Right-Sided Cardio-Pulmonary Relationships in Endurance Athletes: Potential Long-Term Consequences of Higher Pulmonary Pressure Generation during Exercise

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science

Graduate Department of Pharmacology
University of Toronto

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Abstract

Endurance-trained athletes (ETA) demonstrate physiologic cardiac adaptations, however few demonstrate indicators of reduced right-heart (RH) performance. This subset of ETA has not been characterized; they may be among those who generate higher pulmonary pressures (PP) during exercise. With RH catheterization during a graded-exercise protocol, PP during exercise were measured in 7 untrained controls and 16 ETA, with “high” and “low” pressure-generators (HPG, LPG) identified within our ETA cohort. Potential impacts of high-pressure states on long-term RH function were investigated with Echocardiography. A wide range in PP was produced in both cohorts, despite uniform RH enlargement in ETA. Compared to LPG, HPG athletes with peak-systolic PP over the median of 49mmHg demonstrated reduced resting RV systolic strain (p=0.04), slowed RV diastolic rate (p=0.03), and large left-atrial size (p<0.01). HPG demonstrated paradoxical increases in pulmonary vascular resistance in response to light exercise. Higher exercise-induced PP may influence long-term RH performance in ETA.
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"Better than a thousand days of diligent study is one day with a great teacher." – Japanese proverb

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“Real learning comes about when the competitive spirit has ceased.” - Jiddu Krishnamurti

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“Good teaching is more a giving of right questions than a giving of right answers.” – Josef Albers

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List of Abbreviations

AF  atrial fibrillation
ANP  atrial natriuretic peptide
ARVC arrhythmogenic right ventricular cardiomyopathy
BMI body mass index (kg/m2)
BNP brain natriuretic peptide
BSA body surface area (m2)

Cardiac Waveforms:
- myocardial movement during early diastole (passive filling of ventricle)
- myocardial movement during atrial contraction (active filling of ventricle)
- myocardial movement during systole (ventricular contraction)

CO  cardiac output (L/min)
ECG electrocardiogram
Echo Echocardiography
EDD end-diastolic diameters (cm2)
EDV end-diastolic volume
ETA endurance-trained athlete/s
FAC fractional area change
FW free wall
HPG high pressure generators/generating
HR heart rate (beat/min)
LA left atrium/atrial
LPG low pressure generators/generating
LV left ventricle/ventricular
LVEF left ventricular ejection fraction
LVOT left ventricular outflow tract

max maximum/maximal
min minimum/minimal
mPAP mean pulmonary artery pressure
MRI magnetic resonance imaging
PAH pulmonary arterial hypertension
PASP pulmonary arterial systolic pressure
PCWP pulmonary capillary wedge pressure
PTAC pulmonary transit of agitated fluid
PVR pulmonary vascular resistance
RA right atrium/atrial
RAP right atrial pressure
RH right heart
RV right ventricle/ventricular
RVEF right ventricular ejection fraction
RVOT Right ventricular outflow tract
SD standard deviation
STE speckle tracking echocardiography
SV stroke volume (ml/beat)
TAPSE tricuspid annular plane systolic excursion (cm)
TD tissue doppler (cm/sec)
TDI tissue doppler imaging
VTI velocity time integral (cm)
Chapter 1: Introduction

1.1 Rationale

The health benefits of exercise are widely accepted with numerous studies providing indisputable evidence of lower mortality rates, increased longevity, and quality of life (1-4). However, emerging evidence suggests that “excessive” endurance exercise can be complicit in the development of transient and chronic cardiac abnormalities, such as impaired systolic performance, development of fibrosis, and a 5-10 fold risk in endurance athletes to develop arrhythmias compared to healthy untrained individuals (3, 5-20).

Known cardiac adaptations to endurance exercise training involve left ventricular and atrial (LV and LA) remodeling, including an enlargement in chamber size and end-diastolic volume, and increased contractility (6, 21). Such remodeling has been widely accepted as a physiologic response in accommodating the high-volume conditions of exercise, and have collectively been termed as the “Athlete’s Heart” (21, 22). Right-sided adaptation in endurance athletes however is less clear, and has only recently become a focus of research. In fact, there is a high degree of variability in the literature due to several limitations involved in its analysis. These include its complex shape, its thin walls, and poor visibility on echocardiograms. However, few exercise studies looking at right ventricle (RV) structure and function have described some degree of transient RV impairment with associated fibrosis and biomarkers of cardiac damage in a small, limited sample of endurance athletes (18, 23, 24).

