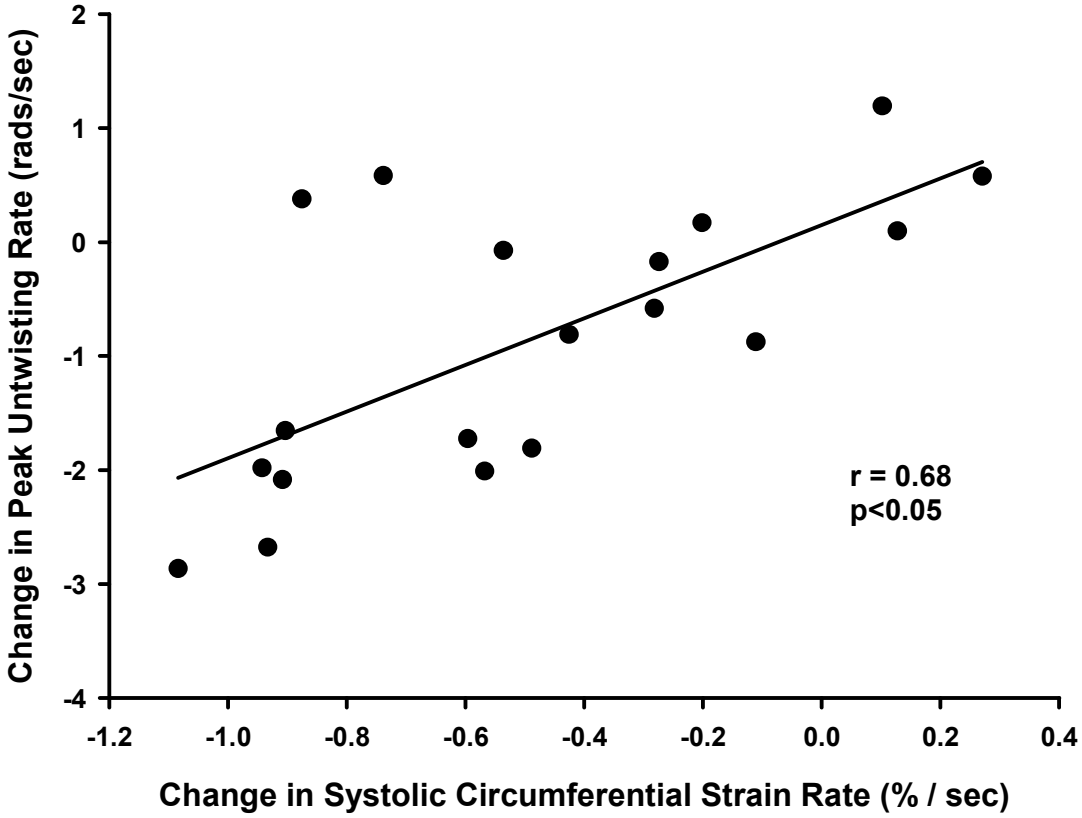


Figure 4.4. Relationship between the change from rest to exercise in the peak rate of untwisting and the change of circumferential strain rate in systole.
The data is combined for all groups ($r=0.68$, $p<0.05$).

4.4 Discussion

Our major new finding was that in response to exercise, HTR did not increase peak torsion or untwisting rate. Although LV peak torsion and peak untwisting rates are augmented in DM with exercise, RM are unable to do so. In addition, exercise resulted in a substantial reduction in the amount of LV untwisting that occurred prior to mitral valve opening in HTR and RM, while DM maintained a similar percentage of untwisting at rest and exercise. The blunted LV untwisting response to exercise observed in HTR, likely contributes to their impaired diastolic function. The similarities between HTR and RM during exercise are notable given that a "younger" denervated donor heart coupled with immunosuppressive therapy and potentially stiff vasculature functions as though it were 25 years older.

4.4.1 Effect of Aging on LV Torsion and Untwisting

Rest

LV torsion and peak untwisting rates were similar between all groups at rest, although RM had the highest torsion. Previous research in healthy aging has shown resting LV torsion to be elevated in older individuals (9, 36), which is thought to be the result of reduced endocardial function (28). Normally, the sub-endocardial and sub-epicardial layers oppose each other during contraction due to their oblique fiber angle orientations (46). Greater force is generated in the epicardial layer as a result of the longer distance from the center of the ventricle (10, 44). This results in the direction of LV rotation favoring the epicardium. Lumens et al. (2006) demonstrated that in healthy aging, sub-endocardial shortening is reduced, resulting in less opposition to epicardial contraction,

ultimately leading to greater LV rotation at rest (28). Specific sub-endocardial dysfunction may occur in older individuals due to the fact that the sub-endocardium is more susceptible to reductions in coronary perfusion and greater incidence of fibrosis (3, 29). Sub-endocardial dysfunction may also occur in HTR as a result of ischemic reperfusion injury or immunosuppressive therapy, however, it did not appear to affect resting LV torsion in this investigation (2, 26, 37).

DM exhibited higher E, E', and IVPG at rest compared to RM and HTR (table 4.2). The disparities in resting diastolic function between DM and RM are likely not as great as previously reported since RM in the present investigation were younger than in other studies (40, 41). Our finding of a similar percentage of LV untwisting prior to mitral valve opening in all groups is supportive of previous findings suggesting isovolumic pressure decay is not reduced in older individuals at rest (22, 53).

Exercise

Reduced endocardial function is a plausible explanation for the high resting LV torsions observed in RM, yet the reasons for an inability to augment torsion with exercise in RM are not explained by this theory. It has been proposed that a high resting torsion simply leaves the LV with little rotational reserve for exercise (9). However, since LV torsion in HTR was not elevated at rest, it is likely that the inability to increase torsion with exercise in HTR may differ in its mechanism from RM.

All groups increased E, E', and IVPG in response to exercise. DM had a 33% larger increase in IVPG compared to RM and HTR which may be related to the greater increases in peak untwisting rate associated with enhance relaxation (40). The drastic reduction in the percentage of untwisting which occurred prior to mitral valve opening

during exercise in RM and HTR also may have had a significant effect on IVPG and ultimately change in end-diastolic volume. LV untwisting that occurs after mitral valve opening is less efficient as it does not contribute to isovolumic pressure decay (34).

Although HTR were unable to increase LV torsion with exercise to the extent DM could, the similarities between RM and HTR should be viewed positively from a clinical standpoint. Given years of immunosuppressive therapy, a stiff vasculature, and pre-transplant heart failure it bodes well for HTR if their hearts are responding similarly to healthy individuals the same age. With that in mind, the inability to augment LV torsion and untwisting with exercise likely contributes to the exercise intolerance commonly observed in HTR.

4.4.2 Potential Mechanisms for Blunted Torsion and Untwisting in HTR during Exercise

Hemodynamic Influence

Although it is possible that the LV torsion response to exercise in HTR may be similar to that of RM because of altered endocardial function, it is likely that exercise torsion in HTR is not increased for different reasons than in a healthy older individual. Increasing end-diastolic volume has been shown to result in increased LV torsion (14). In the present investigation, HTR exhibited the smallest increase in end-diastolic volume which may be related to poor LV compliance (25). In addition, both DM and RM reduced wall stress in response to exercise, whereas HTR exhibited an increase in afterload, a factor which has been related to reductions in LV torsion (14). It is also plausible that the increase in LV afterload in HTR contributed to the inhibition of active relaxation, including LV untwisting, during exercise (17). Immunosuppressive therapy coupled with

pre-transplant vascular dysfunction, may play an important role in affecting how hemodynamics influence LV torsion during exercise in HTR.

Insufficient Catecholamines

It is plausible that in the present investigation the exercise stimulus was not intense enough to provoke a sufficient catecholamine mediated lusitropic response in HTR (8, 15, 38). HTR have a significantly elevated catecholamine response to high intensity exercise compared to healthy controls, with a relatively normal response at lower intensity exercise (8, 15). A higher catecholamine level may be required for a denervated heart to reduce end-systolic volume during exercise. A low end-systolic volume accomplished by forceful myocardial shortening is crucial in order for diastolic benefits to be transferred from systole via spring-like proteins such as titin (16, 23, 33). In the present investigation, HTR neither significantly reduced their end-systolic volume nor increased circumferential strain rate, the two factors that were most strongly related to increases in peak untwisting rate. It appears as though HTR are unable to take advantage of the link LV rotation provides between systolic and diastolic function during exercise (33); this inability may be related to an insufficient catecholamine stimulus.

Previous research examining LV rotation in HTR has demonstrated increased peak torsion and untwisting rates in response to dobutamine infusion (21, 30). These investigations may further suggest an insufficient catecholamine response to exercise in the present investigation. In contrast to exercise, dobutamine administered to HTR results in enhanced relaxation and a reduction in LV end-diastolic pressure (51). Low intensity exercise may simply not provide a sufficient or comparable stimulation to dobutamine to trigger favorable lusitropic benefits. However, caution must be used when

comparing past studied in HTR with the present investigation as they were conducted with different methodologies, primarily implanted myocardial markers.

Heterogeneous Reinnervation

Partial cardiac reinnervation has been shown to occur post transplant (6, 27, 45). Incomplete, heterogeneous reinnervation may partially account for the inability of HTR to augment LV untwisting rate with exercise. In fact, heterogeneous stimulation of β-receptors may have negative consequences for diastolic function (18) and may help explain the blunted peak untwisting rates observed in HTR, particularly if stimulation differs between the endocardium and epicardium. As previously reported in these HTR as part of another investigation, 7 out of 8 HTR displayed functional evidence of partial cardiac sympathetic reinnervation (39, 43, 50).

Material Properties of the Myocardium

Myocardial fibrosis may be related to the reduced LV compliance observed in normal aging (4) and following heart transplantation (25, 26, 37, 38). The relatively non-compliant LV of HTR partially contributes to elevated LV end-diastolic pressures during exercise (25). High end-diastolic pressures and the resulting myocardial stretch may result in increased contractile protein calcium sensitivity which would be beneficial during systole, but detrimental to early relaxation (5). This alteration in calcium sensitivity could, in turn, counteract the lusitropic benefits of increased β-receptor stimulation that occurs with exercise (12, 38, 51). In support of this hypothesis, Hosenpud et al. (1989) found that HTR with the lowest resting and exercising pulmonary wedge pressures had the greatest ability to increase end-diastolic volume with exercise

(24). Of note, in the present investigation resting E/E' was highest in HTR despite having the lowest end-diastolic volume, suggesting lower LV compliance (47).

Irrespective of LV end-diastolic pressure, the material properties of the LV may influence active relaxation. Myocardial fibrosis has been shown to be related to an increased expression of the N2B titin isoform, which is the stiffer isoform (52). A greater proportion of N2B titin may reduce the active recoil properties of the myocardium (23); particularly when compression of titin may be insufficient. In the present study, forceful titin compression may not have occurred as evidenced by smaller changes in ejection fraction and systolic circumferential strain rate in response to exercise in HTR and RM. The structural properties of the LV may provide a link between the reduced chamber compliance and the concomitant blunted active relaxation (including peak untwisting rate) commonly observed in HTR during exercise.

