ATRIAL PHASIC FUNCTION DURING EXERCISE: 
THE ROLE OF ATRIOVENTRICULAR COUPLING

by

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for the degree of Master of Science
Graduate Department of Exercise Sciences
University of Toronto

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Atrial phasic function during exercise: the role of atrioventricular coupling

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ABSTRACT

Left ventricular (LV) filling increases during exercise, but left atrial (LA) phasic function and its contribution to LV filling is poorly understood. Sixteen endurance-trained middle-aged males were studied at rest and during light (LE) and moderate (ME) intensity cycle-ergometry. Atrioventricular-plane displacement (AVPD) increased from rest to LE (from 14±2 mm to 18±2 mm, p<0.01), but did not increase further at ME. LA reservoir volume increased from rest to LE (from 32±8 mL to 40±10 mL, p<0.01). LA passive contribution increased at LE (from 21±5 mL to 27±8 mL, p<0.01), while LA active contribution increased from rest only at ME (from 12±5 mL to 23±9 mL, p<0.01). AVPD, and thus the longitudinal shortening of LV systole, contributes to LA filling primarily during LE, but is a limited mechanism beyond LE. These data suggest that LV filling appears to shift to a reliance on conduit function to increase LV filling at ME.
ACKNOWLEDGEMENTS

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# TABLE OF CONTENTS

ABSTRACT .............................................................................................................................................. ii
ACKNOWLEDGEMENTS ......................................................................................................................... iii
TABLE OF CONTENTS .............................................................................................................................. v
LIST OF TABLES ....................................................................................................................................... viii
LIST OF FIGURES ................................................................................................................................... ix
LIST OF APPENDICES ............................................................................................................................ x
ABBREVIATIONS ...................................................................................................................................... xi
EQUATIONS ............................................................................................................................................. xii

Chapter I: Introduction ............................................................................................................................ 1
  1.1 Rationale ........................................................................................................................................ 1
  1.2 Objectives ................................................................................................................................... 2
  1.3 Hypotheses .................................................................................................................................. 2

Chapter II: Review of Literature ........................................................................................................... 3
  2.1 Introduction ............................................................................................................................... 3
  2.2 Atrial Phasic Function ............................................................................................................. 3
    2.2.1 Reservoir Phase ............................................................................................................... 3
    2.2.3 Conduit Phase ................................................................................................................. 7
    2.2.4 Contractile Phase ............................................................................................................ 8
  2.3 Acute and Chronic Exercise Response ....................................................................................... 10
    2.3.1 Acute Exercise Response ............................................................................................... 10
    2.3.2 Atrial Function During Exercise .................................................................................. 10
    2.3.3 Response to Chronic Training ...................................................................................... 14
    2.3.4 The Influence of Aging ............................................................................................... 17
2.4 Echocardiographic Assessment of Cardiac Function ........................................... 18
  2.4.1 Dimensions and Volumes .................................................................................. 18
  2.4.2 Doppler Echocardiography ............................................................................. 20
  2.4.3 Tissue Tracking Doppler ................................................................................. 22
  2.4.4 Speckle-tracking Echocardiography ................................................................. 23
  2.5 Invasive Assessment ............................................................................................. 24

Chapter III: Manuscript for Journal Submission ......................................................... 25
  3.1 Abstract .................................................................................................................. 25
  3.2 Introduction ............................................................................................................. 26
  3.3 Methods .................................................................................................................. 27
    3.3.1 Experimental Design ....................................................................................... 27
    3.3.2 Subjects ............................................................................................................. 28
    3.3.3 Anthropometrics & Maximal Aerobic Power .................................................. 28
    3.3.4 Cardiac Assessment ......................................................................................... 29
    3.3.5 Exercise Protocol .............................................................................................. 30
    3.3.6 Echocardiography ............................................................................................ 30
    3.3.7 Invasive Hemodynamics ................................................................................. 32
    3.3.8 Statistics ............................................................................................................ 32
  3.4 Results ..................................................................................................................... 32
  3.5 Discussion ............................................................................................................... 37
  3.6 Limitations ............................................................................................................. 42
  3.7 Conclusions ............................................................................................................ 43

Chapter IV: Limitations, Future Directions, and Conclusions .................................... 55
  4.1 Technical Contributions and Acknowledgements ............................................... 55
4.2 Subject Recruitment and Compliance ................................................................. 55
4.3 Exercise Protocol .............................................................................................. 56
4.4 Data Analysis, Limitations, and Future Directions .............................................. 56
4.5 Conclusions ....................................................................................................... 58
References ............................................................................................................... 60
APPENDIX A: CONSENT FORM .............................................................................. 76
APPENDIX B: STUDY RECRUITMENT POSTER ...................................................... 85
APPENDIX C: PAR-Q+ ............................................................................................ 86
APPENDIX D: LIFETIME PHYSICAL ACTIVITY QUESTIONNAIRE ...................... 90
LIST OF TABLES

Table 1. Subject Characteristics............................................................................................................. 44
Table 2. Cardiac volumes at rest and during exercise ............................................................................. 45
Table 3. Doppler characteristics at rest and during exercise ................................................................. 46
Table 4. Atrial myocardial strain and strain rates at rest and during exercise .................................... 47
Table 5. Ventricular myocardial strain and strain rates at rest and during exercise ......................... 48
Table 6. Hemodynamic data at rest and during exercise ....................................................................... 49
LIST OF FIGURES

Figure 1: Representative left atrial volume curve from one subject at rest, light exercise, and moderate exercise as a function of time normalized to R-R interval, beginning at the aortic valve closure.................................................................................................................................................. 50

Figure 2: Absolute contributions of LA volumes to LV stroke volume at rest, light exercise, and moderate exercise.......................................................................................................................................................... 51

Figure 3: Normalized contributions of LA volumes to LV stroke volume at rest, light exercise, and moderate exercise.................................................................................................................................................. 52

Figure 4: Correlation of change in LA maximal volume with change in atrioventricular plane displacement.................................................................................................................................................................. 53

Figure 5: Correlation of LA maximal volume normalized to body surface area with maximal oxygen update normalized to body mass............................................................................................................................................. 54
LIST OF APPENDICES

APPENDIX A: CONSENT FORM ................................................................. 76
APPENDIX B: STUDY RECRUITMENT POSTER ........................................... 85
APPENDIX C: PAR-Q+ ............................................................................. 86
APPENDIX D: LIFETIME PHYSICAL ACTIVITY QUESTIONNAIRE .............. 90
# ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>Late ventricular filling wave</td>
</tr>
<tr>
<td>ALS</td>
<td>Atrial longitudinal strain</td>
</tr>
<tr>
<td>ALSR</td>
<td>Atrial longitudinal strain rate</td>
</tr>
<tr>
<td>AR</td>
<td>Atrial reversal wave</td>
</tr>
<tr>
<td>AV</td>
<td>Atrioventricular</td>
</tr>
<tr>
<td>AVP</td>
<td>Atrioventricular plane</td>
</tr>
<tr>
<td>AVPD</td>
<td>Atrioventricular plane displacement</td>
</tr>
<tr>
<td>bpm</td>
<td>Beats per minute</td>
</tr>
<tr>
<td>cDTI</td>
<td>Color Doppler tissue imaging</td>
</tr>
<tr>
<td>CVP</td>
<td>Central venous pressure</td>
</tr>
<tr>
<td>D</td>
<td>Diastolic wave</td>
</tr>
<tr>
<td>DTI</td>
<td>Doppler tissue imaging</td>
</tr>
<tr>
<td>E</td>
<td>Early ventricular filling wave</td>
</tr>
<tr>
<td>EDV</td>
<td>End-diastolic volume</td>
</tr>
<tr>
<td>ESV</td>
<td>End-systolic volume</td>
</tr>
<tr>
<td>fps</td>
<td>Frames per second</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>IVRT</td>
<td>Isovolumetric relaxation time</td>
</tr>
<tr>
<td>LA</td>
<td>Left atrium/atrial</td>
</tr>
<tr>
<td>LAMAX</td>
<td>Left atrial maximal volume</td>
</tr>
<tr>
<td>LAMIN</td>
<td>Left atrial minimal volume</td>
</tr>
<tr>
<td>LAPRE-A</td>
<td>Left atrial pre-contraction volume</td>
</tr>
<tr>
<td>LAP</td>
<td>Left atrial pressure</td>
</tr>
<tr>
<td>LV</td>
<td>Left ventricle/ventricular</td>
</tr>
<tr>
<td>LVDP</td>
<td>Left ventricular diastolic pressure</td>
</tr>
<tr>
<td>MCFP</td>
<td>Mean circulatory filling pressure</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>PADP</td>
<td>Pulmonary artery diastolic pressure</td>
</tr>
<tr>
<td>PALS</td>
<td>Peak atrial longitudinal strain</td>
</tr>
<tr>
<td>PASP</td>
<td>Pulmonary artery systolic pressure</td>
</tr>
<tr>
<td>PAWP</td>
<td>Pulmonary artery wedge pressure</td>
</tr>
<tr>
<td>PCWP</td>
<td>Pulmonary capillary wedge pressure</td>
</tr>
<tr>
<td>PV</td>
<td>Pulmonary veins/venous</td>
</tr>
<tr>
<td>RA</td>
<td>Right atrium/atrial</td>
</tr>
<tr>
<td>RAP</td>
<td>Right atrial pressure</td>
</tr>
<tr>
<td>RMAX</td>
<td>Right atrial maximal volume</td>
</tr>
<tr>
<td>RMIN</td>
<td>Right atrial minimal volume</td>
</tr>
<tr>
<td>RAPRE-A</td>
<td>Right atrial pre-contraction volume</td>
</tr>
<tr>
<td>RT3DE</td>
<td>Real-time 3 dimensional echo</td>
</tr>
<tr>
<td>RV</td>
<td>Right ventricle/ventricular</td>
</tr>
<tr>
<td>S</td>
<td>Systolic wave</td>
</tr>
<tr>
<td>STE</td>
<td>Speckle tracking echo</td>
</tr>
<tr>
<td>SV</td>
<td>Stroke volume</td>
</tr>
<tr>
<td>TPALS</td>
<td>Time to peak atrial longitudinal strain</td>
</tr>
<tr>
<td>TT</td>
<td>Tissue tracking</td>
</tr>
<tr>
<td>VO2MAX</td>
<td>Maximal oxygen uptake</td>
</tr>
</tbody>
</table>
EQUATIONS

LV Stroke Volume = (LV End-diastolic Volume) – (LV End-systolic Volume)

LA Reservoir Volume = (LA Maximum Volume) – (LA Minimum Volume)

LA Passive Emptying Volume = (LA Maximum Volume) – (LA Pre-contraction Volume)

LA Active Emptying Volume = (LA Pre-contraction Volume) – (LA Minimum Volume)

Conduit Volume = (LV Stroke Volume) – (LA Reservoir Volume)
Chapter I: Introduction

1.1 Rationale

Physical exercise precipitates a host of physiological alterations to meet the elevated oxygen requirement of working muscle, including an increase in cardiac output through increased heart rate (HR) and stroke volume (SV). Some of the increase in stroke volume can be attributed to greater intrinsic contractility leading to a reduced end-systolic volume (ESV); however, a large portion of the increase can be explained by improved diastolic filling and a larger end-diastolic volume (EDV) (Warburton et al., 2002). The atria play a key role in this process, rather than being simple conduits of blood. In fact, the atria have important roles in modulating ventricular filling through their reservoir, conduit, and pump functions. These phasic functions have been well described at rest; however, there is a paucity of data characterizing atrial function during submaximal exercise.

The reservoir function may be influenced by myocardial compliance, ventricular systolic performance, or preload (Barbier et al., 1999; Henein and Gibson, 1999). Atrial filling is mechanically coupled to ventricular emptying through the atrioventricular plane (AVP), as the atria expand passively through external work applied to the AVP by ventricular longitudinal shortening (Carlsson et al., 2007); however, the degree to which preload is simultaneously increased through elevated central venous and pulmonary pressure through the range of exercise intensities is unknown (Cheng et al., 1992; Nose et al., 1994; West, 1998). As HR increases with exercise intensity, a decrease in filling time progressively reduces the period of diastasis, with fusion of the early passive and late active filling waves occurring at heart rates approaching 120 beats per minute (bpm) (Kilner et al., 1997). A consequence of this is a reduced time for conduit phase and an increased volume in the atria at the beginning of atrial pump phase, eliciting an...
increase in active emptying via the Frank-Starling mechanism. Thus, during exercise, the atria serve to modulate the relative atrial phasic contributions to optimize ventricular filling.

Endurance training is known to improve diastolic function both at rest and during exercise (Levy et al., 1993). Although the increased ventricular compliance seen in endurance-trained individuals (Levine et al., 1991) explains some of the improvement in ventricular filling, it is likely that alterations in atrial performance also explain this improvement. Long-term endurance training elicits morphological and functional remodeling in the atria, with increased reservoir volume and passive emptying found at rest in highly trained individuals (Kasikcioglu et al., 2006; D’Andrea et al., 2010; Scharf et al., 2010). These changes likely persist during exercise, with an increase in exercising reservoir volume improving passive ventricular filling.

1.2 Objectives

1) To determine what mechanisms underlie the augmentation of atrial filling during submaximal exercise.

2) To examine how altered left atrial phasic function influences ventricular filling during exercise.

1.3 Hypotheses

1) Improved left ventricular longitudinal shortening increases AVPD, augmenting the reservoir function of the atrium during incremental exercise.

2) Increased left atrial reservoir volume increases passive early atrial emptying progressively during exercise.

3) Greater left atrial reservoir volume and an earlier onset of atrial contraction during incremental exercise results in a larger atrial volume at the onset of contraction, and increases active emptying via the Starling mechanism.
Chapter II: Review of Literature

2.1 Introduction

This review will begin by describing the normal phasic function of the atria, and the physiological factors which influence the reservoir, conduit, and contractile phases. The response of the atria to acute exercise will be discussed, along with the modifications associated with long-term endurance training. Finally, the relevant methods of assessing cardiac function will be reviewed, with a detailed description of the various ways echocardiography can be applied to quantitatively evaluate cardiac function both at rest and during exercise.

2.2 Atrial Phasic Function

Far from being simple conduits for blood returning from systemic and pulmonary circulation, the atria have important roles in the diastolic filling of the ventricles through the rapid transfer of a high volume of blood at low pressure across the atrioventricular valves. Functionally, the atria have been well defined as having three distinct phases, with the reservoir phase occurring during ventricular systole, and the conduit and contractile phases corresponding to early and late ventricular filling, respectively (Blume et al., 2011).

2.2.1 Reservoir Phase

From the closing of the atroventricular (AV) valves, the first phase of atrial function is the reservoir phase, during which a volume of blood is accumulated for rapid transfer to the ventricle (Barbier et al., 1999). This phase can be further subdivided into the early and late components, which are influenced by different variables; the early reservoir phase occurs during atrial myocardial relaxation, while the late component is influenced by myocardial compliance and ventricular longitudinal shortening, which lowers the AV plane, thereby increasing atrial volume.
The beginning of the reservoir phase can be characterized by venous inflow filling the atrium, while the atrial myocardium relaxes following the preceding contraction. Atrial mean and peak filling rates during reservoir phase are significantly correlated with various indices of atrial active emptying from the previous contraction (Toma et al., 1987), as the rate of relaxation is proportionate to contraction force. Appleton et al. have shown that pulmonary venous (PV) and left atrial (LA) pressures equalize just proximal to the PV-LA junction (Appleton and Christopher, 1997). Although early studies suggested that LA filling was influenced by elevated pulmonary venous (PV) pressure secondary to the right ventricular (RV) pressure pulse (Morkin et al., 1965), later work suggested that LA filling is primarily influenced by left heart dynamics (Keren et al., 1985). Recent studies examining the changes in pulmonary venous pressures suggests that the biphasic PV velocity waveform is increased in the early reservoir phase by suction secondary to atrial relaxation, and during the late component by forward propagation of the RV pressure pulse (Castello et al., 1991; Smiseth et al., 1999; Barbier et al., 2000). Thus it seems likely that the early component of atrial filling is attributable to myocardial relaxation.

In the late reservoir phase, the relaxed atrium is passively filled by venous inflow, and augmented by the descent of the cardiac base. Myocardial inactivation and the compliance of the thin-walled atria are important in facilitating filling from venous inflow at low pressures (Barbier et al., 1999). This compliance is important in overall cardiac function, as it buffers pressure changes throughout the cardiac cycle (Suga, 1974; Hoit et al., 1993), allowing the atrium to accept volume during the reservoir phase, while maintaining the viability of passive emptying during the subsequent conduit phase. The right and left atrial appendages are two sac-like structures connected to the atria of distinct embryological origin, and which have a role in overall compliance of the chambers. The compliance of these structures is higher than that of the atria
proper (Davis et al., 1990; Hondo et al., 1995), and allows for greater volume expansion at a given pressure due to their high distensibility. This high compliance may serve a protective role, buffering increases in pulmonary pressure which may otherwise damage the pulmonary capillaries by accepting more volume (Kihara et al., 1988).

Concurrent with the passive filling of the atria, LV contraction is a product of circumferential, radial, and longitudinal fiber contraction. There is a mechanical coupling of ventricular longitudinal contraction and atrial reservoir function (Henein and Gibson, 1999; Carlsson et al., 2007), as the descent of the cardiac base causes chamber expansion of the atria with a reduction in atrial minimal pressure, analogous to the piston in a syringe. This creates a suction effect, and draws blood into the atria from the caval and pulmonary veins (Keren et al., 1988; Fujii et al., 1994), and it has been shown that the rate of LA area change in the late reservoir phase is solely dependent on the change of LV length (Barbier et al., 1999). The effects of atrioventricular plane displacement (AVPD) differ between the left and right heart. It has been shown that the longitudinal contribution to ventricular stroke volume is higher in the right heart than the left (Carlsson et al., 2007; Carlsson et al., 2007), due to a greater AVPD. Accordingly, during ventricular systole a greater amount of filling occurs in the right atrium (RA) than the left (Carlsson et al., 2007), resulting in a larger reservoir volume in the RA than the LA. Inflow characteristics in the late component of the reservoir phase also differ between left and right heart. Although the late component of the pulmonary flow pulse is dominated by a forward-compression wave secondary to the RV systolic pulse (Smiseth et al., 1999), this observation is of the dominant wave-form and may mask the suction effect caused by the descent of the cardiac base. Conversely, inflow from the caval veins demonstrates a larger peak during ventricular
systole with a smaller peak during diastole (Sivaciyan and Ranganathan, 1978; Carlsson et al., 2007).