Because of its thin walls, the RV is more vulnerable to volume and pressure stresses induced by exercise (25). The propensity for acute and chronic RV enlargement may then lead to pathological remodeling and functional impairments after long-term exposure to exercise. Unfortunately, there still remains a high degree of variability in the literature with regards to the development of RV pathologies in endurance athletes; with many conflicting reports in the literature, we may acknowledge that right-sided functional adaptations are not uniform across endurance athletes.
The discrepancies in the data can be attributed to the limited visibility and characterization of the RV, but may also be secondary to limited investigation in cardio-pulmonary relationships during exercise in this population. These interactions have direct effects on right heart function, and must therefore be part the discussion involving right heart adaptations and potential pathological outcomes. The pulmonary response to exercise has also been highly varied within the literature, and the cardiac consequences of such pulmonary pressure elevations have not been investigated in athletes. While pulmonary pressures are expected to increase during exercise (26), their degree of elevation is highly variable across the athletic population. Quite often, pressures can rise above the commonly accepted threshold of a mean pulmonary artery pressure (mPAP) of 30mmHg, and pulmonary artery systolic pressure (PASP) of 40mmHg, a finding that often leads to the diagnosis of “exercise-induced pulmonary hypertension” (26-32) in the sedentary or untrained healthy population. Meanwhile, others have reported a very modest rise in pressures, reaching only 19mmHg (33). Such a range in pulmonary pressures has been previously described (34), illustrate the gap in understanding regarding a “normal” pulmonary response to exercise in this population (27-32, 34, 35).

Such heterogeneity in pulmonary hemodynamics in athletes occurs despite uniform structural right heart adaptations (dilated RVs and RAs) that are considered healthy stretch-induced adaptations to best accommodate the volume loading of endurance exercise. However, functional measures of right heart performance are also highly variable across endurance athletes, as demonstrated in select studies showing indices of impaired systolic performance, fibrosis and arrhythmogenic factors localized in the RV (18, 23, 24). Right-sided “mal-adaptations” may be a product of continued exposure to both high-volume, and high-pressure states of exercise. We are interested in examining the physiological basis of why certain athletes develop RV pathologies, and if they also demonstrate ‘exaggerated’ pulmonary pressure responses to exercise that are considered to be a pathological substrate in other healthy populations.
1.2 Objectives

1) To describe the range of pulmonary pressures reached during exercise in endurance trained athletes (ETA) and untrained controls

2) To identify potential impacts of exercise-induced high pulmonary pressures on right heart function in ETA

1.3 Hypotheses

1) The pressure-flow relationships in a cohort of ETA are heterogeneous, with distinct “high” and “low” pressure-generators (HPG and LPG).

2) HPG and LPG can be characterized by right heart systolic and diastolic functional differences at rest and during exercise.
Chapter 2: Review of Literature

2.1 Introduction

The following review will first introduce potential adverse outcomes of long-term vigorous endurance training. Reasons for such outcomes will be explored by looking at both the left and right side of the heart, and how they adapt in ETA. The review will then focus on the dynamic relationship between the right heart and pulmonary circulation, which may contribute to the development of damaging cardiac stress and outcomes in a select group ETA. Finally, cardiac and hemodynamic measures will be introduced and explained.

2.2 Potential adverse outcomes of long-term high intensity endurance exercise

Routine endurance exercise has long been known to have cardio-protective effects. While it cannot be prescribed, endurance exercise is often recommended as an intervention by physicians and public health professionals. It can in fact exert a somewhat ‘pharmacological’ effect both directly (healthy cardiac pump function) and indirectly (weight loss and metabolic adjustments), yielding an improved cardiovascular performance with exercise, and a reduction of cardiovascular-related and all-cause mortality (1-3). Endurance exercise is met with an increased oxygen demand, which is accommodated by significant increases in cardiac output (CO) (L/min) – sometimes by 5-6 times the normal resting values of 3-5 L/min (36). Recommendations for defining “moderate to vigorous” exercise include up to 150 minutes of aerobic exercise per week. Long-term exposure to vigorous high-volume exercise can induce physiological cardiac remodeling, termed the “Athlete’s Heart”, most typically characterized by uniform chamber enlargement, modest wall thickening, and an increase in contractility (6, 21). A detailed description of the Athlete’s Heart will be given in the following sections.

Cardiac “hypertrophic” remodeling is accepted to be a normal and healthy adjustment to increases in volume load, not to be confused with a pathological diagnosis of myocardial hypertrophy (37-39). However, ‘excessive’ endurance exercise that supersedes the current recommendations – with repeated involvement in marathons or long-distance exercise – is now believed to cause an “overuse pathology” in some athletes (5, 6). More recently, ‘excessive’ exercise has been associated with various observations that are considered adverse, including the
presence of markers of myocardial damage, transient dysfunction, and pro-arrhythmic factors (3, 5-9). Specifically, the risk of atrial fibrillation (AF) is now believed to be 5 to 10-fold more common in endurance athletes, compared to the untrained healthy population (10-13). However, the mechanisms linking exercise-induced cardiac remodeling and adverse cardiac outcomes remain unresolved. The literature is lacking in long-term prospective trials that would be needed to support such a relationship.