4.5 Limitations and Future Directions

The results of this investigation must be interpreted with several limitations in mind. First, we did not assess the circumferential data with respect to sub-endocardial and sub-epicardial layers. Although these techniques have yet to be verified against MRI, others have shown this to be possible with echocardiography (1, 35). Information regarding endocardial and epicardial function during exercise would provide further insight into LV rotation with aging and following heart transplantation. Second, pharmacological assessment of reinnervation (6) may have provided further explanations for the differences in LV rotation observed in this experiment. Despite our small sample size, our results for LV rotation were similar to those previously reported for both young and older healthy individuals during exercise (9, 32). Individuals were compared at the same

relative workload; however, the absolute cardiovascular stress was not the same in all groups. Considering we were comparing a clinical population to healthy young adults, we thought that a similar absolute work rate would provide less valuable information given the large disparities in relative intensity this would have created. Our HTR group heterogeneity with respect to time post transplant may have impacted our findings. To determine the time frame of accelerated aging of the cardiac allograft, future studies sequentially comparing LV torsion and untwisting including HTR of varying ages and times post transplant would be important.

4.6 Conclusions

The results of this investigation confirm previously reported age-related differences in LV torsion and untwisting rates with exercise. These findings are extended to the unique model of HTR who generally have a younger donor heart. Functionally, the donor heart appears to have undergone accelerated aging due to the similarities in exercise response between RM and HTR. An inability to increase LV torsion and untwisting during exercise likely contributes to the classic cardiac response observed during exercise in HTR.

4.7 Chapter Four References

1. **Adamu U, Schmitz F, Becker M, Kelm M, and Hoffmann R.** Advanced speckle tracking echocardiography allowing a three-myocardial layer-specific analysis of deformation parameters. *Eur J Echocardiogr*, 2008.
2. **Alonso de Begona J, Gundry SR, Razzouk AJ, Boucek MM, and Bailey LL.** Prolonged ischemic times in pediatric heart transplantation: early and late results. *Transplant Proc* 25: 1645-1648, 1993.
3. **Anversa P, Puntillo E, Nikitin P, Olivetti G, Capasso JM, and Sonnenblick EH.** Effects of age on mechanical and structural properties of myocardium of Fischer 344 rats. *Am J Physiol* 256: H1440-1449, 1989.
4. **Arbab-Zadeh A, Dijk E, Prasad A, Fu Q, Torres P, Zhang R, Thomas JD, Palmer D, and Levine BD.** Effect of aging and physical activity on left ventricular compliance. *Circulation* 110: 1799-1805, 2004.
5. **Babu A, Sonnenblick E, and Gulati J.** Molecular basis for the influence of muscle length on myocardial performance. *Science* 240: 74-76, 1988.
6. **Bengel FM, Ueberfuhr P, Ziegler SI, Nekolla S, Reichart B, and Schwaiger M.** Serial assessment of sympathetic reinnervation after orthotopic heart transplantation. A longitudinal study using PET and C-11 hydroxyephedrine. *Circulation* 99: 1866-1871, 1999.
7. **Beyar R and Sideman S.** Effect of the twisting motion on the nonuniformities of transmyocardial fiber mechanics and energy demand--a theoretical study. *IEEE Trans Biomed Eng* 32: 764-769, 1985.
8. **Braith RW, Wood CE, Limacher MC, Pollock ML, Lowenthal DT, Phillips MI, and Staples ED.** Abnormal neuroendocrine responses during exercise in heart transplant recipients. *Circulation* 86: 1453-1463, 1992.
9. **Burns AT, La Gerche A, Macisaac AI, and Prior DL.** Augmentation of Left Ventricular Torsion with Exercise is Attenuated with Age. *J Am Soc Echocardiogr*, 2007.
10. **Burns ATM, I.G. Thomas, J.D. MacIsaac, A. and Prior, D.** Doin' the twist: new tools for an old concept of myocardial function. *Heart* 94: 978-983, 2008.
11. **Cheng CP, Igarashi Y, and Little WC.** Mechanism of augmented rate of left ventricular filling during exercise. *Circ Res* 70: 9-19, 1992.
12. **Coudray N, Beregi JP, Lecarpentier Y, and Chemla D.** Effects of isoproterenol on myocardial relaxation rate: influence of the level of load. *Am J Physiol* 265: H1645-1653, 1993.
13. **Devereux RB and Reichek N.** Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. *Circulation* 55: 613-618, 1977.
14. **Dong SJ, Hees PS, Huang WM, Buffer SA, Jr., Weiss JL, and Shapiro EP.** Independent effects of preload, afterload, and contractility on left ventricular torsion. *Am J Physiol* 277: H1053-1060, 1999.
15. **Ferretti G, Marconi C, Achilli G, Caspani E, Fiocchi R, Mamprin F, Gamba A, Ferrazzi P, and Cerretelli P.** The heart rate response to exercise and circulating catecholamines in heart transplant recipients. *Pflugers Arch* 443: 370-376, 2002.

16. **Fukuda N, Sasaki D, Ishiwata S, and Kurihara S.** Length dependence of tension generation in rat skinned cardiac muscle: role of titin in the Frank-Starling mechanism of the heart. *Circulation* 104: 1639-1645, 2001.
17. **Gillebert TC, Leite-Moreira AF, and De Hert SG.** Load dependent diastolic dysfunction in heart failure. *Heart Fail Rev* 5: 345-355, 2000.
18. **Gillebert TC and Lew WY.** Nonuniformity and volume loading independently influence isovolumic relaxation rates. *Am J Physiol* 257: H1927-1935, 1989.
19. **Greenberg NL, Vandervoort PM, Firstenberg MS, Garcia MJ, and Thomas JD.** Estimation of diastolic intraventricular pressure gradients by Doppler M-mode echocardiography. *Am J Physiol Heart Circ Physiol* 280: H2507-2515, 2001.
20. **Greim CA, Roewer N, and Schulte am Esch J.** Assessment of changes in left ventricular wall stress from the end-systolic pressure-area product. *Br J Anaesth* 75: 583-587, 1995.
21. **Hansen DE, Daughters GT, 2nd, Alderman EL, Ingels NB, Stinson EB, and Miller DC.** Effect of volume loading, pressure loading, and inotropic stimulation on left ventricular torsion in humans. *Circulation* 83: 1315-1326, 1991.
22. **Hees PS, Fleg JL, Dong SJ, and Shapiro EP.** MRI and echocardiographic assessment of the diastolic dysfunction of normal aging: altered LV pressure decline or load? *Am J Physiol Heart Circ Physiol* 286: H782-788, 2004.
23. **Helmes M, Lim CC, Liao R, Bharti A, Cui L, and Sawyer DB.** Titin determines the Frank-Starling relation in early diastole. *J Gen Physiol* 121: 97-110, 2003.
24. **Hosenpud JD, Morton MJ, Wilson RA, Pantely GA, Norman DJ, Cobanoglu MA, and Starr A.** Abnormal exercise hemodynamics in cardiac allograft recipients 1 year after cardiac transplantation. Relation to preload reserve. *Circulation* 80: 525-532, 1989.
25. **Kao AC, Van Trigt P, 3rd, Shaeffer-McCall GS, Shaw JP, Kuzil BB, Page RD, and Higginbotham MB.** Central and peripheral limitations to upright exercise in untrained cardiac transplant recipients. *Circulation* 89: 2605-2615, 1994.
26. **Karch SB and Billingham ME.** Cyclosporine induced myocardial fibrosis: a unique controlled case report. *J Heart Transplant* 4: 210-212, 1985.
27. **Kaye DM, Esler M, Kingwell B, McPherson G, Esmore D, and Jennings G.** Functional and neurochemical evidence for partial cardiac sympathetic reinnervation after cardiac transplantation in humans. *Circulation* 88: 1110-1118, 1993.
28. **Lumens J, Delhaas T, Arts T, Cowan BR, and Young AA.** Impaired subendocardial contractile myofiber function in asymptomatic aged humans, as detected using MRI. *Am J Physiol Heart Circ Physiol* 291: H1573-1579, 2006.
29. **Mazhari R, Omens JH, Pavelec RS, Covell JW, and McCulloch AD.** Transmural distribution of three-dimensional systolic strains in stunned myocardium. *Circulation* 104: 336-341, 2001.
30. **Moon MR, Ingels NB, Jr., Daughters GT, 2nd, Stinson EB, Hansen DE, and Miller DC.** Alterations in left ventricular twist mechanics with inotropic stimulation and volume loading in human subjects. *Circulation* 89: 142-150, 1994.
31. **Nikolic SD, Feneley MP, Pajaro OE, Rankin JS, and Yellin EL.** Origin of regional pressure gradients in the left ventricle during early diastole. *Am J Physiol* 268: H550-557, 1995.

32. **Notomi Y, Martin-Miklovic MG, Oryszak SJ, Shiota T, Deserranno D, Popovic ZB, Garcia MJ, Greenberg NL, and Thomas JD.** Enhanced ventricular untwisting during exercise: a mechanistic manifestation of elastic recoil described by Doppler tissue imaging. *Circulation* 113: 2524-2533, 2006.
33. **Notomi Y, Popovic ZB, Yamada H, Wallick DW, Martin MG, Oryszak SJ, Shiota T, Greenberg NL, and Thomas JD.** Ventricular untwisting: a temporal link between left ventricular relaxation and suction. *Am J Physiol Heart Circ Physiol* 294: H505-513, 2008.
34. **Notomi Y, Srinath G, Shiota T, Martin-Miklovic MG, Beachler L, Howell K, Oryszak SJ, Deserranno DG, Freed AD, Greenberg NL, Younoszai A, and Thomas JD.** Maturational and adaptive modulation of left ventricular torsional biomechanics: Doppler tissue imaging observation from infancy to adulthood. *Circulation* 113: 2534-2541, 2006.
35. **Nottin S, Doucende G, Schuster-Beck I, Dauzat M, and Obert P.** Alteration in left ventricular normal and shear strains evaluated by 2D-strain echocardiography in the athlete's heart. *J Physiol* 586: 4721-4733, 2008.
36. **Oxenham HC, Young AA, Cowan BR, Gentles TL, Occleshaw CJ, Fonseca CG, Doughty RN, and Sharpe N.** Age-related changes in myocardial relaxation using three-dimensional tagged magnetic resonance imaging. *J Cardiovasc Magn Reson* 5: 421-430, 2003.
37. **Oyer PE SE, Jamieson SW, Hunt SA, Perlroth M, Billingham M, Shumway NE.** Cyclosporine in cardiac transplantation: a 2 1/2 year follow up. *Transplant Proc* 15: 2546-2552, 1983.
38. **Paulus WJ, Bronzwaer JG, Felice H, Kishan N, and Wellens F.** Deficient acceleration of left ventricular relaxation during exercise after heart transplantation. *Circulation* 86: 1175-1185, 1992.
39. **Pokan R, Von Duvillard SP, Ludwig J, Rohrer A, Hofmann P, Wonisch M, Smekal G, Schmid P, Pacher R, and Bachl N.** Effect of high-volume and -intensity endurance training in heart transplant recipients. *Med Sci Sports Exerc* 36: 2011-2016, 2004.
40. **Popovic ZB, Prasad A, Garcia MJ, Arbab-Zadeh A, Borowski A, Dijk E, Greenberg NL, Levine BD, and Thomas JD.** Relationship among diastolic intraventricular pressure gradients, relaxation, and preload: impact of age and fitness. *Am J Physiol Heart Circ Physiol* 290: H1454-1459, 2006.
41. **Prasad A, Popovic ZB, Arbab-Zadeh A, Fu Q, Palmer D, Dijk E, Greenberg NL, Garcia MJ, Thomas JD, and Levine BD.** The effects of aging and physical activity on Doppler measures of diastolic function. *Am J Cardiol* 99: 1629-1636, 2007.
42. **Rademakers FE, Buchalter MB, Rogers WJ, Zerhouni EA, Weisfeldt ML, Weiss JL, and Shapiro EP.** Dissociation between left ventricular untwisting and filling. Accentuation by catecholamines. *Circulation* 85: 1572-1581, 1992.
43. **Scott JM, Esch BT, Haykowsky MJ, Warburton DE, Toma M, Jelani A, Taylor D, Paterson I, Poppe D, Liang Y, and Thompson R.** Cardiovascular responses to incremental and sustained submaximal exercise in heart transplant recipients. *Am J Physiol Heart Circ Physiol* 296: H350-358, 2009.
44. **Sengupta PP, Khandheria BK, and Narula J.** Twist and untwist mechanics of the left ventricle. *Heart Fail Clin* 4: 315-324, 2008.