2.2.2 Central and Pulmonary Venous Pressure

Due to the influence that central and pulmonary venous filling pressures exert on atrial filling, a brief discussion is warranted. As opposed to the high-pressure arterial vasculature, the venous system operates at a low pressure that functions as a reservoir for volume which can be mobilized when demand increases, with small changes in pressure eliciting a large movement of volume due to its high capacitance (Hainsworth, 1990). Mean circulatory filling pressure (MCFP), the equilibrium pressure of the circulatory system, usually measures in the range of 7-11mmHg, while the pressure of blood returning to the RA through the superior and inferior vena cava normally measures 2-3mmHg (Guyton, 1955). The pressure gradient across the peripheral resistance from the arterial to the venous circulation drives venous return to the heart, influenced by changes in either cardiac output or peripheral resistance, central venous pressure (CVP). The flow in the caval veins is characterized by a large forward flow during systole, followed by a smaller peak during diastole (Sivaciyan and Ranganathan, 1978), with a flow reversal seen in response to RA contraction (Appleton et al., 1987; Cohen et al., 1996).

The pulmonary circulation receives deoxygenated blood from the right ventricle and transports it to the lungs via the pulmonary arteries. Gas exchange occurs as blood transits the pulmonary capillaries, then returns to the left heart via the pulmonary veins. Due to differences between the systemic and pulmonary circulation in structure and function, the pulmonary system operates at a lower range of pressures. RV contraction causes pulmonary arterial pressure to rise to approximately 21 mmHg in the supine position, which decreases during diastole to a minimum of approximately 9 mmHg (Kovacs et al., 2009). As only a relatively small pressure
gradient is required to drive flow from the right heart to the left, in part due to the compliant, low resistance nature of the pulmonary circulation, pulmonary capillary pressure is lower, averaging approximately 7.0 mmHg and ranging from 4-10 mmHg at rest (Thadani and Parker, 1978; Cope et al., 1992), while there is some evidence of increases of up to 20.0 mmHg during exercise stress (Ekelund and Holmgren, 1967; Wagner et al., 1986).

2.2.3 Conduit Phase

Following atrial filling, the conduit phase of atrial function is characterized by passive emptying of blood into the ventricles. Temporally, the conduit phase is defined as beginning with the opening of the AV valves when ventricular pressure drops below atrial pressure, and ending with the onset of atria contraction (Nagueh et al., 2009), as reflected by the P-wave signaling the beginning of the booster-pump phase. With the opening of the AV valves, blood empties from the reservoir in the atria into the ventricles, although it has been demonstrated by Bowman and Kovacs (2004) that blood from both the reservoir volume stored in the LA and from the conduit volume originating in the pulmonary veins crosses the mitral valve simultaneously, suggesting that early ventricular diastolic filling occurs from both atrial and venous volumes in parallel, rather than in a serial sequence where blood from venous origin would follow the complete emptying of the reservoir volume.

The early portion of the conduit phase is associated with a rapid filling of the ventricles; as flow rate relies on the AV pressure gradient, rapid ventricular relaxation is critical to normal conduit function. While the period immediately prior to AV valve opening is characterized by isovolumetric relaxation of the ventricles, ventricular relaxation extends into early diastole (Fioretti et al., 1980). As pressure in the ventricles continues to fall even as volume increases, a mechanical augmentation of filling occurs through the creation of a suction effect which draws
blood into the chamber (Courtois et al., 1988; Brun et al., 1992); this suction effect facilitates the rapid evacuation of the atrial reservoir volumes into the ventricles. It has been demonstrated in the left heart that peak transmitral flow velocity occurs just prior to minimal pressure in the left ventricle (Courtois et al., 1988), highlighting the importance of ventricular relaxation in normal conduit function, and the dynamic interplay which exists between atrium and ventricle. Impaired ventricular relaxation has a negative impact on conduit function through a reduction in passive emptying volume and early ventricular filling (Brun et al., 1992; Nagueh et al., 2009), and for this reason it has been suggested that conduit function may be better described as a property of the left ventricle (Bowman and Kovács, 2004).

The late component of the conduit phase occurs during diastasis, as slow filling of the ventricle occurs with little change in atrial volume. With a reduction in the magnitude of the AV pressure gradient, flow velocity decreases, and the atria serve as true conduits for blood from the caval and pulmonary veins across to the ventricles (Morkin et al., 1965). Following this slow filling, atrial depolarization and contraction occur, signaling the end of the conduit phase.

2.2.4 Contractile Phase

The onset of the P-wave on ECG tracings signals the beginning of atrial contraction, as the depolarization wave spreads from the sino-atrial node across the myocardium of the two chambers. In the healthy normal heart, active atrial emptying explains approximately 15-20 percent of left ventricular filling at rest, with some studies reporting an increase of up to 37 percent during exercise stress at heart rates above 180 beats per minute (bpm) as passive filling time decreases (Mitchell et al., 1965). The variability in the contribution of each phase of filling is important in optimizing filling across varying conditions, and the increase in active emptying can largely be explained by loading conditions, intrinsic contractility, and atrial afterload.
As in the ventricles, atrial output is highly dependent on the Frank-Starling mechanism, and atrial contraction force is a direct function of preload (Alexander Jr et al., 1987). With an increase in atrial volume and pressure, myocardial fibers are subjected to greater mechanical stretch. This stretch augments contractile force through altered calcium sensitivity of Troponin C (Babu et al., 1988), and through mechanical optimization of filament overlap to produce more cross-bridges (Landesberg and Sideman, 1994). Optimal LV sarcomere length is approximately 2.2μm (Weiwad et al., 2000), and the normal range of function is within 10% of the optimal length (Grimm and Whitehorn, 1968); however, this optimal length may be larger in the atrial myocardium. Beyond this optimal length a sharp reduction in contractile force generation is observed in isolated cardiac myofibril preparations due to structural alterations in cardiac sarcomeres, intrinsic changes in titin (Weiwad et al., 2000), and altered myofilament calcium sensitivity (Konhilas et al., 2002). When the sarcomere is stretched, tropomyosin stiffens. The free energy from calcium is then able to activate more neighboring troponin complexes, allowing for greater thin filament activation at a given concentration of calcium (Farman et al., 2010).

Similarly, it has been demonstrated in dogs that the Frank-Starling mechanism holds when using atrial diameter as an index of preload (Payne et al., 1971). With continued atrial expansion from a volume infusion, the effectiveness of atrial systolic contraction is impaired, suggesting a point of ‘critical distension’ beyond which contractile function declines. Also, differences in myosin chain properties, including phosphorylation levels and calcium sensitivity of the myosin light chains are associated with faster shortening velocity in skinned atrial fibers than ventricular fibers, while ventricular myosin light chains are more calcium sensitive (Morano et al., 1988).

The pump function of the atria is also influenced by afterload from the ventricles during late diastole. In the normal heart, ventricular relaxation is complete by mid-diastole, and the
chamber stiffens as volume increases. With impaired or delayed ventricular relaxation, the early
passive filling wave is blunted; this causes an increased volume in the atria at the time of atrial
contraction, and through an augmentation of the Frank-Starling mechanism, a compensatory
increased late filling wave (Appleton et al., 1988; Little et al., 1998). In the face of greatly
increased ventricular stiffness, however, the transfer of volume from the atria during atrial
contraction is blunted (Sanada et al., 1991), and the A-wave is reduced (Thomas and Weyman,
1991), resulting in a failure of the atrial booster-pump to compensate for the loss of early filling.

2.3 Acute and Chronic Exercise Response

2.3.1 Acute Exercise Response

Cardiac function is augmented in response to exercise, with increases in heart rate and
stroke volume resulting in up to a five-fold increase in cardiac output at maximal effort (Vatner
and Pagani, 1976). With the onset of exercise, withdrawal of parasympathetic influence at the
sino-atrial node results in an acute increase in heart rate, which is further elevated by sympathetic
stimulation as exercise progresses in intensity and duration (Nakamura et al., 1993; Dawson et
al., 2005). A consequence of increasing heart rate is a reduction in filling time, however, stroke
volume is maintained or increased despite this (Higginbotham et al., 1986; Sundstedt et al.,
2007); thus, ventricular filling must be enhanced.

2.3.2 Atrial Function During Exercise

During exercise, atrial phasic function is altered to optimize diastolic ventricular filling
despite a reduced filling time. During exercise, early rapid and late filling are both augmented,
with the relative contribution of each component being more equal compared to at rest (Carroll et
al., 1983), while the progressive reduction of diastasis with increasing exercise intensity results
in the disappearance of slow filling (Chung et al., 2004), and fusion of the early and late filling waves (Kilner et al., 1997).

**Early filling**

There is evidence that atrial reservoir function is augmented during exercise (Nishikawa et al., 1994; Gaynor et al., 2005). The reservoir function is determined primarily by compliance and longitudinal displacement of the atroventricular valves (Barbier et al., 1999; Gaynor et al., 2005). During exercise, AVPD increases with heart rate (Saha et al., 2004; Quintana et al., 2005), augmenting the suction effect and increasing atrial filling rate. It has been shown in dogs that during exercise, the increase in LV long-axis shortening occurs in parallel with a reduction in LA minimal pressure and a peak in forward PV flow, suggesting that this increase in atrial filling rate can be attributed to a greater PV-LA pressure gradient, driven by a reduction in minimal atrial pressure rather than an increase in venous pressure (Nishikawa et al., 1994). As the longitudinal component of stroke volume is greater in the RV (Carlsson et al., 2007), a greater amount of venous filling during systole occurs, and the role of AVPD is likely amplified with respect to the RA during exercise. Further, atrial relaxation occurs more quickly during exercise which may reduce the time to peak filling rate. The atria are compliant, thin-walled structures, such that small changes in pressure can elicit significant changes in volume. During exercise, the ventricle ejects a greater amount of blood, which has the effect of reducing intrapericardial pressure. This would have the effect of increasing the ‘effective’ compliance of the atria, allowing for greater filling at a given pressure (Nishikawa et al., 1994). Indeed, pericardiotomy has been shown to increase the compliance of the atrium (Maniar et al., 2003), and cause a shift in function from conduit to reservoir (Gaynor et al., 2005).
The issue of pulmonary and central venous pressure during exercise remains contentious. A number of studies have failed to find a significant change in pulmonary or left atrial pressure during exercise (Carroll et al., 1983; Cheng et al., 1992; Ha et al., 2003), while some authors support an increase (West, 1998). Data from right heart catheterization studies demonstrate that pulmonary arterial pressures may rise above 20mmHg in response to exercise stress, with an increase above 30mmHg in healthy normal individuals not uncommon, particularly in individuals over 50 years of age (Ekelund and Holmgren, 1967; Kovacs et al., 2009). A number of studies have shown elevation of LA and pulmonary capillary wedge pressure (PCWP) during exercise in animals, particularly horses (Erickson et al., 1990; Jones et al., 1992; Manohar, 1993), with evidence of elevations so high as to result in pulmonary hemorrhage (Whitwell and Greet, 1984; West et al., 1993). Some earlier studies suggest that this increase in pulmonary capillary pressure may also occur in humans during exercise (Thadani and Parker, 1978; Kitzman et al., 1991), although the increase of PCWP in controls during exercise from 3.0mmHg to 7.1mmHg observed by Kitzman et al. did not report any significance. There is some evidence that RA pressure may rise acutely with the onset of exercise due to increased venous return secondary to the action of the muscle pump or shunting of blood from splanchnic circulation (Nose et al., 1994; Notarius and Magder, 1996).

Alterations in ventricular performance influence specific aspects of diastolic filling. Despite the fact that mitral valve opening pressure has been shown to be unchanged during exercise, the rates of left ventricular isovolumetric relaxation and pressure decay are increased (Carroll et al., 1983; Cheng et al., 1992), potentially due to more rapid myocardial relaxation or augmented recoil of elastic elements following systolic compression, allowing for filling to begin more quickly (Udelson et al., 1990). The increased rate of pressure decay shifts the early
diastolic portion of the ventricular pressure-volume loop downward, with a development of transient negative pressure of -1.0 mmHg – -3.0mmHg (Miyazaki et al., 1990; Cheng et al., 1992). This phenomenon is possible due to the elastic properties of the myocardium. When fibers are compressed below their equilibrium length (as when ESV is less than the ventricular equilibrium volume), elastic energy is stored in the muscle fibers and collagen matrix. With myocardial inactivation, this energy is released, causing rapid chamber expansion. This phenomenon is difficult to detect clinically, due to the rapidity with which blood is aspirated from the LA into the LV during LV pressure decay. For a more thorough explanation, see an overview by Gilbert and Glantz (1989). As a result of negative ventricular pressure, the AV pressure gradient is greater during early diastole, thereby improving early filling.

**Late filling**

While at rest, a significant portion of the conduit phase is associated with slow filling; however, the increased heart rate and reduced delay in atroventricular conduction (Lister et al., 1965) during exercise results in a shortening of the R-R interval and an alteration of the duration of filling phases. Though the duration of the early and late filling waves is largely independent of R-R duration, an increase in heart rate shortens the period of diastasis (Chung et al., 2004), with fusion of the two filling waves typically seen at heart rates approaching 120 bpm (Kilner et al., 1997), indicating the elimination of the slow-filling phase during moderate- to high-intensity exercise.

A consequence of this is that as the separation between the early and late filling waves is reduced, atrial contraction is initiated with a higher volume remaining in the chamber, and an increase in the contribution of active emptying to ventricular filling is seen in response to exercise. As the atria operate under the Frank-Starling mechanism, an increase in volume at the
time of contraction elicits a more forceful ejection (Braunwald and Frahm, 1961; Yamaguchi et al., 1987). Intrinsic contractility of the atrial myocardium can be modulated by autonomic regulation. While little parasympathetic innervation exists in the ventricles, vagal stimulation exerts a depressing effect on the atrial contractility and can thus reduce ventricular diastolic filling and preload (Sarnoff et al., 1960). Conversely, sympathetic stimulation to the atria increases contractility, resulting in a greater ejection fraction and active emptying volume independent of loading conditions; by increasing atrial pre-contraction volume (LA_{PRE-A}), an augmentation of the Frank-Starling mechanism is achieved, and combined with greater contractility secondary to sympathetic stimulation, an increased active emptying volume occurs during exercise, and the E:A ratio is reduced (Channer and Jones, 1989; Nishikawa, 1994).

2.3.3 Response to Chronic Training

Rest

Chronic exercise training has long been known to elicit morphological and functional changes in the heart, collectively referred to as the 'athlete's heart' (Huston et al., 1985; Fagard, 2003). It was suggested by Morganroth et al. (1975) that different modes of exercise training resulted in divergent paths of cardiac remodeling, with differences seen between the hearts of strength-trained, and endurance-trained athletes. In comparison to the concentric remodeling exhibited by strength-trained individuals, the endurance-trained heart is characterized by eccentric remodeling (Pluim et al., 2000). One of the most salient changes in cardiac function with endurance training is a pronounced resting bradycardia (Smith et al., 1989). This depression in heart rate is driven by an increase in parasympathetic influence (Hall, 1963; Carter et al., 2003) and a parallel reduction in sympathetic control.
The reduction in resting heart rate is offset by an increase in SV to maintain cardiac output (Blomqvist and Saltin, 1983; Goodman et al., 2005). While the increase in SV could be due to an increase in LV EDV, a decrease in ESV, or both, recent literature has failed to detect a significant decrease in LV ESV with endurance training (Warburton et al., 2004; Goodman et al., 2005; Scharf et al., 2010). Thus the increase in resting SV in endurance-trained athletes can be attributed to an increase in EDV compared to sedentary individuals or strength-trained athletes (Stein et al., 1980; Warburton et al., 2004; Goodman et al., 2005; D'Andrea et al., 2010; Scharf et al., 2010).

A variety of factors influence the change in EDV. An expansion of plasma volume is seen early in the training process (Warburton et al., 2004; Goodman et al., 2005), which in part explains the increase in EDV (Convertino, 1991; Spina et al., 1992). Previous work has demonstrated that endurance training alters transmitral filling at rest compared to healthy controls or strength-trained athletes. While late filling has been shown to be reduced (Toutouzas et al., 1996; Vinereanu et al., 2002; D'Andrea et al., 2010) or unchanged (Levy et al., 1993; D'Andrea et al., 2002), early filling is maintained (Vinereanu et al., 2002) or improved (Levy et al., 1993; Toutouzas et al., 1996; D'Andrea et al., 2002; D'Andrea et al., 2010) with endurance training.

The improvement in early filling may be affected by aspects of atrial or ventricular function. Enlargement of both the left (Hauser et al., 1985; Henriksen et al., 1996; Pelliccia et al., 2005; Baldesberger et al., 2008; D'Andrea et al., 2010; Scharf et al., 2010) and right (Hauser et al., 1985; Henriksen et al., 1996; Baldesberger et al., 2008) atria is a consistent finding in highly trained endurance athletes. Krip et al. (1997) showed that following a volume infusion, diastolic filling rate in untrained subjects improved by 48% of the difference between untrained
and endurance-trained subjects. Although SV and cardiac output improved acutely, the
investigators suggested that the myocardium must adapt to optimize filling, and this adaptation
requires time. Aerobic endurance training is associated with increased myocardial compliance
(Levine et al., 1991; Levine, 1993), and LA compliance has been shown to increase with chronic
volume overload (Kihara et al., 1988). Thus, chronic endurance training (Convertino, 1991) and
the associated expansion in blood volume may induce atrial remodeling and chamber
enlargement, with increased reservoir volume improving early diastolic filling.

Chronic endurance training has been shown to improve the compliance of the ventricular
myocardium (Levine et al., 1991; Levine, 1993; Arbab-Zadeh et al., 2004), as well as increase
the rate of relaxation and reduce the time to peak early filling (Kivistö et al., 2006). Further,
atrial conduit function has been shown to be greater in elite endurance athletes than in non-
athletes (Toutouzas et al., 1996). The improvement of ventricular performance during early
diastole likely interacts with atrial alterations to increase early filling rates and maintain the
viability of passive filling during diastasis.

Exercise

The exercise response of both untrained and endurance trained individuals share a
number of similarities, including increased LA volume, augmented early and late ventricular
filling, and a decrease in E:A ratio; however, there are some important differences. While
previously accepted that ventricular SV reaches a plateau at a submaximal heart rate
(Higginbotham et al., 1986), more recent work challenges this concept and has shown that in
highly endurance-trained individuals, SV progressively increases to a maximal effort (Gledhill et
al., 1994; Krip et al., 1997; Warburton et al., 2002; Wang et al., 2012). Improved diastolic filling
has been suggested to be the primary mechanism through which this increased stroke volume is
achieved; significantly greater ventricular filling rates at maximal exercise have been shown in highly trained subjects (Gledhill et al., 1994), and factors including increased early diastolic ventricular filling rate and velocity have been suggested (Warburton and Gledhill, 2008), which may be mediated by improved atrial function, increased rate of ventricular relaxation, or a combination of these factors.