2.3 “Normal” Cardiac Remodeling

There are two main forms of exercise that cause different types of cardiac remodeling. Athletes involved in ‘power’ activities – associated with elevated systemic blood pressure without a commensurate volume increase – will typically show an increase in vascular resistance with little to modest increases in CO, and significant LV wall thickening due to an elevated systemic afterload (6, 40). Endurance (or aerobic) training on the other hand – a volume driven exercise – will show cardiac chamber enlargement and a decrease in vascular resistance to accommodate the high volume conditions of aerobic exercise. These adaptive characteristics are not dichotomous, and may vary along a spectrum of sports (41). While both strength and endurance trained athletes and associated cardiovascular complications with vigorous exercise, this study will only focus on endurance-trained athletes (ETA).

The mechanism of cardiac enlargement in the ETA’s heart is likely secondary to volume-loading that induces a cardiomyocyte response to stretch-sensitive factors to initiate cellular hypertrophy, which can involve regulators like Insulin-like Growth Factor-I (27-32, 34, 35, 42). Its involvement in post-natal cardiac development makes it a likely contributor to exercise-induced chamber enlargement (42). Additionally, ETA cardiomyocytes show augmented calcium uptake by sarcoplasmic reticula, which directly leads to improved and more rapid diastolic relaxation and a resultant increase in end diastolic volumes (EDV) (43, 44). Long-term exposure to high-volume conditions causes chronic eccentric cardiac chamber enlargement, and hemodynamic adaptations seen at rest. Stroke volume (SV)(mL/beat), for example, remains elevated at rest due to the Frank Starling forces induced by larger chamber areas and enhanced diastolic filling (6, 45-47). A description of Frank Starling forces is provided in Appendix A.
Another important chronic adaptation in the Athlete’s Heart is a lower resting heart rate (HR) (48), which offsets the increase in SV to maintain a stabilized CO:

**Equation 1:** \( \text{CO} = \text{SV} \times \text{HR} \)

The marked resting bradycardia in ETA is due to a dominance of parasympathetic activity, and is commonly associated with electrocardiogram (ECG) abnormalities believed to be benign (49). Electrical readings such as J point elevation (a marker for early repolarization), ventricular ectopies (premature heart beats), and increased QRS voltages (a marker for more powerful contractile force) have been associated with LV enlargement and the Athlete’s Heart (50, 51). It is also possible that intrinsic SA nodal function is altered by endurance training to lower heart rate, independent of vagal influence (52).

Both female and male ETA experience cardiac morphological adaptations to exercise, however structural remodeling in females is less apparent than in male counterparts at comparable training volume (6, 53, 54). Additionally, female vagal tone tends to be more pronounced, with lower resting blood pressures (54-56).

### 2.4 The Athlete’s Left Heart

#### 2.4a Left Ventricle (LV)

The first reports of an “Athlete’s Heart” were described as early as the 1890s, when Swedish physician S. Henschen used auscultation and percussion to measure the relative enlargement and enhanced performance of the LV in ETA (51). Since then, Echocardiography (Echo) and cardiac MRI have time and time again confirmed his findings.

In a study by Pelliccia et al, over 1300 elite athletes were assessed for their LV end diastolic diameters (EDD). A wide range in values was reported in both male and female cohorts (38-66 mm in women; 43-70mm in men). It was also noted that endurance athletes’ EDDs were markedly larger than non-endurance athletes (57). LV structural and functional adaptations can be seen even after a 3-month period of intense endurance training (58), and are believed to be reversible in most cases with cessation of training – thereby implying a *non-pathological*
enlargement and adaptation (51). Adaptive responses like increased cavity size, enhanced contractile performance, and rapid filling times will generate powerful Frank Starling forces, which contribute to the higher VO\(_2\)max values, augmented CO and aerobic capacities (22).

The correlation between LV adaptations and negative cardiac effects in ETA has been investigated, with no substantial evidence of a causal relationship. Few have reported reduced LV ejection fraction (LVEF)(59) and minor delays in diastolic relaxation velocities at rest (6). As well, there are reports of non-reversible LV growth even after years-long periods of deconditioning (cessation of training) (60). Such studies suggest that long-term, damaging clinical implications should not be ruled out – even while Athlete’s Heart adaptations have been accepted as physiologic and healthy. Benign ECG abnormalities such as J Point Elevations found in roughly 15% of athletes (51) are also known to be early warning signs of sudden cardiac death (50, 61), however prospective and follow-up studies show no association of these isolated ECG occurrences with sudden cardiac death in ETA (49, 50, 61).