45. **Stark RP, McGinn AL, and Wilson RF.** Chest pain in cardiac-transplant recipients. Evidence of sensory reinnervation after cardiac transplantation. *N Engl J Med* 324: 1791-1794, 1991.
46. **Streeter DD, Jr., Spotnitz HM, Patel DP, Ross J, Jr., and Sonnenblick EH.** Fiber orientation in the canine left ventricle during diastole and systole. *Circ Res* 24: 339-347, 1969.
47. **Sundereswaran L, Nagueh SF, Vardan S, Middleton KJ, Zoghbi WA, Quinones MA, and Torre-Amione G.** Estimation of left and right ventricular filling pressures after heart transplantation by tissue Doppler imaging. *Am J Cardiol* 82: 352-357, 1998.
48. **Taylor DO, Edwards LB, Boucek MM, Trulock EP, Aurora P, Christie J, Dobbels F, Rahmel AO, Keck BM, and Hertz MI.** Registry of the International Society for Heart and Lung Transplantation: twenty-fourth official adult heart transplant report--2007. *J Heart Lung Transplant* 26: 769-781, 2007.
49. **Teichholz LE, Kreulen T, Herman MV, and Gorlin R.** Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence of absence of asynergy. *Am J Cardiol* 37: 7-11, 1976.
50. **Uberfuhr P, Ziegler S, Schwaiblmair M, Reichart B, and Schwaiger M.** Incomplete sympathic reinnervation of the orthotopically transplanted human heart: observation up to 13 years after heart transplantation. *Eur J Cardiothorac Surg* 17: 161-168, 2000.
51. **Vantrimpont PJ, Felice H, and Paulus WJ.** Does dobutamine prevent the rise in left ventricular filling pressures observed during exercise after heart transplantation? *Eur Heart J* 16: 1300-1306, 1995.
52. **Wu Y, Bell SP, Trombitas K, Witt CC, Labeit S, LeWinter MM, and Granzier H.** Changes in titin isoform expression in pacing-induced cardiac failure give rise to increased passive muscle stiffness. *Circulation* 106: 1384-1389, 2002.
53. **Yamakado T, Takagi E, Okubo S, Imanaka-Yoshida K, Tarumi T, Nakamura M, and Nakano T.** Effects of aging on left ventricular relaxation in humans. Analysis of left ventricular isovolumic pressure decay. *Circulation* 95: 917-923, 1997.

[1]CHAPTER FIVE: A New Twist on Orthostatic Stress in Endurance Athletes

5.1 Introduction

Endurance-trained athletes are less tolerant of orthostatic stressors such as standing upright or lower body negative pressure (LBNP) (16). In response to orthostatic stress, endurance athletes exhibit greater reductions in left ventricular (LV) end-diastolic volume (EDV) and stroke volume in comparison to normally active or sedentary individuals (9, 17). These large reductions in LV volumes are related to enhanced LV compliance and reduced ventricular interactions (1, 9, 17). It is possible that other mechanisms, such as less favorable LV rotation, may contribute to the reduced LV filling seen in endurance athletes during orthostatic stress.

Counter-clockwise apical twisting and clockwise basal twisting combine to create LV torsion (3, 26). LV torsion aids the efficient ejection of blood by creating high pressures with less myocardial shortening (2). Beginning early in diastole, circumferential untwisting at the apex and base result in LV recoil. As opposed to radial and long axis relaxation which occur predominantly during filling, approximately 40% of recoil happens prior to mitral valve opening (18). The early nature of LV recoil makes it an important contributor to low LV pressure generation. A lower LV pressure will increase the trans-mitral filling gradient and increase the peak early filling rate (5, 14). Therefore, alterations in LV recoil will likely have significant consequences for LV filling.

The relationship between LV recoil and the large reductions in LV volumes exhibited during orthostatic stress in endurance-trained individuals is unknown. Therefore, the

[1] A version of this chapter will be submitted for publication as: BT Esch, JM Scott, I Paterson, MJ Haykowsky, DER Warburton, K Chow, J Cheng-Baron, RB Thompson. A New Twist on Orthostatic Stress in Endurance Athletes

purpose of this investigation was to examine the effects of an orthostatic challenge on LV torsion and recoil in endurance-trained and normally active individuals using cardiac magnetic resonance imaging (MRI). We hypothesized that an inability to augment LV recoil in endurance athletes may contribute to their large alterations in LV volumes in response to LBNP. A secondary aim was to assess changes in right ventricular volumes during LBNP, as well as any group differences between endurance-trained and untrained individuals which may exist.

5.2 Methods

5.2.1 Participants

We recruited 16 males between the ages of 19 and 44 to participate in this investigation. Participants included eight endurance-trained athletes (2 cyclists, 5 triathletes, 1 biathlete) that trained in excess of 10 hours per week and had done so for greater than five years. The remaining eight participants were normally active individuals who did not partake in regimented aerobic exercise training. Institutional ethics were obtained from the University of Alberta Health Research Ethics Board and all participants provided written informed consent prior to participation.

5.2.2 General Protocol

Upon arrival to the Alberta Cardiovascular and Stroke Research Centre at the Mazankowski Alberta Heart Institute, participants' height and mass were measured. Each individual underwent an incremental exercise test on a cycle ergometer in order to assess maximal aerobic power (VO_2 max). Individuals cycled on an electronically braked ergometer (Ergometrics er800s; Ergoline, Bitz, Germany) where the workload increased

20 to 30 watts every two minutes until anaerobic threshold (30), and then increased 20 to 30 watts every minute until exhaustion. Expired gas analysis was completed using a calibrated metabolic cart (Parvomedics, Salt Lake City, USA).

On a separate day, participants underwent cardiac volumetric and hemodynamic assessment with a 1.5 Tesla MRI scanner (Siemens Sonata, Erlangen, Germany) under two different conditions: 1) supine rest; 2) LBNP of -30mmHg.

5.2.3 Cardiac Magnetic Resonance Imaging Acquisition

Short axis cines covering the length of the right and LV were acquired in order to assess EDV, end systolic volume, stroke volume, and ejection fraction. Image acquisition parameters were as follows: repetition time = 2.2 ms; echo time = 1.1 ms; flip angle = 78°; slice thickness = 6 to 8 mm; matrix = 192x312; field of view = 300 to 380 mm; and temporal resolution = 25 phases. Both long axis and short axis phase contrast cines were acquired to measure early (E) and atrial (A) filling velocities of the blood and peak early diastolic (E′) septal and lateral annular velocities in the LV. Combining through plane velocity data across the area of the mitral valve allowed for calculation of peak early and atrial trans-mitral filling rates (mL/s). Myocardial tissue tagging was applied in order to assess peak torsion and peak recoil rate, as well as circumferential strain. Since myocardial tissue tags fade over time, the tags were applied 250ms after the R-wave in order to assure high resolution tags during early diastole when peak recoil rates occur. The total degrees of rotation, as well as circumferential shortening (strain), were assumed to be the same (only in the reverse direction) during diastole and systole. The acquisition of all data was cardiac gated based on the electrocardiogram and acquired during end-expiratory breath holds. Images were acquired in the order listed above.

5.2.4 Lower Body Negative Pressure

Participants entered a custom built, MRI compatible, LBNP chamber by placing their legs inside the chamber where they were sealed at the level of the iliac crest. Participants remained supine while inside the chamber. The LBNP chamber was built with dimensions to fit the bore of the magnet, and was constructed with a wooden skeleton (half-cylinder shape) covered in a synthetic, air-tight material. The chamber was attached to a vacuum system which was controlled by a variable transformer, allowing modifiable pressure outputs. Pressure inside the chamber was monitored continuously with a calibrated differential pressure manometer, and was held constant throughout the LBNP challenge (± 2mmHg).

After participants had entered the chamber and were inserted into the magnet, a complete resting baseline cardiac MRI scan was completed (approximately 20 minutes). Following baseline assessment of ventricular function, the pressure in the chamber was reduced to 30mmHg below atmospheric pressure. Five minutes of cardiovascular acclimatization at -30mmHg were allowed prior to the onset of image acquisition. After five minutes, a second, identical cardiac MRI evaluation was completed (approximately 20 minutes). Heart rate (electrocardiogram) and blood pressure (automated sphygmomanometer) were also monitored and recorded throughout baseline and LBNP.

5.2.5 Data Analysis

Assessment of right and LV volumes was performed by manual endocardial tracing of short-axis cine images at end diastole and end systole using slices from the entire length of the ventricles (23) (Argus; Siemens Medical Systems). Stroke volume and ejection fraction were calculated using the measures of EDV and end-systolic volume. Papillary

muscles were included as part of the ventricular cavity volume and were excluded for calculation of LV mass (15). LV mass was calculated by using the endocardial trace coupled with an epicardial trace in order to determine myocardial area at each short axis slice level in end-diastole (appendix C). LV length was considered to be the length from the apex to the mitral annulus.

LV cavity diameter and wall thickness of a mid-ventricular (papillary muscles) short axis slice in systole and diastole were utilized to determine LV end-diastolic internal diameter as well as end-systolic wall stress (24). End systolic wall stress was used as an index of afterload.

Custom designed image morphing software was applied to the myocardial tagging images (appendix C). The tag-endocardium intersection points were identified manually and digitized. Angular rotation and rotation rates of the base and apex were calculated using the average rotation of the eight individual endocardial tag intersections. Torsion was calculated as the instantaneous difference between the rotation at the base and apex. Peak untwisting rate was calculated separately for the apex and base, and peak recoil rate was calculated as the maximal difference between apical and basal untwisting rates. The ratio of peak recoil rate/peak torsion was calculated for each individual in order to quantify the amount of recoil that occurred for a given amount of torsion. Circumferential strain was calculated using the tissue tags as the percentage of circumferential lengthening occurring around the myocardium, and was assumed to be the reversal of systolic circumferential strain. Total peripheral resistance was calculated as follows: (1/3 systolic blood pressure + 2/3 diastolic blood pressure) / cardiac output.