2.3.4 The Influence of Aging

Aging is associated with changes in cardiac function. While earlier work suggested that atrial enlargement was a function of age (Triposkiadis, 1995), more recent evidence suggests that it is not part of the normal process of aging, and can usually be attributed to underlying pathology, as atrial filling and reservoir function are largely preserved with age (Spencer et al., 2001; Thomas et al., 2002). Compared to younger sedentary controls, the contribution of passive atrial emptying (Levy et al., 1993; Triposkiadis et al., 1995; Spencer et al., 2001; Baldi et al., 2003) and early mitral annular velocity (Baldi et al., 2003; Innelli et al., 2008) have been shown to be reduced at rest in healthy untrained older males, while active emptying contributes a greater proportion (Cacciapuoti et al., 1992; Triposkiadis et al., 1995; Spencer et al., 2001). As there is evidence of impaired ventricular relaxation (Cacciapuoti et al., 1992) and compliance (Arbab-Zadeh et al., 2004) with age, a blunting of early ventricular filling results in a greater active ejection via the Frank-Starling mechanism (Spencer et al., 2001). Exercise capacity is reduced with increasing age, due in part to a reduction in maximal cardiac output, secondary to a linear decrease in maximal heart rate with increasing age (Tanaka et al., 2001). A reduction in stroke volume explains some of the remaining difference (Ogawa et al., 1992); the impairment of diastolic function at rest persists during exercise, as peak filling rate is reduced (Levy et al.,
1993), which may be related to a decreased responsiveness to beta-adrenergic stimulation (Schulman et al., 1992) or ventricular stiffening.

Endurance training has been shown to improve or defend against these age-related alterations. Endurance-trained older individuals have diastolic function and early filling patterns more similar to younger individuals than older sedentary (Forman et al., 1992; Levy et al., 1993). One of the mechanisms which may explain the maintenance of diastolic function is greater ventricular compliance, which is improved with endurance training (Levine et al., 1991), and may be preserved with long-standing training despite aging (Arbab-Zadeh et al., 2004). Although compliance may be improved in older individuals, and ventricular relaxation is improved with training in younger individuals (Kivistö et al., 2006), the impairment of ventricular relaxation with age may not be affected by endurance training (Nottin et al., 2004). Recent data (Lee et al., 2012) shows that during exercise, endurance-trained older individuals have a lower A-wave velocity and greater E/A ratio than untrained individuals, suggesting that the benefits of increased compliance with training persist during exercise.

2.4 Echocardiographic Assessment of Cardiac Function

While a variety of methods are available for non-invasive cardiac imaging including cardiac magnetic resonance, cardiac computed tomography, and nuclear scintigraphy, the use of echocardiography will be detailed due to its common use in research and clinical settings, and pertinence to the present study.

2.4.1 Dimensions and Volumes

The standard assessment of cardiac function often includes dimensional measures of chamber size from the parasternal long-axis view using M-mode echocardiography (Lang et al., 2006). Unidimensional estimates assume that changes in anteroposterior length are consistent
with changes superior-inferior and medial-lateral dimensions (Lester et al., 1999; Lang et al., 2006); however, their accuracy in estimating atrial size is limited (Wade et al., 1987; Lang et al., 2006) as the atria are not symmetrical structures, and anteroposterior length may be constrained by the thoracic walls (Lang et al., 2006). In pathologically enlarged chambers, the failure of this relationship is exacerbated, and dimensional measures have been shown to be inferior to volumes for the assessment and prediction of risk for atrial fibrillation (Tsang et al., 2001).

Common methods of quantifying chamber volumes include the prolate ellipse, the biplane area-length method, and the biplane Simpson's method, with current guidelines recommending the use of either the biplane area-length or Simpson's methods (Lang et al., 2006). The prolate ellipse method assumes that the chamber is ellipsoid in shape; as the atria are in fact barrel shaped, this method systematically underestimates atrial volume (Khankirawatana et al., 2004; Badano et al., 2008; Jiamsripong et al., 2008; Uno et al., 2010), and is influenced by the anterior-posterior length (Jiamsripong et al., 2008), which as in dimensional measures may not be representative of non-uniform enlargement. While the area-length and Simpson's methods have both been shown to be superior to dimensional measures (Lester et al., 1999; Tsang et al., 2006; Badano et al., 2008) and correlate well with each other (Rodevand et al., 1999; Jenkins et al., 2005; Jiamsripong et al., 2008; Uno et al., 2010), recent work has shown that the modified biplane Simpson's method correlates well with 3D Echo (Khankirawatana et al., 2004; Maddukuri et al., 2006; Badano et al., 2008) and cardiac magnetic resonance imaging (cMRI) (Uno et al., 2010).

Atrial maximum volume (LA_{MAX}) is measured at the end of ventricular systole, and is reached immediately prior to mitral valve opening. Atrial pre-A volume (LA_{PRE-A}) is measured just prior to the onset of atrial contraction. With the closing of the mitral valve, the atrium
reaches its minimum volume \( (L_{\text{MIN}}) \). Subtracting \( L_{\text{MIN}} \) from \( L_{\text{MAX}} \) results in the reservoir or filling volume of the atria, and conduit volume can be calculated as \((\text{Conduit Volume}) = SV_{\text{Ventricular}} - (L_{\text{MAX}} - L_{\text{MIN}})\) (Blume et al., 2011). The difference between the pre-A volume and the minimum atrial volume gives the atrial active emptying or 'booster-pump' volume. These values are commonly expressed relative to body surface area to control for variations in gender and body size.

Due to the lack of standardized orthogonal views, RA volume is commonly assessed by single plane estimates including area-length (DePace et al., 1983) and Simpson's method of discs (Wang et al., 1984). While comparison of RA volume by Echo to other imaging techniques appears to be unavailable, measures by 2D Echo have been shown to correlate well with casts of hearts from autopsy (Bommer et al., 1979). An alternative method of quantification using chamber area in lieu of volume has been used in recent studies (Lönnerholm et al., 2008; Di Salvo et al., 2009). RA area by planimetry is a simple method of size estimation that is reproducible, shows correlations with both atrial casts (Bommer et al., 1979) and 3DE (Müller et al., 2008), and is a better predictor of RA size than linear dimensions. RA maximal area should be traced at end ventricular systole, and tracing should exclude the tricuspid leaflets, the vena cava, and the RA appendage (Otto, 2007).

2.4.2 Doppler Echocardiography

Doppler studies including conventional flow velocities as well as tissue velocities provide useful indices of atrial systolic and diastolic function. In the left heart, atrial filling from pulmonary inflow can be evaluated using pulsed-wave Doppler techniques by placing a sample volume approximately 1cm into the pulmonary veins from the junction with the atrium. The normal flow pattern is quadriphasic (Tabata et al., 2003), with the inflow pattern biphasic (Keren
A systolic wave (S1) occurs, reflecting flow due to atrial relaxation and reservoir function, followed by a second systolic wave (S2), which is the product of ventricular contraction during the late reservoir phase. Another positive peak (D) is seen during the conduit phase, followed by a negative inflection representing flow reversal (AR) with atrial contraction due to the changing pressure gradient (Tabata, 1998; Tabata et al., 2003). A similar interrogation at the mitral valve provides information regarding atrial emptying and ventricular filling, with early (E) and late (A) filling waves from Doppler assessment represent the passive and active emptying of the atrium, while the ratio of these measures reflects the relative contribution of passive and active filling. A reduction in the E:A ratio is commonly seen with increasing age, as decreased LV compliance has consequences for the viability of passive early filling (Arbab-Zadeh et al., 2004). At high heart rates, typically above 120 bpm, the E and A waves may appear to fuse due to the elimination of diastasis and summation of the two filling waves (Kilner et al., 1997).

Doppler tissue imaging (DTI) may be used to assess motion of the mitral annulus. Annular motion can be characterized as triphasic. Following the QRS complex of the ECG, a systolic positive inflection (Sa) occurs as the mitral annulus moves toward the apex during ventricular systole; subsequently, two negative inflections representing annular ascension during early (Ea) and late (Aa) atrial emptying (Ho and Solomon, 2006). Due to structural differences between the septal and lateral (free) walls, velocities at the septal and lateral aspects of the mitral annulus may differ (Alam et al., 1999). The measurement of Sa provides useful information regarding ventricular longitudinal systolic performance, while Ea and Aa provide assessment of diastolic function that is less load dependent than standard Doppler flow measures, and the relation of E to Ea provides a non-invasive estimate of filling pressure (Nagueh et al., 1997).
Assessment of right heart function with Doppler echocardiography may be performed for the same parameters with some differences. RA inflow from the superior vena cava typically shows a triphasic pattern including positive peaks representing systolic and diastolic forward flow, followed by a flow reversal due to RA contraction (Appleton et al., 1987; Cohen et al., 1996). Tricuspid flow velocities are typically lower than transmitral velocities (Zoghbi et al., 1990) due to difference in loading conditions and pressure gradients between the left and right heart (Choong et al., 1987); however, the typical pattern of early and late filling is similar between halves, and the age related decrease in E:A ratio is also characteristic of the right heart (Zoghbi et al., 1990; Cohen et al., 1996).

2.4.3 Tissue Tracking Doppler

Longitudinal displacement of the AV plane has been assessed previously using M-mode echocardiography (Alam and Hoglund, 1992; Owen, 1999) and magnetic resonance imaging (MRI) (Carlsson et al., 2007; Carlsson et al., 2007); however, the utility of these methods is limited by limited access and cost. Tissue Tracking (TT) is a novel method of assessing systolic function, derived from color DTI. This method displays the longitudinal displacement of the myocardium in apical two- and four-chamber views as a series of seven color coded bands representing the degree of movement on a two dimensional image, and a graphic representation of displacement as a function of time is shown. Typically, the highest degree of movement is near the cardiac base, while the least occurs in the apical area. TT has been validated against MRI (Borges et al., 2003), and TT-derived measures of displacement correlate well with M-mode values (Pan et al., 2001). Further, TT has been shown to be feasible in normal, athletic, and clinical populations (Pan et al., 2001; Søgaard et al., 2002; Poulsen et al., 2007), as well as during supine cycle exercise (Saha et al., 2004). Images should be acquired at sampling rates...
above 80fps, and preferably over 100fps for optimal assessment (Lind et al., 2002; Saha et al., 2004; Poulsen et al., 2007).

2.4.4 Speckle-tracking Echocardiography

Two-dimensional strain and strain rate analysis is a method of assessing myocardial function through tissue deformation. While strain derived from color DTI (cDTI) through the estimation of spatial gradients in myocardial velocity has been used previously (Sirbu et al., 2006; Boyd et al., 2011), cDTI can be influenced by interrogation angle (Urheim et al., 2000; Boyd et al., 2011) and cardiac translation (Armstrong et al., 2000; Boyd et al., 2011), and may be affected by tethering (Armstrong et al., 2000; Edvardsen et al., 2002). Speckle tracking echocardiography (STE) is a novel technique in which an observer traces the endocardial border on a 2D image during offline analysis creating region of interest with subsequent analysis of spatial and temporal alterations of acoustic ‘speckles’ in the myocardium, in which their movement is tracked frame-by-frame through the cardiac cycle to calculate myocardial deformation. In comparison to cTDI, STE-derived strain is unaffected by tethering and cardiac translation (Cho et al., 2006; Di Salvo et al., 2009), and is angle-independent (Vianna-Pinton et al., 2009). LA strain by STE shows good feasibility and reproducibility (Cameli et al., 2009; Di Salvo et al., 2009; Kim et al., 2009; Vianna-Pinton et al., 2009; Saraiva et al., 2010), and has been shown to correlate well with tagged Cine-MRI in the LV (Cho et al., 2006). STE analysis is optimized with frame rates between 60-80fps (Cameli et al., 2009; Kim et al., 2009; Vianna-Pinton et al., 2009; Saraiva et al., 2010) for normal resting heart rates. Strain using the cTDI technique has been utilized in the RA (Hui et al., 2004); however, it is limited by the same concerns of tethering, translation, and angle-dependency. STE software has been applied to the RA at frame rates from 50-90fps with good reproducibility (Di Salvo et al., 2009; Padeletti et al.,
2011) and has recently been shown to be feasible (Blume et al., 2011) by measuring in the same manner as LA strain (Cianciulli et al., 2010).

**2.5 Invasive Assessment**

Despite a variety of methods for non-invasive estimation, invasive measurement via cardiac catheter remains the gold standard for the quantification of intracardiac pressure. While early practices for cardiac catheterization required cannulation of a central site, in recent years the cannulation of peripheral veins for central venous catheterization has become prevalent. The procedure for this method has been described previously (Hovsepian, 1993); in general, the upper arm of the subject is sterilized and locally anesthetized. The selected vein is cannulated, a guide wire is advanced under ultrasound guidance, and a sheath is inserted allowing for catheterization. Positioning of the catheter in the pulmonary artery is confirmed through fluoroscopy (Arbab-Zadeh et al., 2004), allowing for determination of RA or pulmonary artery pressures; the balloon-tipped Swan-Ganz catheter is then inflated to create a wedge (Swan et al., 1970). RV pressure is blocked, allowing for the measurement of LA filling pressure from the distal port. Determination of PCWP with a Swan-Ganz catheter (Swan et al., 1970) provides an accurate estimation of left atrial pressure (LAP) and LV filling pressure (Fitzpatrick et al., 1972; Chaliki et al., 2002), while avoiding the necessity for trans-septal puncture or retrograde catheter introduction involved in the direct measurement of LAP. Through this process, right atrial pressure (RAP), pulmonary artery diastolic pressure (PADP), pulmonary artery systolic pressure (PASP), and pulmonary artery wedge pressure (PAWP) may be measured, allowing for the estimation of RV diastolic and systolic pressures, LAP, and left ventricular diastolic pressure (Headley, 2002).
Chapter III: Manuscript for Journal Submission

This chapter contains a modified version of a manuscript to be submitted for publication.

3.1 Abstract

Left ventricular (LV) filling is accomplished through a combination of left atrial (LA) active and passive emptying, both dependent on the efficiency of mitral valve inflow. LV filling is known to increase during exercise, but the contribution of phasic LA function to this response is poorly understood. We hypothesized that LA filling improves acutely during light-intensity exercise due to enhanced atrioventricular-plane displacement (AVPD) during LV systole, and that reduced diastolic filling time at moderate-intensity exercise limits passive LA emptying and increases LA active emptying contribution. Sixteen endurance-trained males (mean age = 55 ± 5 years) were studied at rest and during cycle-ergometry at light (~100 bpm, LE) and moderate (~130 bpm, ME) intensity exercise. Doppler echocardiography was used to assess coupling and diastolic function. LA and LV volumes were measured from 2-dimensional images (2D) in standard apical windows. Simultaneous right-heart catheterization was performed to measure pulmonary capillary wedge pressure (PCWP). Echocardiographic data was available from all subjects, with hemodynamic data from 11. As expected, LV end-diastolic volume (EDV) increased from rest to LE and then to ME. Systolic AVPD increased from rest to LE (from 14 ± 2 mm to 18 ± 2 mm, p < 0.01), but did not increase further at ME. LA reservoir volume increased from rest to LE (from 32 ± 8 mL to 40 ± 10 mL, p < 0.01), and remained constant. In contrast, during LV diastole, LA conduit volume trended modestly upward from rest to LE (from 39 ± 8 mL to 46 ± 11 mL), and increased significantly from LE to ME (from 46 ± 11 mL to 57 ± 11, p < 0.01). LA passive emptying volume increased at LE (from 21 ± 5 mL to 27 ± 8 mL, p < 0.01), then returned to baseline at ME. LA active emptying volume increased from rest only at
ME (from $12 \pm 5$ mL to $23 \pm 9$ mL, $p < 0.01$). Mean PCWP increased during LE (from $10 \pm 3$ mmHg to $19 \pm 3$ mmHg, $p < 0.01$), with partial normalization occurring during ME. AVPD, and thus the longitudinal shortening of LV systole, contributes significantly to LA filling primarily during LE, but is a limited mechanism beyond LE. These data indicate that as exercise intensity increases, AVPD becomes less important and conduit function and active emptying of the LA become primary mechanisms to maintain and increase LV EDV.

3.2 Introduction

Dynamic exercise precipitates numerous physiological alterations to meet the elevated oxygen requirement of working muscle, including an increase in cardiac output through increased heart rate (HR) and stroke volume (SV). Some of the increase in SV can be attributed to greater intrinsic contractility leading to a reduced end-systolic volume (ESV); however, a large portion of the increase is secondary to more rapid and greater diastolic filling, reflected by an increase in end-diastolic volume (EDV) (Goodman et al., 1991; Warburton et al., 2002). However, the contribution of atrial phasic function to the LV’s augmentation during exercise has not been well-documented. Far from being simple conduits of blood, the atria have important roles in modulating ventricular filling through their reservoir, conduit, and pump functions. The reservoir function (atrial filling) is influenced by both diastolic compliance and systolic performance (Barbier et al., 1999; Henein and Gibson, 1999).

Atrial filling is mechanically coupled to ventricular emptying through the atrioventricular plane (AVP), with passive expansion through external work applied to the AVP by ventricular longitudinal shortening (Carlsson et al., 2007); however, the degree to which preload is simultaneously increased through elevated central venous and pulmonary pressure through the range of exercise intensities is unknown (Cheng et al., 1992; Nose et al., 1994; West, 1998).
Atrial conduit flow (the conduit phase) begins with the opening of the mitral valve and the reservoir volume is rapidly transferred to the ventricles, augmented in the LV by untwist-generated suction; concurrently, the conduit volume is drawn into the ventricle dependent on the transmitral (Bowman and Kovács, 2004) or trans-tricuspid pressure gradient. As heart rate increases with exercise intensity, a decrease in filling time progressively reduces the period of diastasis, with fusion of the early passive and late active filling waves occurring at heart rates approaching 120 beats per minute (bpm) (Kilner et al., 1997). Presumably, the duration of the conduit phase is thereby reduced, resulting in a larger pre-contraction atrial volume (the onset of the atrial pump phase), eliciting an increase in active emptying via the Frank-Starling mechanism. While these phases have been well described at rest, there are limited data characterizing atrial phasic function and its interdependence with ventricular performance during submaximal exercise. In addition, while endurance exercise is known to improve LV compliance (Levine et al., 1991) and diastolic function both at rest and during exercise (Levy et al., 1993), atrial performance and training-induced alterations are likely important modulating influences (Kasikcioglu et al., 2006; D'Andrea et al., 2010; Scharf et al., 2010). Therefore, the purpose of this study was to examine atrial function during exercise in highly endurance-trained athletes.

We hypothesized that atrial filling and maximal volume would increase acutely in response to light exercise (LE), related to AVP displacement. We further hypothesized that at LE, passive LV filling would improve, but during moderate exercise (ME) reduced time for diastolic filling would limit passive volume transfer and result in a greater active contribution.