2.4b Left Atrium (LA)

The LA in the Athlete’s Heart has also been studied at length, commonly to find links between LA remodeling and the development of AF. However, a causal relationship between endurance exercise and the development of AF is difficult to establish. Significant LA remodeling and chamber enlargement has been reported in athletes as a function of lifetime training/physical activity hours (32, 62-64) with the largest data-set to date of 1777 competitive athletes demonstrating LA EDD enlargement of over 40mm, and a minimal change in wall thickness(39). LA pressures are typically increased in ETA, which further induces atrial stretch during and after endurance exercise (64, 65).

Both left and right atrial dilatation have been associated with the development and recurrence of AF (10, 66-68). Because of their relatively thinner walls, the LA and RA are more prone to distension during excessive volume loading than the ventricles would be. Consequently, this may lead to a chronic, irreversible dilatation, which has been suggested to cause downstream effects towards the development of cardiac complications like AF. For example, baseline serum pro-ANP levels – a common marker of atrial stretch and distension – have been reported to be higher
in ETA (62). If shown chronically in an untrained and otherwise healthy individual, elevated pro-ANP levels may be a predictor of AF (62, 69, 70).

Atrial remodeling has also been associated with pro-fibrotic pathways in exercise animal models (71), and with acute elevations in pro-inflammatory markers such as C-Reactive Protein, TNF-alpha and Interleukin-6 after exercise (72, 73). However, the clinical consequences of these markers, and of exercise-induced atrial enlargement have been widely debated, as AF has been reported in similar proportions of athletes with and without atrial remodeling (39, 74).

Left sided remodeling and its relationship to the development of adverse cardiac outcomes are poorly understood in the literature. Other plausible hypotheses include the enhanced parasympathetic overdrive in these athletes, which may cause electrical remodeling, that increases the propensity for arrhythmias (6, 37, 52, 75).

2.5 The Athlete’s Right heart

2.5a Right Atrium (RA)

A shift in focus to right-sided remodeling in ETA has only recently been noted in the literature. Right-sided functional and structural adaptations in ETA are now being studied for their implications and associations with adverse cardiac outcomes. Much like the RV, the RA has only recently been studied in athletes. RA remodeling involves enlarged cavity area with long-term endurance training (53, 76-78). More rapid diastolic filling may also be a long-term consequence of endurance training, especially considering the association of aerobic exercise with expansion in blood volume, resulting in healthy and powerful applications of Frank Starling forces (79). Without a correlation with age, RA areas, volumes and their indices (corrected for BSA) may even reach higher values than the LA in male ETA (76, 80). Marked RA enlargement is often characterized as RA maximal (RAmax) area of >18cm² (81), and while such dilatation is often described in pathological conditions, it is deemed a “normal physiologic response” in the endurance athlete (27).

While RA volumes (or size) are known to be augmented, they are not necessarily accompanied by enhanced contractile function. In fact, some studies have shown diminished contractile
function in endurance athletes (77). Such a phenomenon suggests that the RA is responding to boosts in volume loading by increasing its chamber size, but at a high-energy expense, working at elevated wall stress that could impair their long-term contractile reserve.

2.5b Right Ventricle (RV)

Because both right and left ventricles must accommodate the same flow (CO), it was believed that RV and LV remodeling occurs proportionately to each other (6, 82). However there is also evidence supporting a disproportionate compensatory adaptation to endurance exercise in the RV compared to the LV in a subset of athletes, where the RV may be vulnerable to dysfunctional responses to volume and pressure loading of exercise given its relatively thin walls (24, 25, 56, 83).

Structural remodeling of the RV in the Athlete’s Heart includes an increase in cavity size (up to 25%) and volume (15, 84-86) compared to sedentary controls(23) and strength-trained athletes(23, 27, 82). The propensity for stress-induced RV enlargement may lead to adaptations and functional impairments after long-term exposure to intense exercise, and promote abnormal remodeling. Additionally, RVOT enlargement has also been characterized, which is a common finding in ARVC (14, 20, 86).

RV functional adaptations to exercise remain unclear with disparate findings reported. Acute responses to exercise are difficult to measure in the RV, and have only recently begun to be investigated. Improved diastolic function has been reported (27), with no substantial change in systolic function (23, 27). However, some reports have shown significant acute systolic dysfunction, characterized immediately after an endurance event by a reduction in RV wall strain (15, 83, 87), RV EF (15, 65, 88), tricuspid annular displacement, RV fractional area change (24, 89), and increased electromechanical delay(87) in ETA compared to sedentary controls. Additionally, cardiac markers of RV dysfunction have been reported in ETA acutely after exercise, such as a rise in BNP (14, 15, 17), and Troponin I and T (14, 83). Finally, cross-sectional studies have found RV fibrosis in a small subset of long-term ETA with no such markers in the LV (14-17). A postulated theory from RV-focused studies suggests that these cardiac enzymes and biomarkers may reroute the physiologic and electrical landscapes of the RV.
with chronic exposure to endurance exercise, and cause exercise-induced arrhythmias and/or fibrosis (14, 18-20).