5.2.6 Statistics

At rest, group differences were compared using an independent t-test. To compare group responses to LBNP, an independent t-test was applied to the absolute change in a given variable for both groups. Linear regressions were conducted to identify significantly related relationships between two variables. All statistical analysis was preformed using Statistica 6.0 software and significance was set at $p<0.05$.

5.3 Results

5.3.1 Group Characteristics

Participant characteristics are listed in table 5.1. The groups were matched for age, height and mass. By design, endurance-trained athletes had significantly higher absolute and relative VO_2 max. Endurance athletes also had increased LV mass and diameter compared to the normally active group ($p<0.05$).

	Endurance Athletes (n=8)	Normally Active (n=8)
Age (years)	31.0 ± 9.7	33.0 ± 7.3
Height (cm)	179.1 ± 11.2	177.3 ± 7.3
Mass (kg)	74.4 ± 12.0	79.4 ± 7.5
Years Training (years)	11.1 ± 4.5	---
Hours of Training/Week (hrs)	11.5 ± 3.1	---
VO_2 max (mL/kg/min)	66.4 ± 7.2*	41.9 ± 9.0
VO_2 max (L/ min)	5.0 ± 0.7*	3.6 ± 0.6
LV mass (g)	176.8 ± 20.3*	146.1 ± 23.1
LV internal diameter (mm)	60.0 ± 3.6*	53.9 ± 4.2
LV length (cm)	6.6 ± 0.6	5.8 ± 1.2

Table 5.1: Participant physical characteristics and training history
* indicates significantly different from normally active ($p<0.05$). LV: left ventricular

5.3.2 Resting Cardiac Volumes and Hemodynamics

Resting cardiac volumes and hemodynamics are shown in table 5.2. The groups did not differ at rest with respect to systolic or diastolic blood pressure, LV ejection fraction, or cardiac output. Resting heart rate was higher in normally active individuals ($p=0.08$). Endurance athletes had significantly higher resting LV EDV and LV stroke volumes. End-systolic volume was also higher in athletes, but the group differences were not statistically significant ($p=0.06$). Resting right ventricular EDV, end-systolic volume and stroke volume were significantly higher in the endurance athletes. There were no group differences in resting right ventricular ejection fraction. End systolic wall stress and total peripheral resistance were not different between groups at baseline.

The groups did not differ at rest in E, A or E/A (table 5.2). Endurance athletes had a significantly higher peak rate of filling during early diastole, but not during atrial contraction (table 5.2). Both septal and lateral E' were significantly higher in endurance athletes (table 5.2).

	Rest		Change with LBNP	
	ET	**NA**	**ET**	**NA**
Heart Rate (beats/min)	57.3 ± 6.2	68.4 ± 15.3	1.7 ± 4.0	-2.6 ± 6.9
Systolic BP (mmHg)	123.5 ± 4.9	120.7 ± 7.5	-3.0 ± 5.8	-2.1 ± 3.5
Diastolic BP (mmHg)	71.1 ± 6.2	73.7 ± 9.4	1.0 ± 6.9	2.0 ± 4.8
LV EDV (mL)	211.9 ± 31.3*	168.8 ± 38.5	-26.6 ± 8.7*	-17.3 ± 8.6
LV ESV (mL)	83.9 ± 17.8	66.2 ± 16.7	-0.8 ± 7.6	-4.0 ± 5.1
LV SV (mL)	128.0 ± 16.2*	103.2 ± 22.1	-26.0 ± 7.3*	-14.0 ± 9.1
LV EF (%)	60.5 ± 3.7	61.6 ± 2.5	-5.4 ± 3.4	-2.3 ± 3.7
Cardiac output (L/min)	7.3 ± 1.1	6.8 ± 1.1	-1.3 ± 0.6	-1.1 ± 0.8
E (m/s)	0.65 ± 0.11	0.63 ± 0.07	-0.13 ± 0.06	-0.13 ± 0.06
A (m/s)	0.32 ± 0.04	0.35 ± 0.07	-0.04 ± 0.03	-0.3 ± 0.03
E/A	2.06 ± 0.47	1.87 ± 0.41	-0.21 ± 0.30	-0.27 ± 0.28
E filling rate (mL/s)	674.7 ± 108.2*	515.4 ± 80.7	-227.3 ± 69.9*	-126.0 ± 85.2
A filling rate (mL/s)	293.2 ± 34.5	255.2 ± 61.6	-69.5 ± 23.5*	-26.5 ± 39.0
Septal E' (m/s)	0.12 ± 0.02*	0.09 ± 0.01	0.05 ± 0.04*	0.01 ± 0.02
Lateral E' (m/s)	0.17 ± 0.02*	0.14 ± 0.03	0.06 ± 0.03*	0.03 ± 0.02
TPR (mmHg•min/L)	12.8 ± 2.9	12.6 ± 2.4	2.9 ± 2.0	3.2 ± 2.0
Wall stress (10^3 dynes/cm^2)	84.4 ± 11.2	79.3 ± 15.5	-0.3 ± 17.2	1.0 ± 9.0
RV EDV (mL)	233.5 ± 35.5*	182.2 ± 45.5	-38.0 ± 18.4*	-21.6 ± 8.3
RV ESV (mL)	103.9 ± 25.2*	77.8 ± 22.2	-6.1 ± 11.1	-5.8 ± 6.9
RV SV (mL)	129.9 ± 17.6*	104.3 ± 28.0	-32.1 ± 15.2*	-15.8 ± 9.7
RV EF (%)	55.9 ± 5.8	57.4 ± 5.9	-5.7 ± 4.5	-2.5 ± 4.7

Table 5.2: Cardiac volumes and hemodynamics
* indicates significantly different from normally active ($p<0.05$). BP: blood pressure; LV: left ventricle; EDV: end-diastolic volume; ESV: end-systolic volume; SV: stroke volume; EF: ejection fraction; E: early peak mitral blood velocity; A: atrial peak mitral blood velocity; E': early diastolic myocardial annular velocity; TPR: total peripheral resistance; RV: right ventricle.

Neither resting LV torsion nor apical and basal rotations were different between groups (table 5.3). Peak recoil rate, peak basal untwisting rate and peak apical untwisting rate were not different between groups at rest (table 5.3). The ratio of peak recoil rate/peak torsion did not differ between groups at rest (table 5.3). Baseline peak circumferential strain also was not different between groups (table 5.3).

	Rest		Change with LBNP	
	ET	**NA**	**ET**	**NA**
Peak Torsion (°)	11.0 ± 3.4	10.5 ± 3.7	-1.2 ± 2.9	0.9 ± 3.1
Peak Recoil Rate (°/s)	-135.4 ± 39.7	-121.2 ± 29.9	20.3 ± 8.7*	-16.2 ± 32.1
Basal Untwisting rate (°/s)	46.7 ± 26.8	27.7 ± 15.6	-11.5 ± 19.0*	18.6 ± 25.4
Apical Untwisting Rate (°/s)	-106.2 ± 36.7	-109.0 ± 32.5	18.5 ± 17.2	4.0 ± 29.6
Recoil Rate/Torsion	12.7 ± 3.4	12.0 ± 2.1	-0.9 ± 2.5	0.2 ± 1.6
Circumferential Strain (%)	-16.6 ± 2.7	-14.9 ± 1.3	3.2 ± 3.7	0.4 ± 2.3

Table 5.3: LV rotations and strain
*indicates significantly different from normally active ($p<0.05$).

5.3.3 Cardiovascular Responses to LBNP

The change in response to -30mmHg LBNP did not differ for heart rate, systolic blood pressure, diastolic blood pressure or cardiac output between groups (table 5.2). Endurance athletes had a significantly larger reduction in both LV EDV and LV stroke volume compared to the normally active group; however, change in end-systolic volume did not differ between groups. Ejection fraction fell to a greater extent in endurance athletes although group differences were not statistically significant. Furthermore, change in total peripheral resistance and wall stress from baseline to -30mmHg did not differ between groups. Similarly to the LV, right ventricular EDV and stroke volume were reduced with LBNP to a greater extent in endurance athletes ($p<0.05$), yet the change in end-systolic volume was not different between groups.

Change in E and A mitral velocities from rest to -30mmHg did not differ between groups; however, there was a greater reduction in the peak early diastolic filling rate in endurance athletes compared to normally active individuals ($p<0.05$, table 5.2). The reduction in peak filling rate during atrial contraction was also larger in endurance athletes ($p<0.05$, table 5.2). There were no group differences for the change in the ratio of early to atrial peak velocity or peak rate of filling. There was a greater reduction in E' at both the septum and lateral wall in endurance-trained athletes ($p<0.05$, table 5.2).

Change in peak torsion from rest to -30mmHg was not significantly different between groups; however, the normally active group increased peak torsion while the endurance-trained individuals reduced peak torsion in response to LBNP (table 5.3). There were significant group differences in response to LBNP for peak recoil rate, whereby the normally active group increased recoil rate and the endurance athletes reduced their peak

rate of recoil (table 5.3, $p<0.05$). Seven of eight normally active participants increased their peak rate of recoil, whereas seven of eight endurance athletes had a slower peak rate of recoil in response to LBNP (figures 5.1 and 5.2). The change in peak basal rotation rate was significantly different between groups (table 5.3), while the change in peak apical rotation rate was not different (table 5.3). Change in peak recoil rate/peak torsion did not differ between groups in response to LBNP. Circumferential strain was not altered statistically between groups; however, there was a trend towards a greater reduction in circumferential strain following LBNP in endurance athletes (table 5.3, $p=0.09$).