3.3 Methods

3.3.1 Experimental Design
After providing informed written consent and completing the PAR-Q+ and Lifetime Physical Activity Questionnaire, subjects completed a graded exercise test (GXT) on a cycle ergometer to determine VO$_{2\text{MAX}}$, and body composition was determined with bioelectrical impedance. On a subsequent visit separated by at least two, but no more than 14 days after the GXT, subjects were given a comprehensive assessment of cardiac function involving simultaneous exercise echocardiography (ECHO) and right-heart catheterization (RHC). The study was approved by both hospital and university research ethics boards.

### 3.3.2 Subjects

We recruited 16 highly endurance-trained male participants aged 41-69, with a history of 10+ years of vigorous year round training. Inclusion criteria included runners, cyclists, and triathletes who participated in vigorous year-round endurance training of at least 6 hrs or 35 km per week (runners) for a minimum of 10 years, and participation in one or more marathons/road races/triathlons per year. Exclusion criteria included a BMI < 20kgm$^{-2}$ or > 28kgm$^{-2}$, current smoking, diabetes mellitus, hypertension, use of cardioactive drugs, a history of cardiovascular, pulmonary, metabolic, or musculoskeletal disease, current or chronic illness, or prior exposure to chemotherapy.

### 3.3.3 Anthropometrics & Maximal Aerobic Power

Subject’s height and body mass were recorded, and body composition was analyzed using a bioimpedance system (Hydra 4200, Xitron Technologies, San Diego, CA). VO$_{2\text{MAX}}$ was assessed from expired gas analysis during a GXT on an electronically-braked cycle ergometer (Lode Excalibur, Groningen-Holland Medical Technology). Subjects were familiarized with the protocol, and began a 3 minute warm up stage of 25 Watts (W), after which work rate was increased by 50W each 2-minute stage up to 200W after 8 minutes; work rate was then increased
25W each minute until the subject reached exhaustion. Expired gases were collected breath-by-breath and averaged over 20-second intervals (Moxus Modular System, AEI Technologies Inc., Pittsburg, PA). HR was recorded at the end of each minute using a Polar heart rate monitor (810i, Polar Inc.), and continuously with an HRTrak II Heart Rate Tracker (Equilibrated Bio Systems Inc., New York, USA). VO\textsubscript{2MAX} was confirmed by a plateau of oxygen uptake despite increasing work rate; secondary criteria included achievement of age-predicted maximum HR \([208 - (0.7 \times \text{AGE})]\), and a respiratory exchange ratio > 1.15.

### 3.3.4 Cardiac Assessment

The comprehensive exercise cardiac assessment was performed on a separate day from the VO\textsubscript{2MAX} test, in the Cardiac Catheterization Research Lab at Mount Sinai Hospital with simultaneous ECHO. Subjects abstained from intensive training for 48 hours prior to the study and from caffeine for 12 hours prior. Upon arrival, subjects were referred for baseline 12-lead ECG, and had pre-exercise body mass recorded, as well as venous blood sampling for hemoglobin and hematocrit determination. Baseline ECHO was conducted with the subject at rest in the left lateral decubitus position. To determine invasive measures of cardiac function, subjects were catheterized by a trained cardiologist, using a peripheral vein approach. In brief, while in a supine position, the subject’s upper arm was prepared and sterilized from the axilla to the anticubital fossa, then anesthetized with local anesthesia. Under ultrasound guidance (Site Rite 5, Bard Inc., Salt Lake City, UT), the cephalic and basilic veins were identified, and the least challenging vein to cannulate was selected. A 21-gauge cannula was inserted and visualized on ultrasound, then advanced into the lumen of the vein. A 7Fr sheath was inserted, and the catheter (CCombo Volumetrics Pulmonary Artery Catheter, Edwards Lifesciences Inc., Irvine, CA) was advanced toward the thorax. Once the tip reached the vena cava/right atrium junction,
the balloon was inflated and floated into the pulmonary artery, with proper positioning confirmed by fluoroscopy. The subject was then transferred to a purpose-built table-cycle ergometer (Ergoselect 1200E, Ergoline GmbH, Germany), with the subject in a semi-supine (45 degrees) position with slight rotation in a left-lateral decubitus position. HR was monitored with a 3-lead electrocardiogram, and blood pressure was monitored using an automated cuff and monitor (Tango+, SunTech Medical).

3.3.5 Exercise Protocol

Subjects began with a 2-min. warm-up at a work-rate of 50W, then the work-rate was manipulated to elicit a target HR to be held at a steady state for 5-7 min. All subjects performed exercise at three intensities; the first two stages consisted of LE and moderate exercise ME, with HRs of 100 and 130 bpm, respectively. Subjects < 55 years old performed the third stage of intensive exercise (IE) at 150 bpm, while subjects > 55 years old performed at 140 bpm, such that the peak exercise stage for each subject would elicit a HR between 82-88% of age predicted maximum. After 1-2 min. at the start of each stage to allow the subject to reach a steady state, ECHO images were acquired before continuing to the successive stage. Exercise was to be discontinued if fatigue limited exercise or if chest pain, shortness of breath, or a fall in SBP >10 mmHg from baseline or a SBP < 90 mmHg occurred.

3.3.6 Echocardiography

Echo images were acquired at rest and during exercise by a trained sonographer with experience in exercise stress echocardiography, using a commercially available system (Vivid 7, GE Healthcare, Canada; M4S probe). 2D ECHO images were acquired from parasternal (long and short axis) and apical (two- and four-chamber) windows, at frame rates of 60-80 frames per second (fps), and optimized for field of view and image quality. Images for determination of LA
myocardial strain and strain rate were obtained in 2D A4C format using Speckle Tracking Echo (STE) at a frame rate between 60-80 fps. Pulsed-wave Doppler interrogation of transmitral flow was used to measure flow velocities during early (E) and late (A) diastole. Using continuous-wave Doppler, a sample volume was placed in the right ventricle to determine tricuspid regurgitant velocity (TRV). Tissue Doppler imaging (TDI) was used to assess LV relaxation by placing sample volumes in the septal and lateral aspects of the mitral annulus to determine early (E’) and late (A’) annular motion velocities. Echo images were analyzed offline using a proprietary workstation (EchoPAC 11, GE Healthcare) by a single trained observer blinded to study order, subject characteristics, and invasive hemodynamics, in accordance with current ASE guidelines (Lang et al., 2006; Nagueh et al., 2009), averaged over at least three cardiac cycles with gain optimized for delineation of the endocardial border. LV EDV, ESV, and atrial maximum (LAMAX), minimum (LAMIN), and pre-contraction (LPRE-A) volumes were measured in apical two- (A2C) and four-chamber (A4C) views using the modified bi-plane Simpson’s method (Lang et al., 2006). AVPD was quantified using Tissue Tracking Doppler echocardiography. In color TDI images, a sample volume was placed at the septal and lateral annular sites of A4C images, and at the anterior and inferior annular sites of A2C images. AVPD was calculated as an average of the displacement in millimeters (mm) at each of the 4 sample sites. For myocardial strain analysis, the endocardial border was traced using a point-and-click method, after which proprietary software divided the atrial wall into six segments. A cine-loop of the border tracking was previewed before processing, for visual confirmation that the region of interest adequately tracked the endocardium. The strain and strain rate of each segment was averaged to produce a global longitudinal strain and strain rate, with each cardiac cycle gated to the onset of the P-wave of the ECG.
3.3.7 Invasive Hemodynamics

Invasive hemodynamics were measured continuously for right atrial pressure (RAP), and both pulmonary artery systolic pressure (PASP) and diastolic pressure. Pulmonary capillary wedge pressure (PCWP) was measured at steady-state in each stage, with mean, $a$-wave, and $v$-wave pressures calculated, allowing for the estimation of left atrial pressure (LAP). Cardiac output was measured continuously using the thermodilution method, with continuous monitoring equipment (Vigilance II, Edwards Lifesciences Inc., Irvine, CA).

3.3.8 Statistics

Statistical analyses were performed using SPSS Statistics software version 20 (IBM Inc). Continuous variables were analyzed using repeated measures analysis of variance to determine the significance of the main effect. The three levels included were Rest, LE, and ME. Significant main effects were subsequently analyzed post-hoc using Bonferroni-corrected t-tests. The relationship between AVPD and LA functional volumes was explored using Pearson correlations. A p-value < 0.05 was considered statistically significant. All data presented are reported as mean ± standard deviation (SD) unless otherwise noted.

3.4 Results

3.4.1 Subjects

A total of sixteen subjects completed the study. Subject characteristics are reported in Table 1. The mean age of the population was 55 years, with a body mass index (BMI) of 24.4 kg/m$^2$, and a VO$_{2\text{MAX}}$ of 46.5 ml/kg/min. Indices of LV size were within normal ranges. There were no adverse events during any procedure throughout the study.
Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55 ± 5</td>
<td>48 - 65</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>177 ± 6</td>
<td>166 - 187</td>
</tr>
<tr>
<td>Mass (kg)</td>
<td>77 ± 8</td>
<td>63 - 92</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>24.4 ± 2.1</td>
<td>21 - 28</td>
</tr>
<tr>
<td>Body Fat Percentage (%)</td>
<td>16 ± 4</td>
<td>11 - 20</td>
</tr>
<tr>
<td>VO₂MAX (ml/kg/min)</td>
<td>46.5 ± 7.5</td>
<td>36 - 67</td>
</tr>
<tr>
<td>LVIDd (cm)</td>
<td>4.7 ± 0.3</td>
<td>4.0 - 5.1</td>
</tr>
<tr>
<td>LVIDs (cm)</td>
<td>3.0 ± 0.2</td>
<td>2.7 - 3.4</td>
</tr>
<tr>
<td>IVSd (cm)</td>
<td>1.1 ± 0.1</td>
<td>0.9 - 1.3</td>
</tr>
<tr>
<td>LVPWd (cm)</td>
<td>0.8 ± 0.1</td>
<td>0.7 - 0.9</td>
</tr>
</tbody>
</table>

LVIDd, left ventricular internal dimension at end-diastole; LVIDs, left ventricular internal dimension at end-systole; IVSd, interventricular septal wall thickness; LVPWd, left ventricular posterior wall thickness.

3.4.2 Cardiac volumes

Volumes for the left heart are presented in Table 2. LA MAX at rest was 47 ± 13 ml, and was toward the upper bound of the normal range for males. Resting LA MAX was significantly correlated with VO₂MAX (r = 0.52, p = 0.04); when LA MAX was normalized to body surface area, this correlation strengthened (r = 0.60, p = 0.02). LA MAX increased significantly at LE (from 47 ± 13 ml to 54 ± 11 ml, p < 0.01), with no further increase at ME. LA PRE-A volume was 26 ± 11 ml at rest, and remained stable at LE, before increasing significantly during moderate exercise (from 26 ± 10 ml to 33 ± 10 ml, p < 0.01 vs. LE). LA MIN volume was 14 ± 8 ml at rest, and was not changed significantly by exercise. LA RESERVOIR volume increased significantly from rest to LE (from 32 ± 8 ml to 40 ± 10 ml, p < 0.01), and remained steady during ME. The LA PASSIVE emptying volume increased from 21 ± 5 ml at rest to 27 ± 8 ml (p < 0.01) during LE, then returned to baseline values at ME (19 ± 7 ml), while the LA ACTIVE contribution was unchanged by LE, but rose significantly during ME (from 12 ± 5 ml at rest to 23 ± 9 ml, p < 0.01).
Table 2. Cardiac volumes at rest and during exercise

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Range</th>
<th>100 bpm</th>
<th>Range</th>
<th>130 bpm</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV&lt;sub&gt;SV&lt;/sub&gt; (ml)</td>
<td>72 ± 8</td>
<td>60 - 89</td>
<td>86 ± 10&lt;sup&gt;**&lt;/sup&gt;</td>
<td>70 - 114</td>
<td>99 ± 9&lt;sup&gt;**&lt;/sup&gt;;&lt;sup&gt;†&lt;/sup&gt;</td>
<td>85 - 121</td>
</tr>
<tr>
<td>LV&lt;sub&gt;EDV&lt;/sub&gt; (ml)</td>
<td>116 ± 12</td>
<td>100 - 135</td>
<td>123 ± 11&lt;sup&gt;**&lt;/sup&gt;</td>
<td>107 - 142</td>
<td>131 ± 14&lt;sup&gt;**&lt;/sup&gt;;&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>114 - 157</td>
</tr>
<tr>
<td>LV&lt;sub&gt;ESV&lt;/sub&gt; (ml)</td>
<td>45 ± 8</td>
<td>36 - 62</td>
<td>39 ± 8&lt;sup&gt;**&lt;/sup&gt;</td>
<td>32 - 58</td>
<td>32 ± 8&lt;sup&gt;**&lt;/sup&gt;;&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>22 - 46</td>
</tr>
<tr>
<td>LV&lt;sub&gt;EF&lt;/sub&gt; (%)</td>
<td>62 ± 4</td>
<td>55 - 66</td>
<td>69 ± 4&lt;sup&gt;**&lt;/sup&gt;</td>
<td>60 - 75</td>
<td>76 ± 4&lt;sup&gt;**&lt;/sup&gt;;&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>70 - 83</td>
</tr>
<tr>
<td>LA&lt;sub&gt;MAX&lt;/sub&gt; (ml)</td>
<td>47 ± 13</td>
<td>33 - 69</td>
<td>54 ± 11&lt;sup&gt;**&lt;/sup&gt;</td>
<td>42 - 70</td>
<td>52 ± 12</td>
<td>36 - 75</td>
</tr>
<tr>
<td>LA&lt;sub&gt;PRE-A&lt;/sub&gt; (ml)</td>
<td>26 ± 11</td>
<td>13 - 47</td>
<td>27 ± 9</td>
<td>14 - 47</td>
<td>33 ± 10&lt;sup&gt;**&lt;/sup&gt;;&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>20 - 48</td>
</tr>
<tr>
<td>LA&lt;sub&gt;MIN&lt;/sub&gt; (ml)</td>
<td>14 ± 8</td>
<td>7 - 34</td>
<td>13 ± 8</td>
<td>4 - 25</td>
<td>10 ± 6</td>
<td>4 - 26</td>
</tr>
<tr>
<td>LA&lt;sub&gt;Reservoir&lt;/sub&gt; (ml)</td>
<td>32 ± 8</td>
<td>24 - 47</td>
<td>41 ± 9&lt;sup&gt;**&lt;/sup&gt;</td>
<td>24 - 57</td>
<td>42 ± 9&lt;sup&gt;**&lt;/sup&gt;</td>
<td>31 - 58</td>
</tr>
<tr>
<td>LA&lt;sub&gt;Conduit&lt;/sub&gt; (ml)</td>
<td>39 ± 6</td>
<td>27 - 50</td>
<td>45 ± 10</td>
<td>30 - 61</td>
<td>57 ± 11&lt;sup&gt;**&lt;/sup&gt;;&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>40 - 75</td>
</tr>
<tr>
<td>LA&lt;sub&gt;Passive&lt;/sub&gt; (ml)</td>
<td>21 ± 5</td>
<td>13 -32</td>
<td>27 ± 8&lt;sup&gt;**&lt;/sup&gt;</td>
<td>13 - 41</td>
<td>19 ± 7&lt;sup&gt;†&lt;/sup&gt;</td>
<td>9 - 29</td>
</tr>
<tr>
<td>LA&lt;sub&gt;Active&lt;/sub&gt; (ml)</td>
<td>12 ± 5</td>
<td>6 - 21</td>
<td>14 ± 4</td>
<td>10 - 23</td>
<td>23 ± 9&lt;sup&gt;**&lt;/sup&gt;;&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>10 - 40</td>
</tr>
</tbody>
</table>

* p < 0.05 vs. Rest; ** p < 0.01 vs. Rest; † p < 0.05 vs. 100 bpm; ‡ p < 0.01 vs. 100 bpm

LV, left ventricular; SV, stroke volume; EDV, end diastolic volume; ESV, end systolic volume; EF, ejection fraction; LA, left atrial; MAX, maximal volume; PRE-A, pre-contraction volume; MIN, minimal volume; Reservoir, reservoir volume; Conduit, conduit volume; Passive, passive emptying volume; Active, active emptying volume.

LV EDV increased from rest to LE (from 116 ± 12 ml to 123 ± 11 ml, p < 0.01) and from LE to ME (from 123 ± 11 ml to 131 ± 14 ml, p < 0.01), while LV ESV decreased at each stage.

LV SV and EF increased accordingly at each exercise stage.

3.4.3 Doppler Imaging Data:

Data from pulsed-wave Doppler measures of diastolic function at rest and during light and moderate exercise, including transmitral flow velocities and mitral annular motion velocities, are presented in Table 3. Transmitral early and late flow velocities increased proportionately at each subsequent stage of exercise, with the E/A ratio remaining unchanged across the range of HR. Early and Late diastolic mitral motion velocities also increased with HR, at both septal and lateral sampling sites. The mean AVPD increased significantly at LE (from 14 ± 2 mm to 18 ± 2 mm, p < 0.01), with no significant change at ME (17 ± 2 mm). The change in AVPD with increasing intensity was significantly correlated with the change in LA<sub>MAX</sub> (r = 0.51, p < 0.005);
the degree of AVPD was not related to the conduit volume at any heart rate, nor was the change in AVPD between heart rates related to the change in conduit volumes (p > 0.05).

Table 3. Doppler characteristics at rest and during exercise

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>100 bpm</th>
<th>130 bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>E (cm/s)</td>
<td>67 ± 8</td>
<td>108 ± 20**</td>
<td>122 ± 15**</td>
</tr>
<tr>
<td>A (cm/s)</td>
<td>54 ± 14</td>
<td>82 ± 17**</td>
<td>114 ± 22**</td>
</tr>
<tr>
<td>E/A</td>
<td>1.3 ± 0.4</td>
<td>1.4 ± 0.3</td>
<td>1.1 ± 0.3</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>88 ± 7</td>
<td>60 ± 7*</td>
<td>41 ± 8**</td>
</tr>
<tr>
<td>E-Decel (ms)</td>
<td>204 ± 19</td>
<td>163 ± 14**</td>
<td>141 ± 21**</td>
</tr>
<tr>
<td>E' Lateral (cm/s)</td>
<td>12 ± 2</td>
<td>15 ± 3**</td>
<td>17 ± 4**</td>
</tr>
<tr>
<td>A' Lateral (cm/s)</td>
<td>9 ± 2</td>
<td>11 ± 3**</td>
<td>14 ± 3**</td>
</tr>
<tr>
<td>E' Septal (cm/s)</td>
<td>9 ± 2</td>
<td>13 ± 2**</td>
<td>17 ± 2**</td>
</tr>
<tr>
<td>A' Septal (cm/s)</td>
<td>9 ± 1</td>
<td>12 ± 2**</td>
<td>13 ± 4**</td>
</tr>
<tr>
<td>E/E'</td>
<td>7 ± 2</td>
<td>9 ± 2</td>
<td>7 ± 1</td>
</tr>
<tr>
<td>AVPD (mm)</td>
<td>14 ± 2</td>
<td>18 ± 2**</td>
<td>17 ± 2**</td>
</tr>
</tbody>
</table>

* p < 0.05 vs. Rest; ** p < 0.01 vs. Rest; † p < 0.05 vs. 100 bpm; ‡ p < 0.01 vs. 100 bpm

E, peak early transmitral flow velocity; A, peak late transmitral flow velocity; E/A, ratio of peak early to peak late transmitral flow velocity; IVRT, isovolumetric relaxation time; E-Decel, E-wave deceleration time; E', peak early diastolic myocardial tissue velocity; A', peak late diastolic myocardial tissue velocity; Lateral, lateral aspect of mitral annulus; Septal, septal aspect of mitral annulus; E/E', ratio of peak early diastolic myocardial tissue velocity to peak early diastolic myocardial tissue velocity; AVPD, atrioventricular plane displacement during systole.