Importantly, in the range of RV measurements reported tends to be extremely wide – where LV measures are more often uniform. For example, Pagourelias et al reported no RV functional differences at rest between athletes and sedentary controls. Using echo-derived speckle tracking quantitative analysis, RV strain was assessed as the shortening in length during systole (expressed as a percentage change from the original length of a RV wall segment; this is a commonly used measure of contractile performance and will be described in further sections). While systolic RV strain in ETA was not significantly different from controls or strength-trained athletes, ETA did show a wider range of resting strain values, from a strain of a magnitude less than -5% to greater than -40%, whereas other athletes experienced RV strain within a much narrower window (23). (See **Figure 1**)

![Figure 1](image)

**Figure 1.** Box-plot graphs demonstrating RV longitudinal ε (strain) in different subsets of athletic populations and controls (23).

Basal, strain measures at RV basal wall segments; FW, free wall; Global, represents an average of all wall sections

Such a range in results was also reported but not discussed by La Gerche at al, where cardiac biomarkers of stress including Troponin and BNP were measured acutely after an ultra-endurance triathlon in 20 male and 7 female athletes. All participants showed rises in BNP levels immediately post-exercise compared to baseline, with significant difference of the means at each time point. (12.2 ng/L at baseline vs. 42.5 ng/L post exercise; p<0.001). However, only a small
subset of athletes achieved a truly ‘significant’ increase in BNP levels, with only 5 out of 27 athletes (18.5%) producing values above the mean of 42.5 ng/L, one of whom undoubtedly influenced statistical significance by generating values of greater than 250 ng/L. Meanwhile, the majority of athletes studied demonstrated post-race BNP levels closer to baseline values of 12.2 ng/L. Similarly, a rise in troponin I was detected in 15 athletes (58% of participants), producing significant increases from rest to post-race time points (0.17 ug/L at baseline vs. 0.49 ug/L post exercise; p<0.01). Again, only 5 athletes showed substantial increases in Troponin levels above the mean of 0.49 ug/L, two of who produced values between 2.5 and 3.5 ug/L (24). (See Figure 2)

![Figure 2. Pre (within 2 weeks prior to event), post (immediately after) and delayed (1 week post) measures of (left graph) cardiac troponin and (right graph) BNP (24)](image)

The heterogeneity regarding RV systolic and diastolic performance among ETAsuggests that functional impairments are likely results of intrinsic RV hemodynamic characteristics, regardless of exercise history or Athlete’s Heart adaptations (88). Consequently, the development of impaired cardiac performance in a subset of athletes may be a result of the interplay of acute and chronic physiologic responses to exercise. As such, transient RV dysfunction may be a harbinger of long-term RV pathogenesis in a specific athletic cohort that has yet to be defined.

Variability in the literature and within-data regarding RV remodeling could be attributed to two separate factors:

1) The RV is difficult to study in humans due to its thin-walled and complex structure. When observing the RV from a radial cross-section, it has a crescent-shaped structure that wraps around the LV. As well, the RV free wall (FW) is much thinner than the LV
[3-5mm RV FW (90) vs 6-10mm LV FW (91)]. These factors contribute to a sub-optimal visibility of the RV on echo, rendering it challenging to make structural and functional measures that are already sonographer-dependant (81, 90, 92). MRI has reliably measured RV size and volumes, however echo is favoured in clinical research due to its low cost and accessibility. In 2010, the American Society of Echocardiography accumulated enough data from echo-MRI correlation studies to introduce standards and guidelines for the measurement of right heart sizes and volumes using echo(81). Consequently, much of what is known of the right heart in athletes, both at rest and during exercise, has been studied and confirmed with echo within the past 5-10 years.

2) As a population, long-term ETA are a heterogeneous group whose RV function and/or dysfunction are influenced by inherent – possibly genetic – factors that are independent of volume loading. Because of the RV thin walls, the effects of other factors like RA phasic function and pulmonary vascular resistance (PVR) can impact the manner in which the RV responds to exercise acutely and chronically (18, 27). When discussing the right heart, it is important to contextualize its function with pulmonary hemodynamics; many exercise studies have not considered this crucial dynamic relationship in their discussions of RV function.

Right-sided cardio–pulmonary relationship will be a focus in the upcoming sections of this review. There, we will postulate that athletes with right heart functional impairments may also be subject to pulmonary abnormalities as well.

2.6 Terms and Measurements Describing Pulmonary Hemodynamics

Before exploring right-sided cardio-pulmonary relationships in ETA further, a brief overview of dynamic variables describing pulmonary hemodynamics is provided in this section.