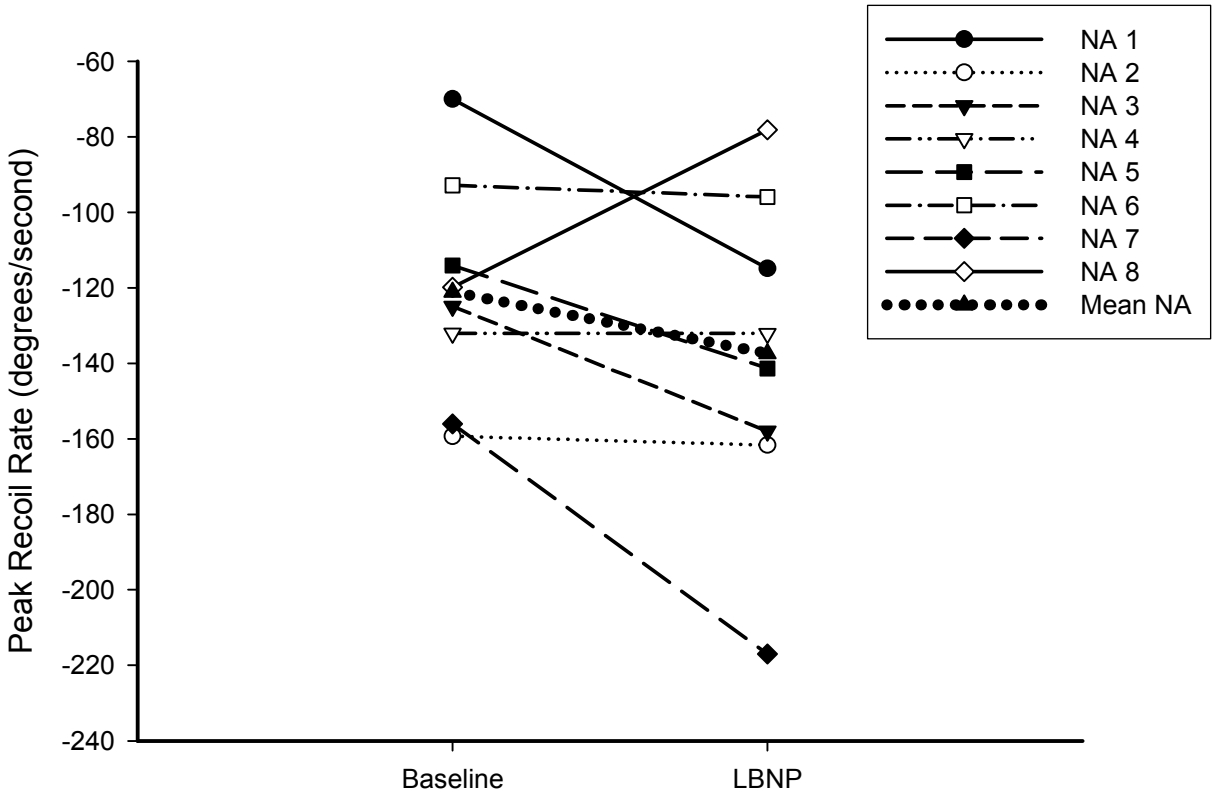


Figure 5.1. Peak recoil rate in normally active individuals.
Data is for each individual, and the group mean (dotted circles) at Baseline and during -30mmHg LBNP.

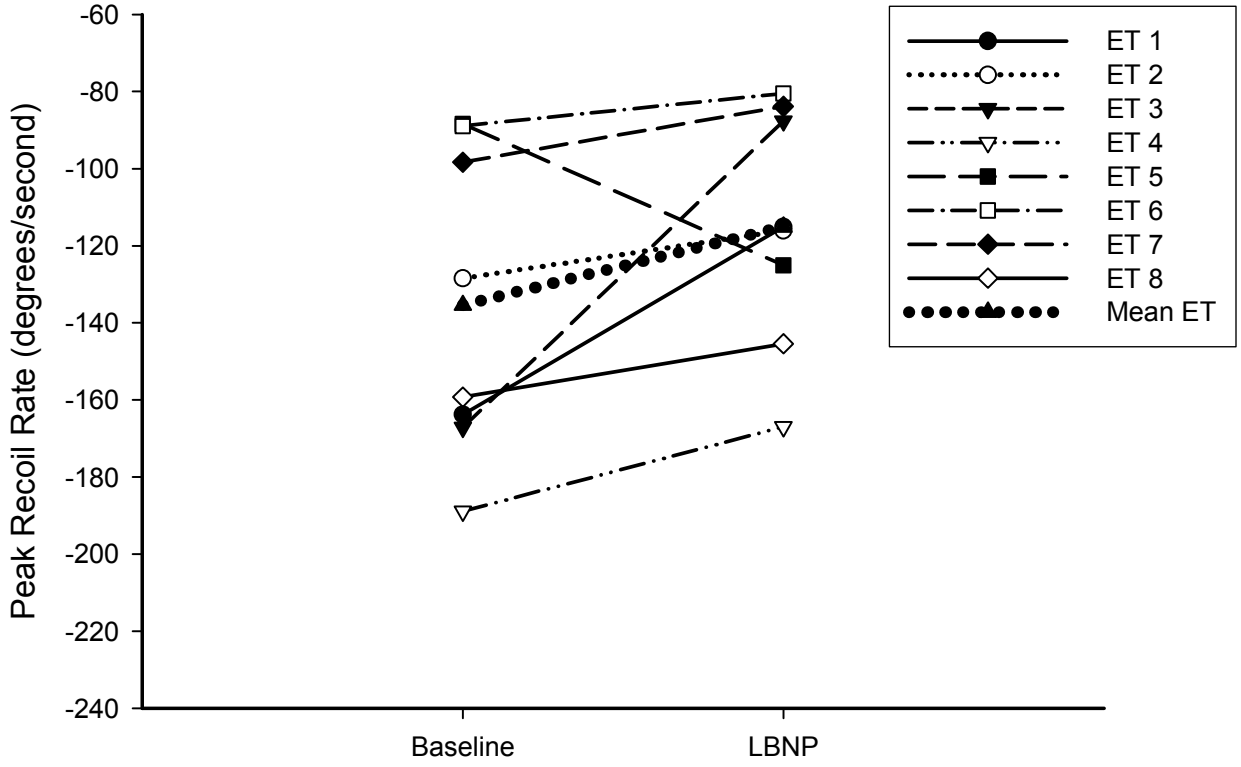


Figure 5.2. Peak recoil rate in endurance-trained athletes.
Data is for each individual, and the group mean (dotted circles) at Baseline and during -30mmHg LBNP.

5.3.4 Correlations

Relative VO_2 max was significantly correlated with change in peak torsion (R= -0.57) and change in peak recoil rate (R= 0.70), whereby the higher VO_2 max an individual had, the greater the reduction in peak torsion and peak recoil rate in response to LBNP. Absolute VO_2 max was related to change in EDV with LBNP (R= -0.61, $p<0.05$), suggesting those with the highest VO_2 max had the largest reductions in EDV. Change in circumferential strain was significantly related to change in EDV (R= 0.60). Change in peak torsion had the strongest relationship to change in peak recoil rate (R= -0.87, $p<0.05$ figure 5.3). Change in peak recoil rate was not significantly related to change in EDV, change in end-systolic volume, change in wall stress or change in peak early filling rate.

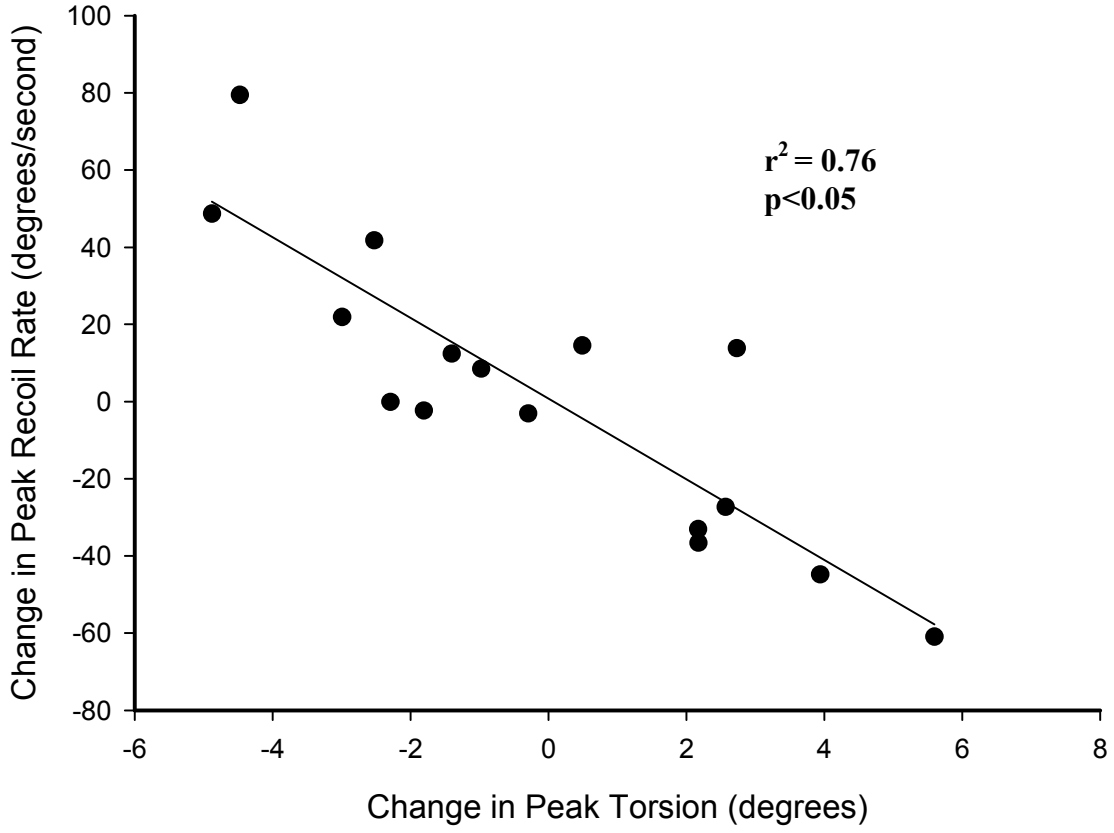


Figure 5.3. Relationship between change in peak torsion and change in peak recoil rate.

5.4 Discussion

To our knowledge, this investigation is the first examination of the acute effects of LBNP on biventricular function using cardiac MRI in endurance trained and normally active individuals. The major new findings of this investigation are: 1) in response to LBNP, peak recoil rate was reduced in endurance athletes but increased in normally active individuals; 2) normally active individuals exhibited an increase in peak torsion during LBNP and endurance athletes displayed a reduction; 3) endurance athletes demonstrated greater reductions in right and LV EDV and stroke volume during LBNP.

5.4.1 Recoil Rate and Diastolic Filling

The early trans-mitral pressure gradient is responsible for early diastolic filling (5, 14). Therefore, alteration of either left atrial or LV pressure will have consequences for early LV filling. By reducing right ventricular stroke volume with LBNP in the present investigation, left atrial pressure would be reduced (1, 17) resulting in a lower trans-mitral filling gradient in both groups. A reduced trans-mitral filling gradient during LBNP is suggested by the observed reduction in peak early filling rate (table 5.2).

In addition to reduced left atrial pressure, alterations to LV early diastolic pressure may also have had a significant impact on the trans-mitral filling gradient and peak early filling rate in this investigation. Approximately 40% of diastolic recoil occurs prior to mitral valve opening making recoil rate important for LV diastolic pressure decay (8, 19). Previous investigations have shown reductions in minimum LV pressure following acute preload reduction (5, 6). This compensatory reduction in LV minimum pressure may be partially related to an increase in peak recoil rate. Normally active individuals

demonstrated an increased peak recoil rate in response to LBNP, whereas endurance athletes did not. This response may help normally active individuals maintain LV EDV and peak early filling rate to a greater extent during orthostatic stress compared to endurance athletes.

5.4.2 Potential Mechanisms for Group Disparities in Recoil Rate during LBNP

There are two potential mechanisms contributing to the findings of divergent LV rotation between groups during LBNP. The first involves the previously established differences in the Frank-Starling relationship between endurance-trained athletes and normally active individuals (17). The second mechanism involves altered sympathetic signaling from the carotid baroreceptors in endurance athletes.