3.4.4 Myocardial deformation mechanics

Measures of LA strain and strain rate at rest and during exercise are shown in Table 4. Speckle-tracking was feasible in 16/16 of subjects at rest (100%), and in 14/16 subjects at LE (88%), however was only feasible in a minority of subjects at a heart rate of 130 bpm (44%) due to poor image quality during exercise acquisitions. Atrial total longitudinal strain (ALS\text{TOTAL}) increased significantly during LE (from 38 ± 7 % to 53 ± 12 %, p < 0.01), driven by increases in both peak positive atrial longitudinal strain (PALS\text{POSITIVE}) (from 22 ± 5 % to 32 ± 9 %, p < 0.05) and peak negative atrial longitudinal strain (PALS\text{NEGATIVE}) (-16 ± 4 % to -22 ± 7 %, p < 0.05). Light exercise was associated with a significant reduction in the time to atrial total longitudinal strain (TATL\text{S}), from 426 ± 48 ms to 308 ± 44 ms (p < 0.01). All indices of atrial strain rate
increased significantly in magnitude from rest to exercise. Indices of ventricular longitudinal strain are presented in Table 5. Ventricular longitudinal strain was unchanged by increasing exercise intensity. However, ventricular longitudinal strain rate during systole increased significantly at LE, as did early diastolic strain rate. Ventricular late diastolic strain rate increased significantly at ME.

Table 4. Atrial myocardial strain and strain rates at rest and during exercise

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>100 bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>TATLS (ms)</td>
<td>426 ± 48</td>
<td>308 ± 44**</td>
</tr>
<tr>
<td>PALS_{POSITIVE} (%)</td>
<td>22 ± 5</td>
<td>32 ± 9*</td>
</tr>
<tr>
<td>PALS_{NEGATIVE} (%)</td>
<td>-16 ± 4</td>
<td>-22 ± 7*</td>
</tr>
<tr>
<td>ALS_{TOTAL} (%)</td>
<td>38 ± 7</td>
<td>53 ± 12**</td>
</tr>
<tr>
<td>ALSR_{EARLY} (%/s)</td>
<td>-1.9 ± 0.4</td>
<td>-3.0 ± 0.6**</td>
</tr>
<tr>
<td>ALSR_{LATE} (%/s)</td>
<td>-2.4 ± 0.7</td>
<td>-3.6 ± 1.1**</td>
</tr>
<tr>
<td>ALSR_{SYSTOLIC} (%/s)</td>
<td>1.9 ± 0.5</td>
<td>3.1 ± 1.0**</td>
</tr>
</tbody>
</table>

* p < 0.05 vs. Rest; ** p < 0.01 vs. Rest

TATLS, time to atrial total longitudinal strain; PALS_{POSITIVE}, peak atrial longitudinal strain during atrial contraction; PALS_{NEGATIVE}, peak atrial longitudinal strain during atrial filling; ALS_{TOTAL}, total atrial longitudinal strain; ALSR_{EARLY}, atrial longitudinal strain rate during early diastole; ALSR_{LATE}, atrial longitudinal strain rate during late diastole; ALSR_{SYSTOLIC}, atrial longitudinal strain rate during systole.

Table 5. Ventricular myocardial strain and strain rates at rest and during exercise

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>100 bpm</th>
<th>130 bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strain (%)</td>
<td>-20.4 ± 1.8</td>
<td>-20.8 ± 2.4</td>
<td>-19.2 ± 2.5</td>
</tr>
<tr>
<td>SR_{SYSTOLIC} (%/s)</td>
<td>-1.0 ± 0.1</td>
<td>-1.3 ± 0.2*</td>
<td>-1.6 ± 0.3*</td>
</tr>
<tr>
<td>SR_{EARLY} (%/s)</td>
<td>1.2 ± 0.3</td>
<td>1.6 ± 0.3*</td>
<td>1.5 ± 0.5†</td>
</tr>
<tr>
<td>SR_{LATE} (%/s)</td>
<td>0.9 ± 0.2</td>
<td>0.9 ± 0.2</td>
<td>1.5 ± 0.6*†</td>
</tr>
</tbody>
</table>

* p < 0.05 vs. Rest; ** p < 0.01 vs. Rest; † p < 0.05 vs. 100 bpm; ‡ p < 0.01 vs. 100 bpm

SR_{EARLY}, strain rate during early diastole; SR_{LATE}, strain rate during late diastole; SR_{SYSTOLIC}, strain rate during systole.

3.4.5 Hemodynamics

Intracardiac hemodynamic data available from a subset of 11 subjects are displayed in Table 6. LE was associated with a rise in pulmonary pressures. Mean PAP increased acutely with
LE (from $16 \pm 4$ mmHg to $32 \pm 8$ mmHg, $p < 0.01$), and remained elevated at ME ($45 \pm 13$ mmHg). PAP\textsubscript{SYSTOLIC} increased from $27 \pm 6$ mmHg to $47 \pm 13$ mmHg at LE ($p < 0.01$), without further change at ME, as did PAP\textsubscript{DIASTOLIC}, which increased from $8 \pm 3$ mmHg to $18 \pm 5$ mmHg ($p < 0.01$). Mean PCWP increased at LE (from $10 \pm 3$ mmHg to $19 \pm 3$ mmHg, $p < 0.01$), then partially normalized at ME ($14 \pm 6$, $p < 0.01$ vs. rest; $p < 0.05$ vs. LE).

Table 6. Hemodynamic data at rest and during exercise

<table>
<thead>
<tr>
<th></th>
<th>Baseline (mmHg)</th>
<th>100 bpm (mmHg)</th>
<th>130 bpm (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP\textsubscript{A-WAVE}</td>
<td>10 $\pm$ 3</td>
<td>16 $\pm$ 7*</td>
<td>13 $\pm$ 7</td>
</tr>
<tr>
<td>RAP\textsubscript{V-WAVE}</td>
<td>8 $\pm$ 2</td>
<td>11 $\pm$ 6</td>
<td>11 $\pm$ 6</td>
</tr>
<tr>
<td>RAP\textsubscript{MEAN}</td>
<td>7 $\pm$ 2</td>
<td>8 $\pm$ 5</td>
<td>7 $\pm$ 5</td>
</tr>
<tr>
<td>PAP\textsubscript{SYSTOLIC}</td>
<td>27 $\pm$ 6</td>
<td>47 $\pm$ 13**</td>
<td>45 $\pm$ 13**</td>
</tr>
<tr>
<td>PAP\textsubscript{DIASTOLIC}</td>
<td>8 $\pm$ 3</td>
<td>18 $\pm$ 5**</td>
<td>17 $\pm$ 7**</td>
</tr>
<tr>
<td>PAP\textsubscript{MEAN}</td>
<td>16 $\pm$ 4</td>
<td>32 $\pm$ 8**</td>
<td>30 $\pm$ 9**</td>
</tr>
<tr>
<td>PCWP\textsubscript{A-WAVE}</td>
<td>16 $\pm$ 4</td>
<td>23 $\pm$ 6**</td>
<td>21 $\pm$ 8</td>
</tr>
<tr>
<td>PCWP\textsubscript{V-WAVE}</td>
<td>15 $\pm$ 4</td>
<td>24 $\pm$ 4*</td>
<td>18 $\pm$ 7</td>
</tr>
<tr>
<td>PCWP\textsubscript{MEAN}</td>
<td>10 $\pm$ 3</td>
<td>19 $\pm$ 3**</td>
<td>14 $\pm$ 6**†</td>
</tr>
</tbody>
</table>

* $p < 0.05$ vs. Rest; ** $p < 0.01$ vs. Rest; † $p < 0.05$ vs. 100 bpm; ‡ $p < 0.01$ vs. 100 bpm

RAP, right atrial pressure; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure.

3.5 Discussion

To the best of our knowledge, this study is the first to characterize the role of the atria in the diastolic filling of the ventricles both at rest and during light and moderate exercise in healthy humans. Our data indicate that the relative contributions of the different phases of atrial function change with heart rate to optimize ventricular filling. Our main finding was that atrial filling improves acutely with the onset of exercise, to a plateau, and altered atrial function contributes to improved LV filling at progressive exercise intensities.

3.5.1 Left Atrial Filling

We hypothesized that atrial filling was related to the longitudinal motion of the AV plane. With the onset of exercise, LA\textsubscript{MAX} increased modestly at an HR of 100 bpm, but did not
change further at 130 bpm exercise. Similarly, AVPD increased significantly at 100 bpm exercise, without further change at 130 bpm. The present data supports and extends the observations of previous research on AVPD during exercise (Quintana et al., 2005), using a similar method of AVPD quantification in younger untrained males. In the current cohort, the same pattern of an acute increase in AVPD at 100 bpm followed by a plateau at 130 bpm was observed. Though there was no significant correlation between the absolute values of LA_{MAX} and AVPD, there was a strong positive correlation between the change in AVPD with HR and the change in LA_{MAX}.

As the atria fill, the ventricles are concurrently in systole, which is the product of longitudinal, radial, and circumferential shortening. The atria and ventricles are mechanically coupled via the AV plane (Carlsson et al., 2007) such that during LV systole, longitudinal ventricular contraction draws the AV plane apically causing descent of the atrial floor. The result is external work applied to the atria inducing passive expansion and a suction effect which aspirates volume into the atria from the caval and pulmonary veins, analogous to the piston in a syringe. This effect can be observed on the pulmonary artery waveform in the wedge position as the x-descent, as atrial pressure drops even as filling occurs. While the LA_{MAX} is the absolute volume to which the atrium fills, the atrial reservoir volume represents the functional filling of the atria, from the minimal volume (at mitral valve closure), to its maximal volume (immediately prior to mitral valve opening); this sequence represents the total atrial contribution to LV filling. The early portion of atrial filling is primarily dependent on myocardial inactivation and atrial relaxation, while Barbier et al. (1999) have previously demonstrated that in the late portion of the reservoir phase, the rate of change in atrial size is solely dependent on LV shortening. As AVPD and LA_{MAX} both plateaued beyond 100 bpm, it appears that the contribution of LV long-axis
shortening to atrial filling with increasing HR is not linear, but may only contribute to LV filling at light-to-moderate exercise intensities.

There are limited data describing the normal PCWP response to exercise in humans, as the invasive nature using conventional approaches limits its feasibility during exercise studies. While some studies have demonstrated significant rises in PCWP during exercise (Wagner et al., 1986), the extent of its elevation during exercise is a topic of contention, as some contend it may be higher in trained athletes (Bevegård et al., 1963), and a recent review by Kovacs et al. (2012) concluded that especially in subjects > 50 years old, PCWP may exceed 20 mmHg during exercise. In the present study, LA pressure was invasively estimated by the PCWP. Mean PCWP increased acutely with LE, then partially normalized at the ME stage, while still remaining elevated compared to resting values. The partial normalization of mean PCWP at ME may be a phenomenon more related to exercise duration than intensity, as has been noted previously (Luepker et al., 1971). Kovacs et al. (2012) note that in individuals > 50 years old, a lack of decrease, or even increase, in total pulmonary resistance with the onset of exercise is often followed by a decrease in total pulmonary resistance, which would represent a mechanism for the decrease in PCWP observed from the light-exercise to moderate-exercise stages. Thus it appears that filling pressure increases sharply with the onset of exercise in middle-aged athletes, then decreases slightly following a delayed reduction in pulmonary vascular resistance, and remaining elevated from rest for the duration of exercise. Based upon the observations of AVPD and mean PCWP in the present study, it appears that the increase in LA filling during exercise can be attributed to the combined effects of AV plane movement creating LA passive expansion and suction, with a concurrent increase in filling pressures.
3.5.2 Atrial Emptying

At rest, approximately 64% of atrial emptying occurred passively during early diastole, while 36% was active during atrial contraction. During exercise, there are reductions in the R-R and P-R interval (Lister et al., 1965), and changes in the relative duration of events. A marked reduction in the duration of diastasis at heart rates above 100 bpm leads to a fusion of the early and late transmitral filling waves (Kilner et al., 1997). From baseline to LE, atrial filling increased, with no change in pre-contraction volume; accordingly, the passive emptying volume increased, with no change in active emptying. As discussed previously, long axis function results in external work applied to the LA by the LV via the AV plane during systole. The result is atrial stretch and expansion, with some of this action stored as elastic energy. With LV myocardial inactivation, this external force is removed, and stored elastic energy in the LA myocardium is released during early diastole (Grant et al., 1964), causing restoration towards an equilibrium point, and drawing of the AV plane back toward the atrial ceiling. Volume is ejected from the LA through movement of the AV plane toward the atrial ceiling, thereby increasing atrial pressure and contributing to the AV pressure gradient (Henein and Gibson, 1999), while at the same time enveloping volume that was previously in the atrium into the ventricle. Concurrently, during the passive phase of LA emptying, external work is applied to the LV in a reciprocal manner during early diastole as during systole. Increased LA strain rate during late diastole suggests that atrial contractility during the pump phase was increased at LE, despite an unchanged LA minimal volume. During LE, there is minimal augmentation of the Frank-Starling mechanism in the LA, because the same volume is reached at the onset of contraction, and atrial active contribution remains steady.
While atrial filling was unchanged from light to moderate exercise, during ME we observed a reversal in the relative contribution of passive and active atrial emptying to ventricular filling, with the passive component decreasing to 45% of emptying, while the active component increased to comprise 55%. At a HR of 130 bpm, diastasis was effectively eliminated and atrial emptying transitioned directly from passive to active phases. As atrial contraction begins relatively earlier within diastole during exercise due to enhanced AV conduction, an enhanced LA preload generates greater output secondary to the Frank-Starling mechanism. While LA strain rate data was not available during the ME stage, we expect that contractility would increase further at this intensity.

3.5.3 Atrioventricular Coupling During Exercise

In trained athletes, LV SV continues to rise to maximal effort (Gledhill et al., 1994), compared to an asymptotic response by moderate exercise intensity in untrained individuals (Higginbotham et al., 1986). This advantage may be in part a result of enhanced LA function. In the present study it was demonstrated that atrial filling improved at LE, but did not improve further at ME. Continued improvement in LV SV at 130 bpm could be primarily attributed to a greater LA atrial conduit volume, since LV filling is dependent on a transmitral pressure gradient throughout diastole, which is a product of LA positive pressure and LV suction. Mean PCWP increased acutely at LE, and remained elevated at ME. This may be a product of multiple factors; atrial v-wave pressure at end-systole may be influenced by forward pressure from the pulmonary vasculature, or by the restorative forces unleashed by AVP release during LV myocardial inactivation, while atrial a-wave pressure generated during atrial contraction may increase by augmented inotropy. Taken together, the present data indicates that LV filling pressure remains elevated throughout exercise, contributing to the improvement in LV filling.
The timing and velocity of LV diastolic recoil is an important factor in generating the transmitral pressure gradient (Notomi et al., 2006). We have previously demonstrated that endurance trained athletes have a faster time-to-peak untwist velocity during exercise compared to healthy age-matched controls, but do not increase the rate of LV untwist compared to rest (Lee et al., 2012), while controls significantly increase LV untwist rate. Differences in the pattern of LV untwist between untrained and trained individuals may influence the ability to recruit a greater conduit volume and augment LV SV through progressive exercise. As the conduit volume did not correlate with AVPD or other indices of atrial function in this study, as others have suggested (Bowman and Kovács, 2004), conduit function may be better described as a property of the LV. Further work is required to characterize the association between LV untwist and the conduit volume, the interplay between AVPD-atrial filling and LV untwist-conduit function, and how this relationship is influenced by age, sex, and training.

3.6 Limitations

This study is not without limitations. We studied middle-aged male subjects, potentially limiting our ability to account for age and sex differences. Biplane 2D ECHO is widely accepted as a method to assess LA volume, however, the unusual geometry of the atrium requires a number of assumptions to be made. As 3D ECHO becomes more widely available, future studies should consider its use when quantifying LA volume. We measured the atrial active contribution to LV SV as the difference between LA_{PRE-A} and LA_{MIN}. This calculation assumes that 100% of the difference in volume crosses the mitral valve and enters the LV, failing to account for retrograde PV flow given the absence of a valve at the PV-LA junction. As such, our method may have overestimated the active contribute to LV filling. However, the approach used in this study is commonly used by other groups, allowing for comparison with other data (Blume et al.,
Finally, dedicated LA strain analysis software is not currently available and like other groups (Saraiva et al., 2010) we applied software developed for the LV, using a similar method of analysis, ensuring that wall segments were tracking appropriately with visual verification.