2.6a Pulmonary Pressures

Pulmonary artery pressures are generated during ventricular systole, and are influenced mainly by three factors: downstream forces from the RV (CO), upstream forces (LA pressure and
function), and intrinsic characteristics in the pulmonary vasculature that differ from person to person (28, 93). Pulmonary pressures are best measured invasively by placing a catheter into the pulmonary artery through the RVOT. Pressures can then be recorded during systole (Pulmonary Artery Systolic Pressure, PASP) and diastole (Pulmonary Artery Diastolic Pressure, PADP), and from these values, a mean Pulmonary Artery Pressure (mPAP) can be estimated by the following formula:

Equation 2: \[ mPAP = \left(\frac{2}{3}\right)PADP + \left(\frac{1}{3}\right)PASP \]

In a young healthy adult, mPAP values typically range between 9 – 18 mmHg, and PASP between 15 – 30 mmHg. During exercise, these values are expected to rise; the degree of pressure elevation however will be a topic for further discussion in this paper.

Advancing a balloon-tipped catheter into pulmonary capillaries that feed into the LA will record the Pulmonary Capillary Wedge Pressure (PCWP); this is used as a surrogate measure for LA pressure. In a young healthy adult, PCWP values typically range between 4 – 12 mmHg.

2.6b Pulmonary Vascular Resistance (PVR)

PVR represents an intrinsic property unique to each individual that affects cardio-pulmonary pressures and function. PVR can differ from one person to another based on a number of factors including the endothelial make-up on the pulmonary vessels, sympathetic tone, medical and family histories, and environmental or occupational forces. It is characterized by a dynamic relationship between right-sided and left-sided pressures, and CO. In a young healthy individual, PVR is proportional to the difference between mPAP and PCWP. And, PVR is inversely proportional to CO, representing the inflow from the RV.

Equation 3: \[ PVR = \frac{(mPAP - PCWP)}{CO} \]

From the equation above, PVR is measured in mmHg·min/L, referred to as a Wood Unit. It is also commonly reported as dynes·sec/cm², by multiplying Wood units by 80.

In young healthy individuals, a normal PVR averages to 0.25 – 1.6 Wood units, or 120 dynes·sec/cm² (94). Importantly, PVR is not usually influenced by training history or exercise habits, as PVR values are typically similar in athletes and sedentary controls (95, 96). Older
subjects will usually show slight increases in their PVR (34, 95), and pulmonary hypertension patients will typically have a PVR of > 3 Wood units (97).

2.6c Pulmonary Vascular Compliance

Compliance of the pulmonary vasculature reflects the elastic properties of its vessels, and better describes the accommodation of pulsed flow. It is inversely related to the pulse-pressure of PASP and PADP (94, 98), and calculated with the following formula:

Equation 4: \( \text{Compliance} = \frac{\text{SV}}{\text{PASP} – \text{PADP}} \)

Compliance will therefore provide a surrogate measure of volume accommodation during the cardiac cycle. The average compliance value for healthy young adults is typically 3.34 L/kPa (99). Vascular compliance tends to decrease in subjects older than 50 years of age (34) and in pulmonary hypertension patients, reflecting the trend in PVR.

2.6d Pressure-Flow Relationship

The Pressure-Flow relationship is a graphical depiction of how the pulmonary vasculature responds to changes in CO. It involves a plot of pulmonary pressures against continuous and simultaneous CO measurements over time. The slope of this line represents how every 1 L/min increase or decrease of CO impacts pulmonary response. Typically in healthy young subjects during exercise, the slope of the mPAP-CO plot is 1 mmHg per 1 L increase of CO (30, 100). An increase of this slope reflects a less compliant, more resistant quality of the vasculature, typically found in older populations (30, 34) and in pulmonary hypertension. The pressure-flow relationship has previously been used to quantify RV afterload during exercise (18, 95, 101).

2.7 Right Heart and Pulmonary Relationships

As mentioned above, there is considerable variability among and within the data regarding right-sided cardiac functional adaptations in ETA. The following sections will focus on pulmonary hemodynamics and how they may in part explain the varying trends of RV function in a heterogeneous athletic population.
The right and left ventricles are required to accommodate the same CO and the RV will face a varying afterload depending on resting or exercise states. **At rest**, in the healthy, young (<60 years) male or female, the pulmonary circulation is a highly compliant, low resistant system. This allows the RV to eject blood at relatively low energy cost compared to the LV, which pumps against a much higher systemic afterload (18). **During exercise** however, the compliance of the pulmonary vasculature is variable. While the systemic circulation responds to increased flow by a 75% reduction in vascular resistance (thereby allowing for greater oxygen supply to skeletal muscles)(46), PVR only reduces by an average of 30% during exercise in healthy trained and untrained individuals (18, 46). Such an asymmetry in the systemic and pulmonary vascular response to exercise translates into a disproportionately greater RV afterload, compared to the LV(18). This may be complicit in inducing acute RV dysfunction after an intensive exercise event; cumulative exposures to these events may further cause a chronic pathological ‘mal-adaptation’ (18, 98, 102).