Alterations in systolic function, mediated by the Frank-Starling mechanism, have an important influence on diastolic function including LV recoil (19). The rotational energy exerted during systole is transferred through the extracellular collagen matrix (29) and spring like proteins, such as titin, to assist rapid diastolic recoil (11, 13, 19). This relationship between systolic and diastolic function is evident by the significant correlation between change in circumferential strain, as well as peak torsion, with change in peak recoil rate. Therefore, factors that influence peak torsion and circumferential strain, such as EDV, will help explain the divergent group response in recoil rate (7). Levine and colleagues (1991) demonstrated that endurance-trained athletes have greater LV compliance and larger reductions in EDV during LBNP (17). These greater reductions in EDV with LBNP would result in shorter end-diastolic myocardial lengths and less myocardial shortening (Frank-Starling mechanism); including less circumferential strain and torsion (7). Lower circumferential strain and peak torsion in

athletes would result in less energy being transferred from systole to diastolic recoil. In addition, an inability of endurance athletes to reduce end-systolic volume in this investigation provides further evidence for insufficient shortening in response to preload reduction (table 5.2). Ultimately, slower recoil may result in slower LV pressure decay and further reductions in EDV (8). In normally active individuals, the smaller reduction in EDV during LBNP resulted in an unchanged circumferential strain and ultimately preserved recoil rate. Increased recoil rate in the normally active group may have helped to offset reduced left atrial pressure and better maintain the peak early filling rate.

A second possible mechanism which may explain the group differences in peak recoil rate may be mediated by sympathetic nervous output in response to carotid baroreceptor stimulation. Recent investigations have shown that peripheral baroreceptors are indeed active during low levels of LBNP (10, 21). In addition, Sarnoff et al. (1960) demonstrated that carotid sinus hypotension results in increased contractility and an increased rate of early relaxation (25). The findings of Sarnoff and colleagues are similar to the increased peak torsion and recoil rate observed with LBNP in normally active individuals in our investigation. Carotid stimulation due to hypotension increases LV contractility by augmenting atrial contraction, ultimately elevating EDV (compared to the initial reduction) causing greater myocardial stretch and contraction via the Frank-Starling mechanism. Similarly, in our investigation, the peak rate of diastolic filling during atrial contraction was better preserved (although still reduced) in normally active individuals.

The contractile influence of the carotid sinus is withdrawn when sympathetic outflow is inhibited (25), which may be the case in endurance athletes. In addition to responding to absolute blood pressure, the carotid baroreceptors have been shown to be sensitive to

the pulsating nature of blood flow (4). Given that athletes have larger stroke volumes and slower heart rates, it has been proposed that their higher pulse amplitudes and lower pulse frequencies act to partially restrain sympathetic outflow from the carotid sinus (16). Sympathetic activity from the carotid baroreceptors may also be inhibited by the predominance of parasympathetic activation observed in endurance athletes (27). This inhibition of carotid sympathetic activity in endurance athletes may contribute to a reduced compensatory increase in atrial contraction (table 5.2). This sympathetic inhibition could contribute to larger reductions in EDV which could ultimately reduce circumferential strain and recoil rate in response to LBNP. Regardless of the mechanism responsible, the reduced LV recoil rate in endurance athletes may be a significant contributing factor to the orthostatic intolerance commonly observed in this population.

5.4.3 Right Ventricular Function

The majority of previous investigations examining cardiac responses to orthostatic stress have either ignored the right ventricle, or simply measured ventricular diameters or areas (1, 9, 12, 17, 22). Our findings of larger right ventricular volume reductions in endurance athletes during LBNP are suggestive of either a more compliant right ventricle or greater vascular capacitance (28). Some investigations suggest right ventricular adaptations to endurance training (20), but to our knowledge an assessment of right ventricular compliance in athletes has not been completed. Overall, greater reductions in right ventricular volume in endurance athletes may contribute to their reduced orthostatic tolerance.

Contrary to the findings of this investigation, we have previously demonstrated similar changes in right ventricular area between endurance-trained and normally active

individuals in response to LBNP (9). We observed differences between groups in the right ventricular volume response to LBNP in the present investigation; however, numerous methodological differences such as the time course and intensity of LNBP, as well as the temporal delay in image acquisition, are likely responsible for the divergent findings in right ventricular volumes during LBNP between this and our previous investigations.

5.4.4 Limitations

The results of this investigation should be interpreted with several limitations in mind. Due to the short-lived nature of MRI tissue tagging, rotational information was acquired during diastole only. This necessitated the extrapolation of peak torsion and peak circumferential strain based on the reversal of their systolic actions. We believe this to be a valid assumption, and any error it created would be systematic in nature. Secondly, we have made no invasive measures of left atrial or LV pressures and can therefore only infer the effects of LBNP on the trans-mitral gradient based on hemodynamic events. However, previous investigations have demonstrated the effects of preload reduction on the trans-mitral filling gradient (5, 14). Additionally, no measures of baroreceptor function or nervous activity were made, and so we can only speculate about their impact on our results. Finally, we assessed LV rotation under moderate LBNP. Examining recoil rates as individuals approach pre-syncope may provide further insights into how this mechanism ultimately affects orthostatic intolerance.

5.5 Conclusions

Using cardiac MRI, this investigation demonstrated a differential LV rotation response to altered preload between endurance-trained athletes and normally active individuals. Ultimately, it appears as though larger alterations in EDV result in reduced contractile function leading to slower peak recoil rates in endurance-trained athletes. These slower recoil rates in athletes may further reduce EDV and contribute to the higher prevalence of orthostatic intolerance observed in this population.

5.6 Chapter Five References

1. **Arbab-Zadeh A, Dijk E, Prasad A, Fu Q, Torres P, Zhang R, Thomas JD, Palmer D, and Levine BD.** Effect of aging and physical activity on left ventricular compliance. *Circulation* 110: 1799-1805, 2004.
2. **Beyar R and Sideman S.** Effect of the twisting motion on the nonuniformities of transmyocardial fiber mechanics and energy demand--a theoretical study. *IEEE Trans Biomed Eng* 32: 764-769, 1985.
3. **Burns ATM, I.G. Thomas, J.D. MacIsaac, A. and Prior, D.** Doin' the twist: new tools for an old concept of myocardial function. *Heart* 94: 978-983, 2008.
4. **Chapleau MW, Hajduczok G, and Abboud FM.** Pulsatile activation of baroreceptors causes central facilitation of baroreflex. *Am J Physiol* 256: H1735-1741, 1989.
5. **Courtois M, Vered Z, Barzilai B, Ricciotti NA, Perez JE, and Ludbrook PA.** The transmitral pressure-flow velocity relation. Effect of abrupt preload reduction. *Circulation* 78: 1459-1468, 1988.
6. **Dauterman K, Pak PH, Maughan WL, Nussbacher A, Arie S, Liu CP, and Kass DA.** Contribution of external forces to left ventricular diastolic pressure. Implications for the clinical use of the Starling law. *Ann Intern Med* 122: 737-742, 1995.
7. **Dong SJ, Hees PS, Huang WM, Buffer SA, Jr., Weiss JL, and Shapiro EP.** Independent effects of preload, afterload, and contractility on left ventricular torsion. *Am J Physiol* 277: H1053-1060, 1999.
8. **Dong SJ, Hees PS, Siu CO, Weiss JL, and Shapiro EP.** MRI assessment of LV relaxation by untwisting rate: a new isovolumic phase measure of tau. *Am J Physiol Heart Circ Physiol* 281: H2002-2009, 2001.
9. **Esch BT, Scott JM, Haykowsky MJ, McKenzie DC, and Warburton DE.** Diastolic ventricular interactions in endurance-trained athletes during orthostatic stress. *Am J Physiol Heart Circ Physiol* 293: H409-415, 2007.
10. **Fu Q, Shibata S, Hastings JL, Prasad A, Palmer MD, and Levine BD.** Evidence for unloading arterial baroreceptors during low levels of lower body negative pressure in humans. *Am J Physiol Heart Circ Physiol* 296: H480-488, 2009.
11. **Fukuda N, Sasaki D, Ishiwata S, and Kurihara S.** Length dependence of tension generation in rat skinned cardiac muscle: role of titin in the Frank-Starling mechanism of the heart. *Circulation* 104: 1639-1645, 2001.
12. **Guazzi M, Pepi M, Maltagliati A, Celeste F, Muratori M, and Tamborini G.** How the two sides of the heart adapt to graded impedance to venous return with head-up tilting. *J Am Coll Cardiol* 26: 1732-1740, 1995.
13. **Helmes M, Lim CC, Liao R, Bharti A, Cui L, and Sawyer DB.** Titin determines the Frank-Starling relation in early diastole. *J Gen Physiol* 121: 97-110, 2003.
14. **Ishida Y, Meisner JS, Tsujioka K, Gallo JI, Yoran C, Frater RW, and Yellin EL.** Left ventricular filling dynamics: influence of left ventricular relaxation and left atrial pressure. *Circulation* 74: 187-196, 1986.
15. **Katz J, Milliken MC, Stray-Gundersen J, Buja LM, Parkey RW, Mitchell JH, and Peshock RM.** Estimation of human myocardial mass with MR imaging. *Radiology* 169: 495-498, 1988.

16. **Levine BD.** Regulation of central blood volume and cardiac filling in endurance athletes: the Frank-Starling mechanism as a determinant of orthostatic tolerance. *Med Sci Sports Exerc* 25: 727-732, 1993.
17. **Levine BD, Lane LD, Buckey JC, Friedman DB, and Blomqvist CG.** Left ventricular pressure-volume and Frank-Starling relations in endurance athletes. Implications for orthostatic tolerance and exercise performance. *Circulation* 84: 1016-1023, 1991.
18. **Notomi Y, Martin-Miklovic MG, Oryszak SJ, Shiota T, Deserranno D, Popovic ZB, Garcia MJ, Greenberg NL, and Thomas JD.** Enhanced ventricular untwisting during exercise: a mechanistic manifestation of elastic recoil described by Doppler tissue imaging. *Circulation* 113: 2524-2533, 2006.
19. **Notomi Y, Popovic ZB, Yamada H, Wallick DW, Martin MG, Oryszak SJ, Shiota T, Greenberg NL, and Thomas JD.** Ventricular untwisting: a temporal link between left ventricular relaxation and suction. *Am J Physiol Heart Circ Physiol* 294: H505-513, 2008.
20. **Ozdogan O, Yilmaz GM, Gurgun C, Kayikcioglu M, and Cinar CS.** Right ventricular adaptations along with left ventricular remodeling in older athletes. *Echocardiography* 26: 237-245, 2009.
21. **Pannier B, Slama MA, London GM, Safar ME, and Cuche JL.** Carotid arterial hemodynamics in response to LBNP in normal subjects: methodological aspects. *J Appl Physiol* 79: 1546-1555, 1995.
22. **Pepi M, Guazzi, M., Maltagliati, A., Berna, G., Tamborini, G.** Diastolic Ventricular Interaction in Normal and Dialted Heart During Head-up Tilting. *Clinical Cardiology* 23: 665-672, 2000.
23. **Peshock RM, Willett DL, Sayad DE, Hundley WG, Chwialkowski MC, Clarke GD, and Parkey RW.** Quantitative MR imaging of the heart. *Magn Reson Imaging Clin N Am* 4: 287-305, 1996.
24. **Reichek N, Wilson J, St John Sutton M, Plappert TA, Goldberg S, and Hirshfeld JW.** Noninvasive determination of left ventricular end-systolic stress: validation of the method and initial application. *Circulation* 65: 99-108, 1982.
25. **Sarnoff SJ, Gilmore JP, Brockman SK, Mitchell JH, and Linden RJ.** Regulation of ventricular contraction by the carotid sinus. Its effect on atrial and ventricular dynamics. *Circ Res* 8: 1123-1136, 1960.
26. **Sengupta PP, Khandheria BK, and Narula J.** Twist and untwist mechanics of the left ventricle. *Heart Fail Clin* 4: 315-324, 2008.
27. **Smith ML, Hudson DL, Graitzer HM, and Raven PB.** Exercise training bradycardia: the role of autonomic balance. *Med Sci Sports Exerc* 21: 40-44, 1989.
28. **Snell PG, Martin WH, Buckey JC, and Blomqvist CG.** Maximal vascular leg conductance in trained and untrained men. *J Appl Physiol* 62: 606-610, 1987.
29. **Waldman LK, Nosan D, Villarreal F, and Covell JW.** Relation between transmural deformation and local myofiber direction in canine left ventricle. *Circ Res* 63: 550-562, 1988.
30. **Wasserman K.** Determinants and detection of anaerobic threshold and consequences of exercise above it. *Circulation* 76: VI29-39, 1987.