3.7 Conclusions

Left atrial phasic function has differential effects on LV performance during exercise. During LE, passive atrial emptying is augmented and continues to be responsible for the majority of atrial emptying, due to increased atrial filling secondary to greater AVPD. During ME, atrial contraction occurs relatively earlier in the cardiac cycle at a greater pre-contraction volume, and increases the active portion of LA emptying via the Frank-Starling mechanism; despite the absence of significant decreases in LA minimal volumes, an increase in LA strain rate during late LV diastole, indicates that LA contractility was increased as anticipated. The total atrial contribution to LV performance does not increase, indicating that during ME, the increase in LV SV is attributed to a greater conduit volume during LV diastole. The LA plays an important role in optimizing LV filling, acting as a reservoir during LE, shifting to a booster pump and conduit during ME, working synergistically with elevated filling pressure to improve LV stroke volume.
<table>
<thead>
<tr>
<th>Table 1. Subject Characteristics</th>
<th>Baseline</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55 ± 5</td>
<td>48 - 65</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>177 ± 6</td>
<td>166 - 187</td>
</tr>
<tr>
<td>Mass (kg)</td>
<td>77 ± 8</td>
<td>63 - 92</td>
</tr>
<tr>
<td>Body Mass Index (kg/m$^2$)</td>
<td>24.4 ± 2.1</td>
<td>21 - 28</td>
</tr>
<tr>
<td>Body Fat Percentage (%)</td>
<td>16 ± 4</td>
<td>11 - 20</td>
</tr>
<tr>
<td>VO$_{2\text{MAX}}$ (ml/kg/min)</td>
<td>46.5 ± 7.5</td>
<td>36 - 67</td>
</tr>
<tr>
<td>LVIDd (cm)</td>
<td>4.7 ± 0.3</td>
<td>4.0 - 5.1</td>
</tr>
<tr>
<td>LVIDs (cm)</td>
<td>3.0 ± 0.2</td>
<td>2.7 - 3.4</td>
</tr>
<tr>
<td>IVSd (cm)</td>
<td>1.1 ± 0.1</td>
<td>0.9 - 1.3</td>
</tr>
<tr>
<td>LVPWd (cm)</td>
<td>0.8 ± 0.1</td>
<td>0.7 - 0.9</td>
</tr>
</tbody>
</table>

LVIDd, left ventricular internal dimension at end-diastole; LVIDs, left ventricular internal dimension at end-systole; IVSd, interventricular septal wall thickness; LVPWd, left ventricular posterior wall thickness.
<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Range</th>
<th>100 bpm</th>
<th>Range</th>
<th>130 bpm</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV&lt;sub&gt;SV&lt;/sub&gt; (ml)</td>
<td>72 ± 8</td>
<td>60 - 89</td>
<td>86 ± 10&lt;sup&gt;**&lt;/sup&gt;</td>
<td>70 - 114</td>
<td>99 ± 9&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>85 - 121</td>
</tr>
<tr>
<td>LV&lt;sub&gt;EDV&lt;/sub&gt; (ml)</td>
<td>116 ± 12</td>
<td>100 - 135</td>
<td>123 ± 11&lt;sup&gt;**&lt;/sup&gt;</td>
<td>107 - 142</td>
<td>131 ± 14&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>114 - 157</td>
</tr>
<tr>
<td>LV&lt;sub&gt;ESV&lt;/sub&gt; (ml)</td>
<td>45 ± 8</td>
<td>36 - 62</td>
<td>39 ± 8&lt;sup&gt;**&lt;/sup&gt;</td>
<td>32 - 58</td>
<td>32 ± 8&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>22 - 46</td>
</tr>
<tr>
<td>LV&lt;sub&gt;EF&lt;/sub&gt; (%)</td>
<td>62 ± 4</td>
<td>55 - 66</td>
<td>69 ± 4&lt;sup&gt;†&lt;/sup&gt;</td>
<td>60 - 75</td>
<td>76 ± 4&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>70 - 83</td>
</tr>
<tr>
<td>LA&lt;sub&gt;MAX&lt;/sub&gt; (ml)</td>
<td>47 ± 13</td>
<td>33 - 69</td>
<td>54 ± 11&lt;sup&gt;**&lt;/sup&gt;</td>
<td>42 - 70</td>
<td>52 ± 12</td>
<td>36 - 75</td>
</tr>
<tr>
<td>LA&lt;sub&gt;PRE-A&lt;/sub&gt; (ml)</td>
<td>26 ± 11</td>
<td>13 - 47</td>
<td>27 ± 9</td>
<td>14 - 47</td>
<td>33 ± 10&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>20 - 48</td>
</tr>
<tr>
<td>LA&lt;sub&gt;MIN&lt;/sub&gt; (ml)</td>
<td>14 ± 8</td>
<td>7 - 34</td>
<td>13 ± 8</td>
<td>4 - 25</td>
<td>10 ± 6</td>
<td>4 - 26</td>
</tr>
<tr>
<td>LA&lt;sub&gt;Reservoir&lt;/sub&gt; (ml)</td>
<td>32 ± 8</td>
<td>24 - 47</td>
<td>41 ± 9&lt;sup&gt;**&lt;/sup&gt;</td>
<td>24 - 57</td>
<td>42 ± 9&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>31 - 58</td>
</tr>
<tr>
<td>LA&lt;sub&gt;Conduit&lt;/sub&gt; (ml)</td>
<td>39 ± 6</td>
<td>27 - 50</td>
<td>45 ± 10</td>
<td>30 - 61</td>
<td>57 ± 11&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>40 - 75</td>
</tr>
<tr>
<td>LA&lt;sub&gt;Passive&lt;/sub&gt; (ml)</td>
<td>21 ± 5</td>
<td>13 - 32</td>
<td>27 ± 8&lt;sup&gt;**&lt;/sup&gt;</td>
<td>13 - 41</td>
<td>19 ± 7&lt;sup&gt;†&lt;/sup&gt;</td>
<td>9 - 29</td>
</tr>
<tr>
<td>LA&lt;sub&gt;Active&lt;/sub&gt; (ml)</td>
<td>12 ± 5</td>
<td>6 - 21</td>
<td>14 ± 4</td>
<td>10 - 23</td>
<td>23 ± 9&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>10 - 40</td>
</tr>
</tbody>
</table>

* p < 0.05 vs. Rest; ** p < 0.01 vs. Rest; † p < 0.05 vs. 100 bpm; ‡ p < 0.01 vs. 100 bpm
LV, left ventricular; SV, stroke volume; EDV, end diastolic volume; ESV, end systolic volume; EF, ejection fraction; LA, left atrial; MAX, maximal volume; PRE-A, pre-contraction volume; MIN, minimal volume; Reservoir, reservoir volume; Conduit, conduit volume; Passive, passive emptying volume; Active, active emptying volume.
Table 3. Doppler characteristics at rest and during exercise

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>100 bpm</th>
<th>130 bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>E (cm/s)</td>
<td>67 ± 8</td>
<td>108 ± 20</td>
<td>122 ± 15</td>
</tr>
<tr>
<td>A (cm/s)</td>
<td>54 ± 14</td>
<td>82 ± 17</td>
<td>114 ± 22</td>
</tr>
<tr>
<td>E/A</td>
<td>1.3 ± 0.4</td>
<td>1.4 ± 0.3</td>
<td>1.1 ± 0.3</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>88 ± 12</td>
<td>60 ± 7*</td>
<td>41 ± 8**</td>
</tr>
<tr>
<td>E-Decel (ms)</td>
<td>204 ± 19</td>
<td>163 ± 14</td>
<td>141 ± 21</td>
</tr>
<tr>
<td>E’ Lateral (cm/s)</td>
<td>12 ± 2</td>
<td>15 ± 3†</td>
<td>17 ± 4**</td>
</tr>
<tr>
<td>A’ Lateral (cm/s)</td>
<td>9 ± 2</td>
<td>11 ± 3**</td>
<td>14 ± 3**</td>
</tr>
<tr>
<td>E’ Septal (cm/s)</td>
<td>9 ± 2</td>
<td>13 ± 2**</td>
<td>17 ± 2**†</td>
</tr>
<tr>
<td>A’ Septal (cm/s)</td>
<td>9 ± 1</td>
<td>12 ± 2**</td>
<td>13 ± 4**</td>
</tr>
<tr>
<td>E/E’</td>
<td>7 ± 2</td>
<td>9 ± 2</td>
<td>7 ± 1</td>
</tr>
<tr>
<td>AVPD (mm)</td>
<td>14 ± 2</td>
<td>18 ± 2**</td>
<td>17 ± 2**</td>
</tr>
</tbody>
</table>

* p < 0.05 vs. Rest; ** p < 0.01 vs. Rest; † p < 0.05 vs. 100 bpm; ‡ p < 0.01 vs. 100 bpm

E, peak early transmitral flow velocity; A, peak late transmitral flow velocity; E/A, ratio of peak early to peak late transmitral flow velocity; IVRT, isovolumetric relaxation time; E-Decel, E-wave deceleration time; E’, peak early diastolic myocardial tissue velocity; A’, peak late diastolic myocardial tissue velocity; Lateral, lateral aspect of mitral annulus; Septal, septal aspect of mitral annulus; E/E’, ratio of peak early diastolic myocardial tissue velocity to peak early diastolic myocardial tissue velocity; AVPD, atrioventricular plane displacement during systole.
Table 4. Atrial myocardial strain and strain rates at rest and during exercise

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>100 bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>TATLS (ms)</td>
<td>426 ± 48</td>
<td>308 ± 44**</td>
</tr>
<tr>
<td>PALS&lt;sub&gt;POSITIVE&lt;/sub&gt; (%)</td>
<td>22 ± 5</td>
<td>32 ± 9*</td>
</tr>
<tr>
<td>PALS&lt;sub&gt;NEGATIVE&lt;/sub&gt; (%)</td>
<td>-16 ± 4</td>
<td>-22 ± 7*</td>
</tr>
<tr>
<td>ALS&lt;sub&gt;TOTAL&lt;/sub&gt; (%)</td>
<td>38 ± 7</td>
<td>53 ± 12**</td>
</tr>
<tr>
<td>ALSR&lt;sub&gt;EARLY&lt;/sub&gt; (%/s)</td>
<td>-1.9 ± 0.4</td>
<td>-3.0 ± 0.6**</td>
</tr>
<tr>
<td>ALSR&lt;sub&gt;LATE&lt;/sub&gt; (%/s)</td>
<td>-2.4 ± 0.7</td>
<td>-3.6 ± 1.1**</td>
</tr>
<tr>
<td>ALSR&lt;sub&gt;SYSTOLIC&lt;/sub&gt; (%/s)</td>
<td>1.9 ± 0.5</td>
<td>3.1 ± 1.0**</td>
</tr>
</tbody>
</table>

* p < 0.05 vs. Rest; ** p < 0.01 vs. Rest;
† p < 0.05 vs. 100 bpm; ‡ p < 0.01 vs. 100 bpm

TATLS, time to atrial total longitudinal strain; PALS<sub>POSITIVE</sub>, peak atrial longitudinal strain during atrial contraction; PALS<sub>NEGATIVE</sub>, peak atrial longitudinal strain during atrial filling; ALS<sub>TOTAL</sub>, total atrial longitudinal strain; ALSR<sub>EARLY</sub>, atrial longitudinal strain rate during early diastole; ALSR<sub>LATE</sub>, atrial longitudinal strain rate during late diastole; ALSR<sub>SYSTOLIC</sub>, atrial longitudinal strain rate during systole.
Table 5. Ventricular myocardial strain and strain rates at rest and during exercise

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>100 bpm</th>
<th>130 bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strain (%)</td>
<td>-20.4 ± 1.8</td>
<td>-20.8 ± 2.4</td>
<td>-19.2 ± 2.5</td>
</tr>
<tr>
<td>SR&lt;sub&gt;SYSTOLIC&lt;/sub&gt; (%/s)</td>
<td>-1.0 ± 0.1</td>
<td>-1.3 ± 0.2 *</td>
<td>-1.6 ± 0.3 *</td>
</tr>
<tr>
<td>SR&lt;sub&gt;EARLY&lt;/sub&gt; (%/s)</td>
<td>1.2 ± 0.3</td>
<td>1.6 ± 0.3 *</td>
<td>1.5 ± 0.5 +</td>
</tr>
<tr>
<td>SR&lt;sub&gt;LATE&lt;/sub&gt; (%/s)</td>
<td>0.9 ± 0.2</td>
<td>0.9 ± 0.2</td>
<td>1.5 ± 0.6 +†</td>
</tr>
</tbody>
</table>

* p < 0.05 vs. Rest; ** p < 0.01 vs. Rest; † p < 0.05 vs. 100 bpm; ‡ p < 0.01 vs. 100 bpm

SR<sub>EARLY</sub>, strain rate during early diastole; SR<sub>LATE</sub>, strain rate during late diastole; SR<sub>SYSTOLIC</sub>, strain rate during systole.
Table 6. Hemodynamic data at rest and during exercise

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>100 bpm</th>
<th>130 bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP_A-WAVE (mmHg)</td>
<td>10 ± 3</td>
<td>16 ± 7*</td>
<td>13 ± 7</td>
</tr>
<tr>
<td>RAP_V-WAVE (mmHg)</td>
<td>8 ± 2</td>
<td>11 ± 6</td>
<td>11 ± 6</td>
</tr>
<tr>
<td>RAP_MEAN (mmHg)</td>
<td>7 ± 2</td>
<td>8 ± 5</td>
<td>7 ± 5</td>
</tr>
<tr>
<td>PAP_SYSTOLIC (mmHg)</td>
<td>27 ± 6</td>
<td>47 ± 13**</td>
<td>45 ± 13**</td>
</tr>
<tr>
<td>PAP_DIASTOLIC (mmHg)</td>
<td>8 ± 3</td>
<td>18 ± 5**</td>
<td>17 ± 7**</td>
</tr>
<tr>
<td>PAP_MEAN (mmHg)</td>
<td>16 ± 4</td>
<td>32 ± 8**</td>
<td>30 ± 9**</td>
</tr>
<tr>
<td>PCWP_A-WAVE (mmHg)</td>
<td>16 ± 4</td>
<td>23 ± 6**</td>
<td>21 ± 8</td>
</tr>
<tr>
<td>PCWP_V-WAVE (mmHg)</td>
<td>15 ± 4</td>
<td>24 ± 4*</td>
<td>18 ± 7</td>
</tr>
<tr>
<td>PCWP_MEAN (mmHg)</td>
<td>10 ± 3</td>
<td>19 ± 3**</td>
<td>14 ± 6**†</td>
</tr>
</tbody>
</table>

* p < 0.05 vs. Rest; ** p < 0.01 vs. Rest; † p < 0.05 vs. 100 bpm; ‡ p < 0.01 vs. 100 bpm

RAP, right atrial pressure; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure.
**Figure 1.** Representative left atrial volume curve from one subject at rest, light exercise, and moderate exercise as a function of time normalized to R-R interval, beginning at the aortic valve closure.
Figure 2. Absolute contributions of LA volumes to LV stroke volume at rest, light exercise, and moderate exercise.
Figure 3. Normalized contributions of LA volumes to LV stroke volume at rest, light exercise, and moderate exercise.
**Figure 4.** Correlation of change in LA maximal volume with change in atrioventricular plane displacement.
Figure 5. Correlation of LA maximal volume normalized to body surface area with maximal oxygen uptake normalized to body mass.
Chapter IV: Limitations, Future Directions, and Conclusions

4.1 Technical Contributions and Acknowledgements

I acknowledge the following individuals who directly contributed to this project:

1. Dr. Jack Goodman
   Dr. Goodman contributed intellectually to the design of this project.

2. Dr. Susanna Mak
   Dr. Mak contributed intellectually to the design of this project. She also was responsible for the catheterization of subjects, for the determination of invasive hemodynamics.

3. Dr. Scott Thomas
   Dr. Thomas contributed intellectually to the design of this project.

4. Dr. Felipe Fuchs
   Dr. Fuchs was responsible for monitoring pulmonary arterial catheters during exercise.

5. Dr. Anjala Chelvanathan
   Dr. Chelvanathan was responsible for acquiring echocardiographic images at rest.

6. Joan Persaud
   Joan Persaud was responsible for acquiring echocardiographic images during exercise.

7. Sue Kelly, Dianne Locke, Sandra Nip, Joyce Hill, & Thom Benson
   The research nursing staff were responsible for assisting with instrumenting the subjects during the study, and for monitoring the pulmonary arterial catheters throughout the studies.

8. Taylor Gray
   Taylor contributed intellectually to the design of this project. He also contributed equally to recruitment, and data collection during the baseline and exercise studies.

   I contributed intellectually to the design of this project. I also contributed equally to recruitment, and data collection during the baseline and exercise studies. I was solely responsible for analysis of all echocardiographic images generated from the study, the review of literature, statistical analyses, generation of figures and tables, and writing of this document.

4.2 Subject Recruitment and Compliance

The recruiting approach in this study consisted of contacting the organizers of running, cycling, and triathlon clubs and teams, and distributing the study recruitment poster to the membership via email list-serv. Of approximately 10 clubs contacted, about half generated replies. From these clubs, we received over 80 inquiries to participate; of these, approximately 30 withdrew or ceased responding during the screening process, approximately 30 failed to meet inclusion/exclusion criteria, and 18 were recruited into the study. Two individuals withdrew prior
to participating due to training-related injuries. The invasiveness of the cardiac catheterization procedure proved to be a significant concern for a number of prospective participants. A detailed explanation of the procedure, discussion of the risks, and answering any questions helped reduce the anxiety of a number of subjects, who went on to successfully complete the study. No adverse events occurred as a result of the procedure. Following completion of the protocol, a number of subjects commented that once they were in the lab it was less intimidating than they had anticipated, the catheterization procedure was not painful as they had expected, and overall had a positive experience and would do it again or refer friends if given the opportunity.

4.3 Exercise Protocol

Our exercise protocol during the cardiac assessment originally consisted of 3 subsequent stages of cycle-exercise with workload manually manipulated to elicit heart rates of 100, 130, and 150 bpm, with each stage lasting 5-7 minutes. It became apparent that the stage at 130 bpm frequently lasted close to 8 minutes, and immediately proceeding to the 150 bpm stage made it extremely difficult for the subject to maintain the requisite intensity. We modified the protocol to include a 2 minute “break” between the 130 and 150 bpm conditions, with workload reduced to 50W, to allow the subject to briefly recover, before resuming the high-intensity exercise. This was more tolerable for the subjects. As we expanded our age range to 41-69, the 150 bpm condition would require older subjects to work at intensities as high as 94% of age-predicted maximal heart rate. We adjusted the target HR such that subjects > 55 years old performed at 140 bpm, so that the peak exercise stage for each subject anywhere along the range of 41-69 years would elicit a HR between 82-88% of age predicted maximum.

4.4 Data Analysis, Limitations, and Future Directions

Acquiring quality echocardiographic images during exercise remains challenging due to factors such as body position, movement, and respiratory variation. The use of the Ergoselect
table-ergometer allowed for the capture of images in a left lateral position during continuous exercise, which is an improvement over the alternatives of exercising in a standard semi-recumbent position, or pausing exercise to temporarily move into a left lateral position; however, at high workrates, the Ergoline had a tendency to oscillate in a rocking pattern which limited stable image acquisition for multiple cardiac cycles. Also, the respiratory patterns of the athletes included in this study were exacerbated at the highest intensity exercise, further limiting image quality. At HRs at and above 130 bpm, image quality suffered due to the aforementioned reasons. 2D images remained analyzable for chamber volumes at 130 bpm in most subjects, but at 150 bpm the large majority of images had wall segments drop out throughout the cardiac cycle, resulting in an inability to quantify EDV, ESV, LAMAX, or LAMIN. While spectral Doppler imaging of transmitral flow has been considered difficult to analyze at HRs greater than ~110 bpm due to decreased atrioventricular delay and subsequent transmitral E- and A-wave fusion, by manipulating the horizontal sweep of the Doppler spectral, we were able to consistently determine the peak E- and A-wave velocities at HRs up to and including 130 bpm.