**2.8 The Pulmonary Response to Exercise**

**2.8a Pulmonary Pressure Trends During Exercise**

Across the healthy population, there does exist a general trend in the pulmonary response to exercise. Characterized by Lonsdorfer-Wolf et al (100) and multiple times thereafter, during a 30 minute cycling protocol, healthy subjects generated an increase in mPAP from 13.5 ± 2.0 at rest to 26.5 ± 5.6 mmHg at peak exercise. Rising pressures may be attributed to greater RV output, and/or increases in LA pressure. However, it was only during the first 5 minutes of the protocol – which occurred before peak exercise – where peak mPAP was rapidly reached (24.0 ± 5.0 mmHg). After peak mPAP was reached, a steady plateau was generated, followed by a minimal decline in pressure towards the later stages of the protocol (100).

It has also been suggested that ETA generate higher PASPs compared to untrained healthy individuals. Using cMRI and echo, La Gerche et al (25) measured the resting and exercise-induced PASPs of 14 non-athletes, and 39 ETA with a mean age of 36 years. Subjects were required to cycle until exhaustion, with incremental increases in their workload and had their PASPs measured every 2 minutes. At peak exercise, the PASPs generated by ETA were
significantly greater than the sedentary controls (61.1 ± 12.7 in ETA vs. 47.0 ± 6.5 mmHg in controls). This difference was evident despite the similar resting PASPs in both groups.

2.8b Heterogeneity in ETA Pulmonary Response to Exercise

While pulmonary pressures (PASP, PADP and mPAP) are expected to increase during exercise (26) and to follow the described trend, their degree of elevation is highly variable across the athletic population. Quite often, pressures rise above the accepted “normal” limits of an mPAP of 30mmHg, and PASP of 40mmHg (27-32). Meanwhile, others studies have reported a very modest rise in pressures, reaching only 19mmHg (33). Higher pressures at rest and during exercise tend to be a common finding in the older athletic and non-athletic population (96), however elevated PASP at rest and during exercise have been reported in younger ETA as well (25, 27, 29). Such variability in exercise-induced pressure generation may in part be attributed to inherent PVR responses that differ from athlete to athlete. As discussed briefly above, during exercise, PVR only reduces by an average of 30% (18, 46), and this makes the pulmonary pressure response less predictable in ETA (PVR is inversely correlated to pressure). While CO and RVEF are known to be greater in ETA compared to non-athletic healthy controls, their pulmonary vascular function may not necessarily accommodate these greater volumes in a predictable, uniform manner.

A 2010 study, La Gerche et al explored the variable pulmonary response to exercise in 40 endurance athletes and 15 sedentary healthy controls. Each performed a maximal exercise test while receiving bolus injections of agitated contrast fluid, which could then be tracked and quantified with simultaneous echo Doppler imaging. Pulmonary transit of the agitated contrast (PTAC) was measured before and during the exercise protocol, and was used as a surrogate measure of pulmonary vascular compliance; the more contrast accumulated in the LV after a set number of cardiac cycles, the greater the blood flow through the pulmonary circulation (95). The bubbles in the agitated fluid were not expected to pass through pulmonary capillaries at rest, however during exercise when a reduction in resistance typically occurs, bubbles would then be able to enter the vasculature. PTAC was therefore detected in 52 of the 55 subjects at peak exercise. Both athletes and non-athletes demonstrated variable PTAC scores at peak exercise, with higher values correlating with lower PVR and PASP generation. As expected, subjects with
a lower PTAC value also generated much steeper pressure-volume slopes. Importantly, echo-derived PASP measures across all subjects ranged from 33 to over 80 mmHg, which reflects a pulmonary heterogeneity in the athletes studied (95).

Such a range in pulmonary pressures has been previously described (34), and point to a gap in our understanding regarding a “normal” pulmonary response to exercise (27-32, 34, 35). It is quite possible that the variability exists because of technical differences in exercise protocols. Endurance-related cardiac function and pulmonary hemodynamics are best assessed in an exercise protocol with graded increases in workloads, however not every lab uses such a study design, nor common endpoints (e.g. target heart rate or duration of exercise). Additionally, measuring methodologies are not uniform across exercise studies. Each of these factors may influence the data generated.