CHAPTER SIX: General Summary and Conclusions

6.1 Overview of the Field of Study

In chapter two, the importance of studying LV rotation was explored and emphasized by examining the current state of the literature. The set of experiments presented in chapters three through five demonstrated the potential of LV rotation for providing insights beyond traditional assessment of LV function for the understanding of cardiac adaptations to endurance training and aging.

Ventricular rotation was described as early as the 1600s (9), and continues to be an area of interest for cardiac mechanics researchers up to the present day (17, 18, 22, 26). Previous studies on LV rotation were primarily conducted using isolated animal models (4, 7) with some instances of human experiments using implanted myocardial markers in patients undergoing heart transplantation (8, 14). MRI tissue tagging was developed and applied in human investigations (23, 28), yet limited access to MRI, as well as the complex nature of tagging data analysis made it an unwelcoming avenue for many cardiac researchers.

Advances in echocardiographic techniques such as tissue Doppler and speckle-tracking imaging have rekindled interest and improved accessibility for the study of LV rotation (10, 16, 19). The ability to non-invasively, and relatively inexpensively, quantify LV rotation has made large scale, and population specific investigations more realistic to accomplish. With new techniques at the disposal of cardiac scientists, much of the recent work with echocardiography has concentrated on describing LV rotation in different populations under varying conditions. Regardless of technique, little information has been acquired in athletes; therefore the series of investigations presented in this document

adds significantly to the knowledge base of LV rotation in young and old endurance-athletes. However, with new research tools comes the possibility to answer previously unanswerable questions, leaving much work to be done.

6.2 Integration and Applications of Thesis Results

The results presented in chapter three suggest that long-term aerobic endurance training can preserve LV rotation despite advancing age. Endurance training has previously been shown to have similar benefits for other diastolic indices of cardiac function (1, 21), although this is not always the case (2, 6). Numerous investigations have shown LV torsion to be elevated and untwisting rates to be prolonged in older sedentary individuals (13, 24, 27). These alterations in resting LV rotation have been shown to be disadvantageous during exercise, as there is no torsion reserve in older individuals (3). Our results suggest that prolonged aerobic exercise training can prevent the alterations in LV rotation at rest, and this preservation of function may additionally be beneficial during exercise. However, we did not measure exercising LV rotation in our older athletes, and so we can only speculate about exercise responses.

The lack of exercise data was the major limitation in the study presented in chapter three, and so the use of physiological stressors (i.e. exercise and LBNP) was applied in the subsequent investigations in order to better discern group differences in LV rotation. Despite the absence of exercise data, the LV rotational information presented in chapter three is the largest data set (sample size) of athletes reported to date. Very few previous studies have examined LV rotation in athletes (15, 20, 23) regardless of age, and so this data set will contribute substantially to the current knowledge in the field.

The majority of initial human studies of LV rotation were performed on individuals that had undergone heart transplantation; however none had examined LV rotation during exercise (8, 14). Heart transplantation provides a unique model of aging, whereby the average HTR is given a donor heart nearly two decades younger than their current age (25). To discern the effects of aging we compared HTR with individuals matched to the age of the recipient as well as the age of the donor in chapter four. Our control subjects responded to exercise similarly to what had been previously reported for young and older individuals (3, 17). The major finding of the investigation was that HTR responded similarly to older individuals despite having a relatively young heart. This suggests that since transplantation, the donor heart has aged rapidly, accounting for the similarities between older and HTR. However, this conclusion must be tempered somewhat, as heart transplantation is a very complex procedure involving cardiac denervation, ischemia, and a host of anti-rejection medications following surgery. These complex factors do not even consider the pre-transplant state of the patient, which may include factors such as hypertension, inactivity, diabetes, and obesity which may persist following transplant. Functionally, in terms of LV rotation, HTR appear to display accelerated aging of the cardiac allograft. But clinically, the fact that HTR did not respond worse than individuals the same age is encouraging.

In chapter four, it was important to make use of exercise to determine group differences between HTR and healthy controls. HTR function relatively normally at rest, yet with exercise their limitations are exposed (11). In addition, the results of this investigation support previous research (18), as well as the findings from chapter five, that emphasize the importance of systolic contraction for rapid diastolic recoil.

The data from chapter five are an extension of previous work from our laboratory, examining right and LV function during LBNP in endurance athletes (5). Cardiac adaptations have been shown to be significant contributors to the increased incidence of orthostatic intolerance in endurance athletes (1, 12); however, the influence of diastolic recoil has not been previously investigated. Similar to the findings in chapter four, a physiological stress was required to elicit group differences that were not present during rest. The consistency with which the peak recoil rate of endurance athletes slowed (seven of eight athletes) and increased in normally active individuals (seven of eight) was convincing. These data suggest that an inability to maintain or increase peak recoil rate in response to reductions in preload may be an important contributing mechanism to orthostatic intolerance in endurance-trained individuals.

The major limitation of the investigation presented in chapter five was the fact that LV rotation was not assessed during pre-syncope. This would have allowed us to make more definitive statements about the relationship between LV recoil and orthostatic intolerance. However, the safety of conducting orthostatic tolerance tests to pre-syncope inside an MRI scanner while in an LBNP chamber may not be ideal for participants. Despite these limitations, this investigation used the "gold-standard" measurement technique (cardiac MRI) for the assessment of cardiac volumes (right and left), and LV rotation. This fact, as well as the intriguing findings, will ensure this investigation makes a significant contribution to the literature.

6.3 Future Research

This series of investigations has produced new information regarding the LV rotational responses in HTR, endurance-trained athletes and older individuals. Previous

investigations examining resting LV rotation in endurance athletes and sedentary individuals are contradictory (20, 23). Our results showing the impact of endurance training on age related changes in LV rotation and rotational responses to LBNP demonstrate that endurance training has a significant impact on LV rotation; however, these alterations in rotation were not apparent at rest.

The remaining major question in the area of LV rotation, endurance training and aging is: How does endurance training influence LV rotation during exercise? Exercise is the stimulus for these adaptations to LBNP and aging, yet how exercising LV rotation differs between trained and untrained individuals, both young and old, remains unknown. Answering this question completely would not be simple, particularly with current technology. At rest, cardiac ultrasound images can usually be optimized; however, during exercise, movement and breathing artifacts can drastically reduce image quality. It is for that reason that in our HTR exercise experiment, individuals exercised at a relatively low intensity (heart rate of approximately 120 beats per minute) with their back supported. To adequately image an individual, particularly an athlete, at high ventilations under severe strain during near maximal exercise would be extremely difficult. It should be noted that data for LV rotational analysis needs to be of a significantly higher quality than that which can be considered acceptable for simple volume or area analysis. As well, the physical constraints of MRI coupled with the necessity for breath holds during image acquisition also do not make myocardial tagging with MRI an option to compare differences between athletes and controls during exercise. Hopefully, future advances in imaging technology may make the ability to assess LV rotation in athletes near maximal exercise feasible.

An additional factor to be considered in future investigations on LV rotation is the incorporation of exercise training studies rather than cross-sectional analysis. Training studies could help determine the time course of ventricular adaptations in LV rotation. It appears as though cardiac adaptations, such as improved LV compliance, take years of endurance training to manifest (12), yet the time course of alterations in LV rotation remain uncertain.

6.4 Chapter Six References

1. **Arbab-Zadeh A, Dijk E, Prasad A, Fu Q, Torres P, Zhang R, Thomas JD, Palmer D, and Levine BD.** Effect of aging and physical activity on left ventricular compliance. *Circulation* 110: 1799-1805, 2004.
2. **Baldi JC, McFarlane K, Oxenham HC, Whalley GA, Walsh HJ, and Doughty RN.** Left ventricular diastolic filling and systolic function of young and older trained and untrained men. *J Appl Physiol* 95: 2570-2575, 2003.
3. **Burns AT, La Gerche A, Macisaac AI, and Prior DL.** Augmentation of Left Ventricular Torsion with Exercise is Attenuated with Age. *J Am Soc Echocardiogr*, 2007.
4. **Dong SJ, Hees PS, Huang WM, Buffer SA, Jr., Weiss JL, and Shapiro EP.** Independent effects of preload, afterload, and contractility on left ventricular torsion. *Am J Physiol* 277: H1053-1060, 1999.
5. **Esch BT, Scott JM, Haykowsky MJ, McKenzie DC, and Warburton DE.** Diastolic ventricular interactions in endurance-trained athletes during orthostatic stress. *Am J Physiol Heart Circ Physiol* 293: H409-415, 2007.
6. **Fleg JL, Shapiro EP, O'Connor F, Taube J, Goldberg AP, and Lakatta EG.** Left ventricular diastolic filling performance in older male athletes. *Jama* 273: 1371-1375, 1995.
7. **Gibbons Kroeker CA, Tyberg JV, and Beyar R.** Effects of load manipulations, heart rate, and contractility on left ventricular apical rotation. An experimental study in anesthetized dogs. *Circulation* 92: 130-141, 1995.
8. **Hansen DE, Daughters GT, 2nd, Alderman EL, Ingels NB, Stinson EB, and Miller DC.** Effect of volume loading, pressure loading, and inotropic stimulation on left ventricular torsion in humans. *Circulation* 83: 1315-1326, 1991.
9. **Harvey W.** *Cardiac Classics*. London, England: Henry Kimpton, 1941.
10. **Helle-Valle T, Crosby J, Edvardsen T, Lyseggen E, Amundsen BH, Smith HJ, Rosen BD, Lima JA, Torp H, Ihlen H, and Smiseth OA.** New noninvasive method for assessment of left ventricular rotation: speckle tracking echocardiography. *Circulation* 112: 3149-3156, 2005.
11. **Kao AC, Van Trigt P, 3rd, Shaeffer-McCall GS, Shaw JP, Kuzil BB, Page RD, and Higginbotham MB.** Central and peripheral limitations to upright exercise in untrained cardiac transplant recipients. *Circulation* 89: 2605-2615, 1994.
12. **Levine BD, Lane LD, Buckey JC, Friedman DB, and Blomqvist CG.** Left ventricular pressure-volume and Frank-Starling relations in endurance athletes. Implications for orthostatic tolerance and exercise performance. *Circulation* 84: 1016-1023, 1991.
13. **Lumens J, Delhaas T, Arts T, Cowan BR, and Young AA.** Impaired subendocardial contractile myofiber function in asymptomatic aged humans, as detected using MRI. *Am J Physiol Heart Circ Physiol* 291: H1573-1579, 2006.
14. **Moon MR, Ingels NB, Jr., Daughters GT, 2nd, Stinson EB, Hansen DE, and Miller DC.** Alterations in left ventricular twist mechanics with inotropic stimulation and volume loading in human subjects. *Circulation* 89: 142-150, 1994.
15. **Neilan TG, Ton-Nu TT, Jassal DS, Popovic ZB, Douglas PS, Halpern EF, Marshall JE, Thomas JD, Picard MH, Yoerger DM, and Wood MJ.** Myocardial