STE was applied to the LA to quantify indices of atrial myocardial deformation. While dedicated atrial software has yet to be developed, a number of groups have applied LV strain analysis to the LA successfully at rest. In general, the application of STE to the LA was straightforward and similar to the LV analysis, with some differences. Tracking in the septal and lateral “apical” segments had to be visually confirmed carefully, as when applied to the atria, these segments fall over the pulmonary veins, and may be falsely negatively labeled by the tracking software. While the atrial septal wall was often easily tracked, the annular segment of the free wall frequently required manual adjustment to optimize tracking. We extended the STE application to quantify atrial deformation during exercise. The use of STE was feasible in the
large majority of subjects at 100 bpm, but was not as robust at 130 bpm. At an HR of 130 bpm, a
number of factors worked against STE application. Respiratory and body movement resulted in
continual motion of the chest wall under the probe. This resulted in frequent drop out of the LA
endocardium in images and made the wall difficult to track. The use of STE for the assessment
of LA function during exercise may be improved by narrowing the field of view in the A4C view
to focus on the left heart, and increasing the frame rate to the range of 110-130 fps, however this
may result in the movement of the LA wall out of the frame during moderate-to-intense exercise.
Thus, future studies examining LA function at high heart rates may find pharmacological stress
echocardiography more feasible to image.

As mentioned previously, LV filling is dependent on a transmitral pressure gradient,
which is influenced by both atrial and ventricular pressures. While this study focused on the
function of the LA, further work is required to better characterize the transmitral pressure
gradient during exercise, and to elucidate what mechanisms underlie its maintenance as exercise
intensity progresses. A more focused examination of the pulmonary wedge pressure waveform,
including peak a- and v-wave pressures, as well as minimal pressure at the trough of the x-
descent should be considered. This, along with a detailed analysis of LV twist mechanics is
warranted, since its contribution to LV filling relative to AVPD, is unknown. Data from the
present study suggests that atrial reservoir function may contribute to LV filling predominately
during light exercise with minimal improvement during moderate exercise, and thus at moderate
to high intensity exercise, the conduit function and LV suction may become the mechanism of
further increase in LV SV.

4.5 Conclusions

The primary hypothesis of this study was that greater AVPD during exercise would
increase atrial filling during exercise. This hypothesis is accepted; at light exercise, both AVPD
and LA\textsubscript{MAX} increased, and the increase in LA\textsubscript{MAX} and the increase in AVPD were significantly correlated. However, contrary to our expectations, there was no further improvement in either of these indices at moderate exercise, despite variations in pulmonary pressure and LV SV. This suggests that AVPD is the primary determinant of augmenting LA filling. A secondary hypothesis was that increased atrial filling would maintain or improve LA passive emptying during exercise. This hypothesis was partially accepted. At light exercise the passive emptying volume significantly increased from baseline. As this volume is a functional volume calculated from the difference between LA\textsubscript{MAX} - LA\textsubscript{PRE-A}, and LA\textsubscript{PRE-A} was unchanged, the increase in passive emptying may be attributed to greater filling. However, at ME, the passive emptying was significantly reduced and returned to near baseline values, related to our third hypothesis. Our third hypothesis was that active emptying contribution would increase during exercise via additional recruitment of the Frank-Starling mechanism, and this was also partially accepted. At LE there was no change in active emptying contribution, despite increases in left atrial strain rate during atrial contraction, indicating increased contractility. At ME, active emptying increased significantly with no change in atrial filling and a commensurate decrease in passive emptying. This likely can be attributed to additional recruitment of the Frank-Starling mechanism and altered timing of cardiac events. During exercise, a reduced R-R interval causes an earlier atrial contraction at a larger initial volume, though LA\textsubscript{MIN} was not significantly reduced, we expect that the increased atrial contractility indicated at LE would persist or increase during moderate exercise, suggesting that the Frank-Starling mechanism and intrinsic contractility both contribute to increased LA active emptying during moderate exercise.
References


Maddukuri, PV, Vieira, MLC, DeCastro, S, Maron, MS, Kuviny, JT, Patel, AR and Pandian, NG. (2006). What is the best approach for the assessment of left atrial size? Comparison of


APPENDIX A: CONSENT FORM

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Title
Right heart hemodynamics and atrial phasic function during exercise: the influence of chronic endurance training

Investigator
Dr. Jack Goodman (T) 416-978-6095

Co-Investigators
Dr. Susanna Mak, Dr. Filipe Fusch, Taylor Gray, Steve Wright

Introduction
You are being asked to take part in a research study. Please read this explanation about the study and its risks and benefits before you decide if you would like to take part. You should take as much time as you need to make your decision. You should ask the study doctor or study staff to explain anything that you do not understand and make sure that all of your questions have been answered before signing this consent form. Before you make your decision, feel free to talk about this study with anyone you wish. Participation in this study is voluntary.

Background
It is becoming increasingly recognized that cardiac enlargement is associated with longstanding athletic training. The heart is a muscular pump consisting of four hollow chambers: 2 atrial chambers (which receive blood returning from the body and the lungs), and 2 ventricles (which send blood away from the heart). Highly trained endurance athletes exhibit altered cardiac function at rest, driven by increased stroke volumes (the volume of blood pumped from one ventricle during each heart beat), and reduced heart rate. This effect is exaggerated during submaximal exercise, where increased stroke volumes can largely be explained by an increase in volume within the ventricles at the end of the diastole (the period of time when the heart is filling with blood). This increase in volume of blood stretches the wall of the ventricle causing the cardiac muscle contract more forcefully, a mechanism known as the Frank-Starling mechanism. Altered function of the atria may be responsible for the improved diastolic filling of the ventricles during exercise; however, in the right heart, increased ventricular stroke volume may cause an increase in lung artery pressure that is greater in trained athletes. The lung artery carries blood from the right ventricle to the lungs to become oxygenated. This study is designed to examine the effect of exercise on atrial function and lung pressures and the influence of long term endurance training on the cardiac response to exercise.
Purpose

The purposes of this study is to examine the effect of short-duration submaximal exercise on atrial, right ventricular, and pulmonary function in untrained and highly trained males; and to observe the influence of long-term endurance training on cardiac and pulmonary function at rest and during submaximal exercise.

You have been asked to take part in this research study because you have expressed an interest in furthering the understanding of the training differences in heart function. There are 2 groups we wish to enroll, both involving males between the ages of 45-65 years, with 12 participants in each group. The first group includes men with a long-standing history of competitive endurance exercise training. The second group includes recreationally active individuals, not training for or competing in endurance events. You will undergo the same tests and measures regardless of which group you are in.

Study Design

In order for us to understand the mechanisms responsible for the behavior of the heart in highly trained and recreationally trained men we must be able to accurately assess the pressures inside your heart at rest and during exercise.

The current experiment is an observational study using a cross-sectional design. There will be 2 visits during this study, with the first visit taking approximately 1 hour, and the second approximately 3 hours. The 2 visits will take place within one week of each other.

Study Visits and Procedures

Visit 1: Screening/Baseline

During the screening/baseline visit, you will meet with one of our graduate students involved with this study who will show you the laboratory space and explain the research procedures during each visit. Your height, weight, heart rate, seated blood pressure, and anthropometrics will be measured. These procedures are part of the standard-of-care with research of this nature. Additionally, a Physical Activity Readiness Questionnaire and Lifetime Total Physical Activity Questionnaire will be completed, which is done solely for the purpose of this study to examine your exercise history. You may refuse to answer any questions asked. The results of the tests/questions at the screening visit help the researchers to decide whether you can continue in this study.

You will then be familiarized with a cycle ergometer used to determine your maximal oxygen consumption (VO₂max). Once accustomed to the cycle, you will be equipped with a Polar heart rate monitor and a mouthpiece/headset attached to a metabolic cart. A maximal exercise test will then be performed using standard lab protocol, and the metabolic cart will measure breath-by-breath recordings of gas volumes and concentrations. The exercise protocol is designed to take no longer than 15 minutes and the total duration of this visit will be approximately 1 hour. The results of this test will be used to establish the workload during the exercise protocol used in Visit 2.
Visit 2: Cardiac Assessment

The second visit will take place at the Clinical Cardiovascular Research Laboratory of Mount Sinai Hospital and will involve insertion of a right-heart catheter (RHC). When you arrive on the morning of the study visit, we will need to place a sheath (a hollow plastic tube with a one-way valve) in your arm vein to allow us to measure the pressures on the right side of your heart. The pressure measurement is often done in patients with heart failure but in your case it is to allow us to obtain accurate pressures inside your heart. Usually it is performed by placement of a catheter (a long, thin hollow plastic tube that can measure pressure) into the right side of your heart and also into the large lung blood vessels. This test is mostly performed from a large vein of the leg (femoral vein) or the neck (internal jugular vein) following administration of local anesthetic or freezing because these are relatively large blood vessels and relatively easy to access. However, in this study it is performed through the arm under direct ultrasound guidance because of the lower risk of injury to major arteries and nerves. We will place an ultrasound probe on your arm and this will help us identify the precise location of the vein. We have already safely used this approach in a safety study of 10 patients prior to commencing this study.

We will also insert a small cannula (plastic tube) into your radial (wrist) artery, which will allow us to continuously and accurately measure your blood pressure throughout the study. Similar to the venous sheath insertion, we will freeze the skin before inserting the cannula. You may feel some discomfort during this procedure.

You will then undergo a short but detailed ultrasound (pictures taken using sound waves) assessment of your heart, which will allow us to measure the function of your heart.

This initial setup process with pressure measurement, wrist monitor, and echocardiogram may take up to 1-1.5 hours.

With you lying on your back in a semi-supine position (shown in figure below), you will be fitted to a specialized bed-bicycle, which consists of a separate ergometer/bike and a computer display that contains preset and customizable exercise protocols, in which workload is increased in stages. To maintain cadence (rhythm) during exercise, the computer has a light indicator which indicates whether you are pedaling too fast or too slow to produce the desired workload.
During exercise, you will be monitored continuously by 12 lead electrocardiogram (ECG). In this test patches attached by wires to a machine will be put on your chest, so that the machine can record the pattern of your heart beats. In some cases we may need to trim or shave your body hair. We will also monitor your heart and lung pressures, blood pressure as well as heart ultrasound for measurement of heart volumes and function.

The test will be stopped if you notice fatigue, any chest pain, or shortness of breath. The test will also be stopped if there is a fall in your blood pressure of more than 10 mm Hg from baseline or if your blood pressure is less than 90 mm Hg.

The study protocol will consist of 5 stages, including a resting stage, a 2-minute warm-up stage, and three 5-minute stages of submaximal exercise at step-wise increasing intensities based on achieving a heart rate of 100, 130 and 150 beats per minute. In each of the resting and submaximal exercise stages, following 2-minutes to achieve steady state, data collection will begin. Intracardiac and pulmonary pressures will be acquired from the catheter located in your heart. Echocardiographic assessment will be performed by a trained sonographer. The risk for healthy volunteers is minimal. Among a large series of subjects without known disease, there were approximately < 1 to 5 serious complications (including heart attack or other events requiring hospitalization) and 0.5 deaths for every 10,000 tests performed.

As stated, during each of these stages we will obtain readings from your heart, the arterial line as well as information from brief echocardiographic assessments. You will not feel any discomfort during these measurements.

Overall, this entire visit duration is expected to last 2-3 hours from start to finish. If at any stage of the study you feel unwell or would like us to stop, then please let us know and no further test will be performed and we will remove all lines.

Once the exercise protocol is complete, all lines will be removed. Once all lines are removed (arm vein sheath and the wrist cannula) and you have had a chance to rest and ask any questions about the procedures, you are free to leave. You will be given ample time to review these procedures to make sure you understand what is involved before we commence the study procedure.

**Calendar of Visits**

Boxes marked with an X show what will happen at each visit:

<table>
<thead>
<tr>
<th>Visit</th>
<th>Questionnaire</th>
<th>Exercise</th>
<th>ECG</th>
<th>Ultrasound</th>
<th>Catheterization</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening/Baseline</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>1 hour</td>
</tr>
<tr>
<td>Cardiac Assessment</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>3 hours</td>
</tr>
</tbody>
</table>


Reminders

It is important to remember the following things during this study:

- You should not consume any food, caffeine or alcohol after 9 pm on the night before your study visits (12 hours prior to visit)
- Do not take medications before visits
- No prolonged exercise on day before study visits
- Tell study staff anything about your health that has changed
- Tell your study team if you change your mind about being in this study

Risks Related to Being in the Study

There are risks associated with this study. We will take every precaution to ensure that the risk you are exposed to and development of any possible adverse event are minimized. During Visit 2 we will use ultrasound and fluoroscopy guidance to ensure that we will obtain venous access as quickly and safely as possible. If in the instance that we cannot successfully access your arm vein on 3 attempts (including an attempt on your other arm), we will stop the study and you will still be remunerated for your time even though we won’t be proceeding with the other study procedures.

There are no additional risks to pressure measurements from the arm approach. The risk of local bruising is similar to RHC from the neck or the leg. The risk of blood clots and bleeding are less than 1% and are more easily managed than those arising from the leg or the neck. The risk of nerve damage, and catheter related infection is rare and less than 1%.

The risk related to pressure measurement is minimal with no serious complications arising since commencement of this practice at our Catheterization Laboratory. Extrasystoles (extra heart beats) occur frequently, but do not cause significant consequences and are fully reversible by withdrawing the catheter.

Risks related to exercise is also very low. In the case of undiagnosed coronary artery disease, you may notice chest discomfort during exercise and there may be electrocardiographic abnormalities that we can detect on the monitor. In such circumstances, we will stop the exercise and let you recover. You will be excluded from further participation but you will be reimbursed for the $250.00 In addition, appropriate and timely further investigations will be arranged for you to further assess your symptoms and to rule out any underlying coronary artery disease you may have.

You may feel some local discomfort when we administer freezing to your wrist before we insert a small sheath inside your wrist (radial) artery, which will help us continuously monitor your blood pressure during the research procedure. Once the sheath is in you will not feel any further discomfort. There may be local bruising that develops where the sheath was inserted. The risk associated with causing damage to the wrist artery and bleeding is rare at about 1%.
Fluoroscopy (or x-rays) may be used to guide RHC placement if we have difficulty placing the RHC into the lung blood vessels. We expect that fluoroscopy use will be minimal as in most cases the RHC will float into the lung blood vessels quite easily. If we have to use fluoroscopy, you will be exposed to minimal amounts of radiation of less than 1 millisievert (mSv) equivalent to less than a third of the background radiation dose you are exposed to in a year (3mSv) or less radiation than you would receive on a transatlantic commercial airplane flight.

Please feel free to notify the study investigators during the procedure at any time you feel unwell or if you experience any discomfort (chest pain, palpitations or shortness of breath). If for any reason we feel that you should not proceed further with the research study because of development of symptoms or an unexpected reaction, you will still be remunerated $250.00 for your travel and time for this study visit.

We do not expect to find any abnormal findings with RHC and exercise challenges. In the rare instance that abnormal findings are found, for example, the discovery of high lung pressures or abnormal heart function, we will disclose these findings to you and will arrange timely appropriate follow-up for any abnormal findings. The investigators of this study are all cardiologists who are trained in further investigations and management of any abnormal cardiac findings. There will be no cost to you as a result of tests required for the follow-up of any abnormal/incidental findings. We will also relay any abnormal findings to your family physician.

**Benefits to Being in the Study**

You will not receive any direct benefit from being in this study. Information learned from this study may help further our understanding of the effect of acute submaximal exercise on atrial, right ventricular, and pulmonary function and the influence of chronic endurance exercise on these responses.

**Voluntary Participation**

Your participation in this study is voluntary. You may decide not to be in this study, or to be in the study now and then change your mind later. You may leave the study at any time without affecting your future care. You may refuse to answer any question you do not want to answer, or not answer an interview question by saying “pass”.

We will give you new information that is learned during the study that might affect your decision to stay in the study.

**Alternatives to Being in the Study**

You do not have to join this research study if you do not wish.
Confidentiality

If you agree to join this study, the study doctor and his/her study team will look at your personal health information and collect only the information they need for the study. Personal health information is any information that could be used to identify you and includes your:

- name,
- address,
- date of birth,
- new or existing medical records, that includes types, dates and results of medical tests or procedures.

The information that is collected for the study will be kept in a locked and secure area by the study doctor for 7 years. Only the study team or the people or groups listed below will be allowed to look at your records. Your participation in this study also may be recorded in your medical record at this hospital.

Representatives of the Mount Sinai Hospital Research Ethics Board may look at the study records and at your personal health information to check that the information collected for the study is correct and to make sure the study followed proper laws and guidelines.

All information collected during this study, including your personal health information, will be kept confidential and will not be shared with anyone outside the study unless required by law. You will not be named in any reports, publications, or presentations that may come from this study.

If you decide to leave the study, the information about you that was collected before you left the study will still be used. No new information will be collected without your permission.

In Case You Are Harmed in the Study

If you become ill, injured or harmed as a result of taking part in this study, you will receive care. The reasonable costs of such care will be covered for any injury, illness or harm that is directly a result of being in this study. In no way does signing this consent form waive your legal rights nor does it relieve the investigators, sponsors or involved institutions from their legal and professional responsibilities. You do not give up any of your legal rights by signing this consent form.

Expenses Associated with Participating in the Study

You will not have to pay for any of the procedures involved with this study.

You will be reimbursed $250.00 for transportation and time upon completion of both study visits. If you wish to voluntarily withdraw from the study at any point and for any reason after completion of Visit 1, you will receive $25.00 remuneration for your time. Should you experience an adverse response during Visit 1 (ex. injury) that prevents you from completing the visits, you will receive $25.00 but no further compensation. If you must involuntarily
withdraw during Visit 2 (i.e., if a vein cannot be successfully cannulated), you will be entitled to full compensation ($250.00).

Conflict of Interest

All of the people involved with this study have an interest in completing this study. Their interests should not influence your decision to participate in this study. You should not feel pressured to join this study.

Questions About the Study

If you have any questions, concerns or would like to speak to the study team for any reason, please call: Dr. Jack Goodman at 416-978-6095

If you have any questions about your rights as a research participant or have concerns about this study, call Ronald Heslegrave, Ph. D., Chair of the Mount Sinai Hospital Research Ethics Board (REB) or the Research Ethics office number at 416-586-4875. The REB is a group of people who oversee the ethical conduct of research studies. These people are not part of the study team. Everything that you discuss will be kept confidential.
Consent

This study has been explained to me and any questions I had have been answered. I know that I may leave the study at any time. I agree to take part in this study.

Print Study Participant's Name  Signature  Date

(You will be given a signed copy of this consent form)

My signature means that I have explained the study to the participant named above. I have answered all questions.

Print Name of Person Obtaining Consent  Signature  Date

Was the participant assisted during the consent process? □ YES □ NO

If YES, please check the relevant box and complete the signature space below:

□ The person signing below acted as a translator for the participant during the consent process and attests that the study as set out in this form was accurately translated and has had any questions answered.

Print Name of Translator  Signature  Date

Relationship to Participant  Language

□ The consent form was read to the participant. The person signing below attests that the study as set out in this form was accurately explained to, and has had any questions answered.