adaptation to short-term high-intensity exercise in highly trained athletes. *J Am Soc Echocardiogr* 19: 1280-1285, 2006.
16. **Notomi Y, Lysyansky P, Setser RM, Shiota T, Popovic ZB, Martin-Miklovic MG, Weaver JA, Oryszak SJ, Greenberg NL, White RD, and Thomas JD.** Measurement of ventricular torsion by two-dimensional ultrasound speckle tracking imaging. *J Am Coll Cardiol* 45: 2034-2041, 2005.
17. **Notomi Y, Martin-Miklovic MG, Oryszak SJ, Shiota T, Deserranno D, Popovic ZB, Garcia MJ, Greenberg NL, and Thomas JD.** Enhanced ventricular untwisting during exercise: a mechanistic manifestation of elastic recoil described by Doppler tissue imaging. *Circulation* 113: 2524-2533, 2006.
18. **Notomi Y, Popovic ZB, Yamada H, Wallick DW, Martin MG, Oryszak SJ, Shiota T, Greenberg NL, and Thomas JD.** Ventricular untwisting: a temporal link between left ventricular relaxation and suction. *Am J Physiol Heart Circ Physiol* 294: H505-513, 2008.
19. **Notomi Y, Setser RM, Shiota T, Martin-Miklovic MG, Weaver JA, Popovic ZB, Yamada H, Greenberg NL, White RD, and Thomas JD.** Assessment of left ventricular torsional deformation by Doppler tissue imaging: validation study with tagged magnetic resonance imaging. *Circulation* 111: 1141-1147, 2005.
20. **Nottin S, Doucende G, Schuster-Beck I, Dauzat M, and Obert P.** Alteration in left ventricular normal and shear strains evaluated by 2D-strain echocardiography in the athlete's heart. *J Physiol* 586: 4721-4733, 2008.
21. **Prasad A, Popovic ZB, Arbab-Zadeh A, Fu Q, Palmer D, Dijk E, Greenberg NL, Garcia MJ, Thomas JD, and Levine BD.** The effects of aging and physical activity on Doppler measures of diastolic function. *Am J Cardiol* 99: 1629-1636, 2007.
22. **Streeter DD, Jr., Spotnitz HM, Patel DP, Ross J, Jr., and Sonnenblick EH.** Fiber orientation in the canine left ventricle during diastole and systole. *Circ Res* 24: 339-347, 1969.
23. **Stuber M, Scheidegger MB, Fischer SE, Nagel E, Steinemann F, Hess OM, and Boesiger P.** Alterations in the local myocardial motion pattern in patients suffering from pressure overload due to aortic stenosis. *Circulation* 100: 361-368, 1999.
24. **Takeuchi M, Nakai H, Kokumai M, Nishikage T, Otani S, and Lang RM.** Age-related changes in left ventricular twist assessed by two-dimensional speckle-tracking imaging. *J Am Soc Echocardiogr* 19: 1077-1084, 2006.
25. **Taylor DO, Edwards LB, Boucek MM, Trulock EP, Aurora P, Christie J, Dobbels F, Rahmel AO, Keck BM, and Hertz MI.** Registry of the International Society for Heart and Lung Transplantation: twenty-fourth official adult heart transplant report--2007. *J Heart Lung Transplant* 26: 769-781, 2007.
26. **Torrent-Guasp F, Ballester M, Buckberg GD, Carreras F, Flotats A, Carrio I, Ferreira A, Samuels LE, and Narula J.** Spatial orientation of the ventricular muscle band: physiologic contribution and surgical implications. *J Thorac Cardiovasc Surg* 122: 389-392, 2001.
27. **van Dalen BM, Soliman OI, Vletter WB, ten Cate FJ, and Geleijnse ML.** Age-related changes in the biomechanics of left ventricular twist measured by speckle tracking echocardiography. *Am J Physiol Heart Circ Physiol* 295: H1705-1711, 2008.

28. **Zerhouni EA, Parish DM, Rogers WJ, Yang A, and Shapiro EP.** Human heart: tagging with MR imaging--a method for noninvasive assessment of myocardial motion. *Radiology* 169: 59-63, 1988.

APPENDIX A: ETHICS CERTIFICATE OF APPROVAL

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

ETHICS CERTIFICATE OF EXPEDITED APPROVAL: RENEWAL

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

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

Institution	Site
UBC	Vancouver (excludes UBC Hospital)
N/A	N/A

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

CO-INVESTIGATOR(S):
N/A

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

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

EXPIRY DATE OF THIS APPROVAL: April 17, 2010

APPROVAL DATE: April 17, 2008

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

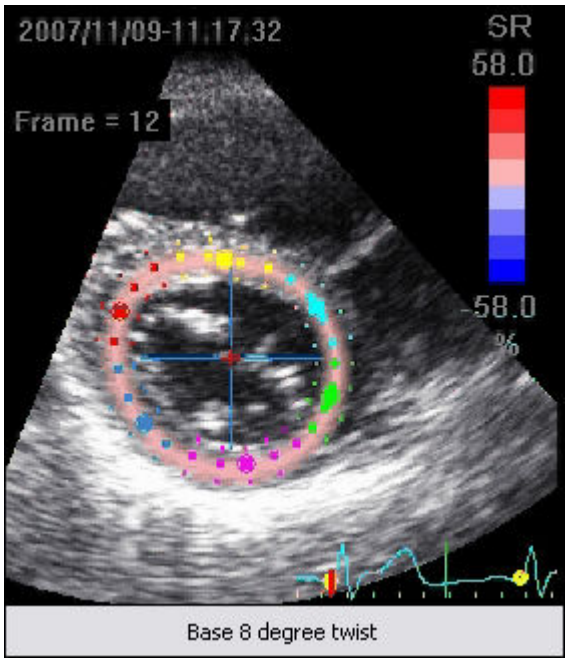
The Chair of the UBC Clinical Research Ethics Board has reviewed the documentation for the above named project. The research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved for renewal by the UBC Clinical Research Ethics Board.

Approval of the Clinical Research Ethics Board by :

Dr. Stephen Hoption Cann , Associate Chair

APPENDIX B: SPECKLE TRACKING IMAGING ANALYSIS

A.



B.

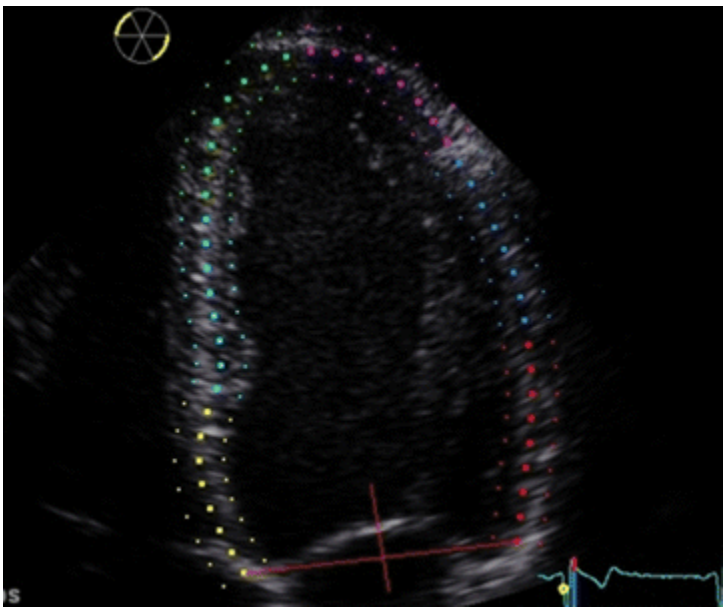


Figure B.1 Measurement of left ventricular strain and rotation by two-dimensional speckle tracking analysis
A) Left ventricular rotation as well as radial and circumferential strain data (as well as the velocities of each) were derived using the width of the myocardium in a parasternal short axis view; B) Longitudinal strain and strain rate were derived from the width of the myocardium using an apical 4-chamber view.

APPENDIX C: CARDIAC MAGNETIC RESONANCE IMAGING ANALYSIS

A. B.

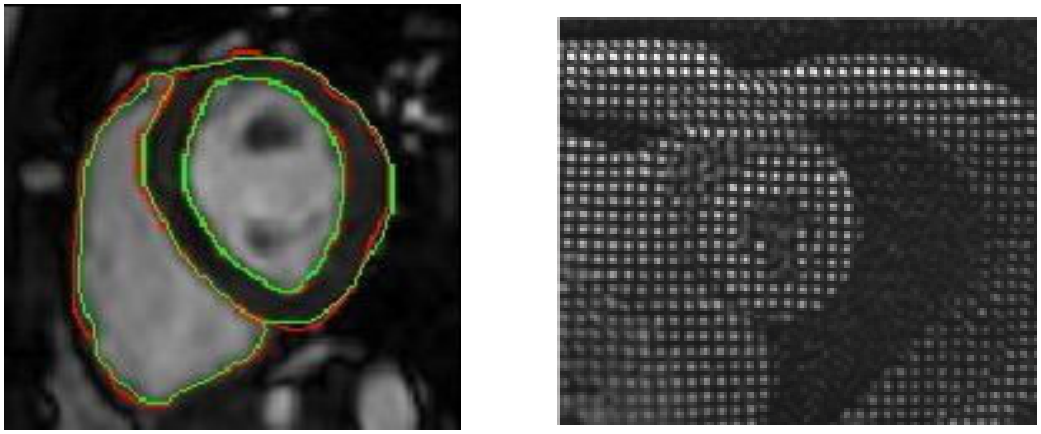


Figure C.1 Measurement of ventricular volumes, rotation and strain by MRI
A) Assessment of right and LV volumes was performed by manually tracing segments of short-axis cines at end diastole and end systole; B) Myocardial tissue tagging assessment of ventricular rotation and circumferential strain. Tagged images were analyzed using a custom designed image morphing software package.