Print Name of Witness  Signature  Date

Relationship to Participant
APPENDIX B: STUDY RECRUITMENT POSTER

The Graduate Department of Exercise Science at the University of Toronto is conducting a study to examine the influence of long-term endurance training on the cardiac response to exercise in middle-aged men (45-65 years of age). We will be studying the mechanisms that contribute to the increase in cardiac function in response to a single bout of exercise, and how training influences these mechanisms.

Who Can Participate?
Participants must be MALE and 45-65 years of age. We are looking for 2 groups of individuals:

- **Long-standing competitive endurance athletes** (i.e. marathon/triathlon)
  - currently training at least 6hrs per week of running or cycling
  - participation in at least 1 competitive endurance event per year
  - vigorous year round training for the past 20 years

- **Recreationally active individuals**
  - aerobic exercise 3-5 times per week for at least 5 years
  - no participation in competitive endurance events >10 km in length

What’s Involved?
The study will include 2 separate days of testing:

**Visit 1** (About 1 hour) - Athletic Centre, University of Toronto
- Signing of consent form and physical activity questionnaire
- Overview of protocol and study visits
- VO2max test that measures overall fitness

**Visit 2** (About 3 hours) – Mt. Sinai Hospital
- Right-heart catheterization to obtain resting and exercise data on the cardiac response to exercise
- Echocardiographic imaging of the heart during rest and exercise

What’s in it for You?

- Measurement of your VO2max
- Cardiac assessment with state-of-the-art medical equipment
- Compensation for your time

Further Questions?
Please feel free to contact either of the investigators listed below with further questions you may have concerning the study and your possible participation.

Contact:
**Taylor Gray**
email: taylor.gray@mail.utoronto.ca
**Steve Wright**
email: steve.wright@mail.utoronto.ca

Or by phone at the Cardiovascular Regulation Laboratory: 416-978-0762
APPENDIX C: PAR-Q+

PAR-Q+
The Physical Activity Readiness Questionnaire for Everyone

Regular physical activity is fun and healthy, and more people should become more physically active every day of the week. Being more physically active is very safe for MOST people. This questionnaire will tell you whether it is necessary for you to seek further advice from your doctor OR a qualified exercise professional before becoming more physically active.

GENERAL HEALTH QUESTIONS

Please read the 7 questions below carefully and answer each one honestly: check YES or NO.

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Has your doctor ever said that you have a heart condition OR high blood pressure?</td>
<td></td>
</tr>
<tr>
<td>2) Do you feel pain in your chest at rest, during your daily activities of living, OR when you do physical activity?</td>
<td></td>
</tr>
<tr>
<td>3) Do you lose balance because of dizziness OR have you lost consciousness in the last 12 months? Please answer NO if your dizziness was associated with over-breathing (including during vigorous exercise).</td>
<td></td>
</tr>
<tr>
<td>4) Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)?</td>
<td></td>
</tr>
<tr>
<td>5) Are you currently taking prescribed medications for a chronic medical condition?</td>
<td></td>
</tr>
<tr>
<td>6) Do you have a bone or joint problem that could be made worse by becoming more physically active? Please answer NO if you had a joint problem in the past, but it does not limit your current ability to be physically active. For example, knee, ankle, shoulder or other.</td>
<td></td>
</tr>
<tr>
<td>7) Has your doctor ever said that you should only do medically supervised physical activity?</td>
<td></td>
</tr>
</tbody>
</table>

If you answered NO to all of the questions above, you are cleared for physical activity.

Go to Page 4 to sign the PARTICIPANT DECLARATION. You do not need to complete Pages 2 and 3.

- Start becoming much more physically active – start slowly and build up gradually.
- Follow Canada's Physical Activity Guidelines for your age (www.csep.ca/guidelines).
- You may take part in a health and fitness appraisal.
- If you have any further questions, contact a qualified exercise professional such as a Canadian Society for Exercise Physiology - Certified Exercise Physiologist* (CSEP-CEP) or a CSEP Certified Personal Trainer* (CSEP-CPT).
- If you are over the age of 45 yr and NOT accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional (CSEP-CEP) before engaging in this intensity of activity.

If you answered YES to one or more of the questions above, COMPLETE PAGES 2 AND 3.

Delay becoming more active if:

✓ You are not feeling well because of a temporary illness such as a cold or fever - wait until you feel better
✓ You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the ePARmed-X+ at www.eparmedx.com before becoming more physically active
✓ Your health changes - answer the questions on Pages 2 and 3 of this document and/or talk to your doctor or qualified exercise professional (CSEP-CEP or CSEP-CPT) before continuing with any physical activity program.

CSEP SCPE

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01-11-2011
FOLLOW-UP QUESTIONS ABOUT YOUR MEDICAL CONDITION(S)

1. **Do you have Arthritis, Osteoporosis, or Back Problems?**
   - If the above condition(s) is/are present, answer questions 1a-1c
   - If **NO** go to question 2
   1a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments) **YES** **NO**
   1b. Do you have joint problems causing pain, a recent fracture or fracture caused by osteoporosis or cancer, displaced vertebra (e.g., spondylolisthesis), and/or spondylolisthesis/pars defect (a crack in the bony ring on the back of the spinal column)? **YES** **NO**
   1c. Have you had steroid injections or taken steroid tablets regularly for more than 3 months? **YES** **NO**

2. **Do you have Cancer of any kind?**
   - If the above condition(s) is/are present, answer questions 2a-2b
   - If **NO** go to question 3
   2a. Does your cancer diagnosis include any of the following types: lung/breast/ovarian, multiple myeloma (cancer of plasma cells), head, and neck? **YES** **NO**
   2b. Are you currently receiving cancer therapy (such as chemotherapy or radiotherapy)? **YES** **NO**

3. **Do you have Heart Disease or Cardiovascular Disease? This includes Coronary Artery Disease, High Blood Pressure, Heart Failure, Diagnosed Abnormality of Heart Rhythm**
   - If the above condition(s) is/are present, answer questions 3a-3e
   - If **NO** go to question 4
   3a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? **YES** **NO**
   3b. Do you have an irregular heart beat that requires medical management? (e.g., atrial fibrillation, premature ventricular contraction) **YES** **NO**
   3c. Do you have chronic heart failure? **YES** **NO**
   3d. Do you have a resting blood pressure equal to or greater than 160/90 mmHg with or without medication? (Answer **YES** if you do not know your resting blood pressure) **YES** **NO**
   3e. Do you have diagnosed coronary artery (cardiovascular) disease and have not participated in regular physical activity in the last 2 months? **YES** **NO**

4. **Do you have any Metabolic Conditions? This includes Type 1 Diabetes, Type 2 Diabetes, Pre-Diabetes**
   - If the above condition(s) is/are present, answer questions 4a-4c
   - If **NO** go to question 5
   4a. Is your blood sugar often above 13.0 mmol/L? (Answer **YES** if you are not sure) **YES** **NO**
   4b. Do you have any signs or symptoms of diabetes complications such as heart or vascular disease and/or complications affecting your eyes, kidneys, and the sensation in your toes and feet? **YES** **NO**
   4c. Do you have other metabolic conditions (such as thyroid disorders, pregnancy-related diabetes, chronic kidney disease, liver problems)? **YES** **NO**

5. **Do you have any Mental Health Problems or Learning Difficulties? This includes Alzheimer’s, Dementia, Depression, Anxiety Disorder, Eating Disorder, Psychotic Disorder, Intellectual Disability, Down Syndrome**
   - If the above condition(s) is/are present, answer questions 5a-5b
   - If **NO** go to question 6
   5a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer **NO** if you are not currently taking medications or other treatments) **YES** **NO**
   5b. Do you ALSO have back problems affecting nerves or muscles? **YES** **NO**
6. Do you have a Respiratory Disease? This includes Chronic Obstructive Pulmonary Disease, Asthma, Pulmonary High Blood Pressure
   If the above condition(s) is/are present, answer questions 6a-6d
   If NO go to question 7
6a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies?
   (Answer NO if you are not currently taking medications or other treatments)
   YES □ NO □
6b. Has your doctor ever said your blood oxygen level is low at rest or during exercise and/or that you require
c    supplemental oxygen therapy?
   YES □ NO □
6c. If asthmatic, do you currently have symptoms of chest tightness, wheezing, laboured breathing, consistent cough
   (more than 2 days/week), or have you used your rescue medication more than twice in the last week?
   YES □ NO □
6d. Has your doctor ever said you have high blood pressure in the blood vessels of your lungs?
   YES □ NO □

7. Do you have a Spinal Cord Injury? This includes Tetraplegia and Paraplegia
   If the above condition(s) is/are present, answer questions 7a-7c
   If NO go to question 8
7a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies?
   (Answer NO if you are not currently taking medications or other treatments)
   YES □ NO □
7b. Do you commonly exhibit low resting blood pressure significant enough to cause dizziness, light-headedness,
    and/or fainting?
   YES □ NO □
7c. Has your physician indicated that you exhibit sudden bouts of high blood pressure (known as Autonomic
    Dysreflexia)?
   YES □ NO □

8. Have you had a Stroke? This includes Transient Ischemic Attack (TIA) or Cerebrovascular Event
   If the above condition(s) is/are present, answer questions 8a-8c
   If NO go to question 9
8a. Do you have difficulty controlling your condition with medications or other physician-prescribed therapies?
   (Answer NO if you are not currently taking medications or other treatments)
   YES □ NO □
8b. Do you have any impairment in walking or mobility?
   YES □ NO □
8c. Have you experienced a stroke or impairment in nerves or muscles in the past 6 months?
   YES □ NO □

9. Do you have any other medical condition not listed above or do you have two or more medical conditions?
   If you have other medical conditions, answer questions 9a-9c
   If NO read the Page 4 recommendations
9a. Have you experienced a blackout, fainted, or lost consciousness as a result of a head injury within the last 12
    months OR have you had a diagnosed concussion within the last 12 months?
    YES □ NO □
9b. Do you have a medical condition that is not listed (such as epilepsy, neurological conditions, kidney problems)?
    YES □ NO □
9c. Do you currently live with two or more medical conditions?
    YES □ NO □

 GO to Page 4 for recommendations about your current medical condition(s) and sign the PARTICIPANT DECLARATION.
PAR-Q+

If you answered NO to all of the follow-up questions about your medical condition, you are ready to become more physically active - sign the PARTICIPANT DECLARATION below:

- It is advised that you consult a qualified exercise professional (e.g., a CSEP-CEP or CSEP-CPT) to help you develop a safe and effective physical activity plan to meet your health needs.
- You are encouraged to start slowly and build up gradually - 20-60 min of low to moderate intensity exercise, 3-5 days per week including aerobic and muscle strengthening exercises.
- As you progress, you should aim to accumulate 150 minutes or more of moderate intensity physical activity per week.
- If you are over the age of 45 yr and NOT accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional (CSEP-CEP) before engaging in this intensity of activity.

If you answered YES to one or more of the follow-up questions about your medical condition:

You should seek further information before becoming more physically active or engaging in a fitness appraisal. You should compile the specially designed online screening and exercise recommendations program - the ePARmed-X+ at www.eparmedx.com and/or visit a qualified exercise professional (CSEP-CEP) to work through the ePARmed-X+ and for further information.

Delay becoming more active if:

- You are not feeling well because of a temporary illness such as a cold or fever - wait until you feel better.
- You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the ePARmed-X+ at www.eparmedx.com before becoming more physically active.
- Your health changes - talk to your doctor or qualified exercise professional (CSEP-CEP) before continuing with any physical activity program.

- You are encouraged to photocopy the PAR-Q+. You must use the entire questionnaire and NO changes are permitted.
- The PAR-Q+ Collaboration, the Canadian Society for Exercise Physiology, and their agents assume no liability for persons who undertake physical activity. If in doubt after completing the questionnaire, consult your doctor prior to physical activity.

PARTICIPANT DECLARATION

- Please read and sign the declaration below:
- If you are less than the legal age required for consent or require the assent of a care provider, your parent, guardian or care provider must also sign this form.

I, the undersigned, have read, understood to my full satisfaction and completed this questionnaire. I acknowledge that this physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if my condition changes. I also acknowledge that a Trusted Person (such as my employer, community/fitness centre, health care provider, or other designate) may retain a copy of this form for their records. In these instances, the Trusted Person will be required to adhere to local, national, and international guidelines regarding the storage of personal health information ensuring that they maintain the privacy of the information and do not misuse or wrongfully disclose such information.

NAME

SIGNATURE

DATE

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER

WITNESS

For more information, please contact
www.eparmedx.com or
Canadian Society for Exercise Physiology
www.csep.ca

The PAR-Q+ was created using the evidence-based AGREE process (1) by the PAR-Q+ Collaboration chaired by Dr. Darren E. R. Warburton with Dr. Norman Gloin, Dr. Veronika Jarrett, and Dr. Donald C. McKenzie (2). Production of this document has been made possible through financial contributions from the Public Health Agency of Canada and the BC Ministry of Health Services. The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada or the BC Ministry of Health Services.

Citation for PAR-Q+

Key References
APPENDIX D: LIFETIME PHYSICAL ACTIVITY QUESTIONNAIRE

The Lifetime Total Physical Activity Questionnaire


The next section will be about your physical activity patterns over your lifetime. Specifically, I will be asking you about your occupational, household and exercise/sports activities.

**Occupational Activities**

Starting with your occupational activities, please tell me what jobs (paid or volunteer) that you have done at least 8 hours a week for four months of the year over your lifetime. We will start with your first job and end with the job that you had in your reference year. Please describe the job that you had, the age that you started working at this job and the age when you ended doing this particular job. For each job we also need to know the number of years, the number of months per year, the number of days per week, the number of hours per day and the intensity of the job.

<table>
<thead>
<tr>
<th>No.</th>
<th>Description of Occupational Activity</th>
<th>Age Started</th>
<th>Age Ended</th>
<th>No. of months/year</th>
<th>No. of days/week</th>
<th>Time per day</th>
<th>Intensity of Activity (1,2,3,4)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hours Minutes</td>
</tr>
</tbody>
</table>

* Intensity of occupational activity defined as
1 = jobs that require only sitting with minimal walking
2 = jobs that require a minimal amount of physical effort such as standing and slow walking with no increase in heart rate and no perspiration
3 = jobs that require carrying light loads (5-10 lbs), continuous walking, mainly indoor activity that would increase the heart rate slightly and cause light perspiration
4 = jobs that require carrying heavy loads (>10 lbs), brisk walking, climbing, mainly outdoor activity, that increase the heart rate substantially and cause heavy sweating

**Household Activities**

Now I am going to ask you to report what household and gardening activities that you have done over your lifetime. Again, we will start with your past activity and then continue up to your reference year. Please include only those activities that you have done at **least 7 hours per week for 4 months of the year**. It may help you to consider what a typical day is for you. Then think about how many hours of household and gardening or yard work you do in a typical day. For seasonal activities, such as gardening, you can report those separately from all other household activities that are done all year.

<table>
<thead>
<tr>
<th>No.</th>
<th>Age Started</th>
<th>Age Ended</th>
<th>No. of months/year</th>
<th>No. of days/week</th>
<th>Time per day</th>
<th>Hours per day spent in activities that were in category:*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hours</td>
<td>Minutes</td>
</tr>
</tbody>
</table>

* Intensity of household activity defined as
1 = activities that can be done while sitting
2 = activities that require minimal effort such as those done standing, sitting or with slow walking, that do not require much physical effort
3 = activities that are not exhausting, that increase the heart rate slightly and that may cause some light perspiration
4 = activities that increase the heart rate and cause heavy sweating such as those requiring lifting, moving heavy objects, rubbing vigorously for fairly long periods
Exercise/Sports Activities

Now I would like to know all your exercise or sports activities that you did during your lifetime starting with childhood and continuing to your reference year. Please report the activities that you have done at least 2 hours per week for at least 4 months of the year. Please tell us what exercise and sports activities you have done at least 10 times during your lifetime. Besides sports and exercise, we are also interested in knowing whether you walked or biked to work. If you have done this, please report all the information as for the other sports activities. Please begin by telling me the activities that you did during your school years including your physical education (gym) classes.

<table>
<thead>
<tr>
<th>No.</th>
<th>Description of Exercise/Sports Activity</th>
<th>Age Started</th>
<th>Age Ended</th>
<th>Frequency of Activity</th>
<th>Time/Day</th>
<th>Intensity of Leisure Activity (2, 3 or 4)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>2 3 4</td>
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<td>Hours Minutes</td>
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<td>Day Week Month Year</td>
</tr>
</tbody>
</table>

* Intensity of exercise/sports activity defined as
  1 = activities that are done sitting
  2 = activities that require minimal effort
  3 = activities that are not exhausting, that increase the heart rate slightly and that may cause some light perspiration
  4 = activities that increase the heart rate and cause heavy sweating
ESTIMATION OF OUTCOME VARIABLES

a) Average number of hours per week spent in occupational activity over lifetime =
Equation 1A. The average number of hours per week spent in occupational activity over a
lifetime was estimated separately for sedentary, light, moderate, and heavy occupational
activity.

Equation 1A:

$$\sum \frac{[(\text{Age finished} - \text{Age started}) \times (\text{Months/yr}) \times (4.33 \text{ wks/month}) \times (\text{No. of d-wk}^{-1}) \times (\text{Hr/day})]}{52}\text{ Number of years}$$

b) Average number of hours per week spent in household activity over lifetime =
Equation 1B. Average number of hours per week spent in household activity over
lifetime was estimated separately for light, moderate, and heavy household activity.

Equation 1B

$$\sum \frac{[(\text{Age finished} - \text{Age started}) \times (\text{Months/year}) \times (4.33 \text{ wk/month}) \times (\text{No. of days/week}) \times (\text{Hr/day})]}{52}\text{ Number of years}$$

c) Average number of hours per week spent in exercise/sports activities over lifetime =
If respondent reported per day: Equation 1C

$$\sum \frac{[(\text{Age finished} - \text{Age started}) \times 365 \text{ d/yr} \times (\text{No. of times/day}) \times (\text{Hr/exercise session})]}{52}\text{ Number of years}$$
If respondent reported per week: Equation 1D

\[
\sum \frac{[(\text{Age finished} - \text{Age started}) \times 52 \text{ wk/yr} \times (\text{No. of times/week}) \times (\text{Hr/exercise session})]}{\text{Number of years}}/52
\]

If respondent reported per month: Equation 1E

\[
\sum \frac{[(\text{Age finished} - \text{Age started}) \times 12 \text{ months/yr} \times (\text{No. of times/month}) \times (\text{Hr/exercise session})]}{\text{Number of years}}/52
\]

If respondent reported per year: Equation 1F

\[
\sum \frac{[(\text{Age finished} - \text{Age started}) \times (\text{No. of times/yr}) \times (\text{Hr/exercise session})]}{\text{Number of years}}/52
\]