2.9 Exercise-Induced Pulmonary Arterial Hypertension (PAH)

Despite the vast range in measurements, a “cut off” has been identified in the untrained healthy individuals, beyond which a diagnosis of exercise-induced pulmonary arterial hypertension (PAH) may be made. In an invasive study by Tolle et al (26), 109 subjects participated in a cycling protocol as part of a pulmonary hemodynamic assessment to characterize the phenotype of this condition. An individual with this response would typically have a normal mPAP at rest, but would generate an “exaggerated” pressure elevation of a mPAP > 30mmHg and a PASP > 40 mmHg during exercise (26). Tolle characterized 78 subjects as having exercise-induced PAH, with an increase from resting mPAP of 18.6 ± 3.2, to 36.6 ± 5.7 mmHg during exercise at an average workload of 90.3 ± 41.7 W. These values were contrasted against a mPAP of 48.4 ± 11.1 in the clinically diagnosed PAH cohort. Importantly, PVR decreased in all groups in response to exercise, however the control subjects achieved a marked decrease of approximately 60% (1.9±0.8 Wood units to 0.8±0.25 Wood units), while those with PAH or exercise-induced PAH decreased by only 16% and 27%, respectively.

Tolle et al concluded that exercise-induced PAH should be assessed as an important, early phase in the progression of PAH(26). While exercise-induced PAH has been previously used to describe a phenotype in the nonathletic population, its description has been applied to the subset
of ETA who generate “exaggerated” responses to exercise. Recently though, the accepted cut-off of “normal” (mPAP < 30 mmHg and PASP < 40 mmHg during exercise) has been questioned because of several reports describing pressures significantly exceeding those values during exercise (34). In truth, our understanding of the ‘normal pulmonary response to exercise’ in ETA is very limited.

2.10 Pulmonary Hemodynamics and the Right Heart

Even in the presence of significant and uniform right-sided enlargement across the endurance-trained population, a wide range in pressure response is clearly evident. How the “above-normal” or “exaggerated” increases in pulmonary pressures affect right-sided cardiac function however remains largely unknown, yet suggestions of such responses range from being benign to that of a pro-arrhythmic or fibrotic substrate. Studying the right heart in the context of pulmonary hemodynamic heterogeneity (and possibly “exercise-induced pulmonary hypertension) may help bridge the gap between exercise-induced adaptations and RV mal-adaptations. We may then find that athletes who develop RV or RA pathologies may also be among those athletes who demonstrate ‘exaggerated’ pressure responses to exercise.

Davila-Roman et al (83) studied RV dysfunctional response in 14 runners participating in a 163-km high-altitude marathon. 5 out of the 14 had developed dramatic RV dilation, paradoxical septal motion, and a marked reduction in RV Fractional Area Change (FAC, a measure of systolic performance) immediately after the race, as imaged with echo. These same five runners experienced wheezing during the race, and demonstrated an “exaggerated” PASP of 55 ± 10 mmHg immediately post-race. These values represented an almost 100% increase in PASP from their resting value of 28 ± 2 mmHg, and were described as having a phenotype of “reversible pulmonary hypertension” (83), or what others would call ‘exercise-induced PAH’.

Returning to the 2008 La Gerche study on PTAC described previously (95), an important finding showed that all measures of RV contractile function during exercise were significantly reduced in those with lower PTAC scores, including RV myocardial systolic velocity (High PTAC 21.5 cm/s vs. Low PTAC 18.9 cm/s; p=0.009) and RV iso-volemic acceleration (High PTAC 6.9 cm/s² vs. Low PTAC 5.1 cm/s²; p=0.001). Finally, at peak exercise, BNP levels were increased in both groups, however more substantially in those with lower PTAC values (p=0.003) (95).
Previously, BNP has been associated with acute RV dysfunction in athletes and PAH patients at rest and during exercise (14, 15, 103, 104).

2.11 Pulmonary Arterial Hypertension (PAH) and the Right Heart

In order to determine whether RV dysfunction in a subset of ETA occurs as result of their higher pulmonary pressures during exercise, or visa-versa, long-term prospective studies must be conducted in a large heterogeneous athletic population. In the meantime, we may draw minor inferences or parallels from the PAH literature.

Much like the adverse RV functional adaptations reported in few ETA, RV dysfunction has been well characterized in patients with PAH. The disease commonly results in a reduction of resting and stressed RV global and FW strain/strain rate (105), tricuspid annular displacement (106), and a diminished exercise tolerance due to an inability of the RV contractile reserve to match a stable and required CO (18). RA sizes in long-term PAH patients are also known to be markedly dilated, or “remodeled” in response to a pressure overload (107-110). The relationship between the RA, RV and pulmonary hemodynamics is so important that right-sided function is commonly considered one of the more important determinants of PAH prognosis and patient survival (106, 108, 110-112). It is therefore important to understand how the right heart adapts to abnormal pressure elevations. Acutely, when the RV encounters sudden increases in afterload (for example, mPAP >35 mmHg), its walls cannot respond adequately to dramatic pressure elevations. It therefore expends more energy, which can result in transient reduction in function, as evidenced by serological markers of cardiac remodeling, often considered damage (112). Such responses wouldn’t be termed “adaptations”, as they are typically reversible upon reduction of RV afterload.

During sustained, or chronic, increases in afterload however, the RV is expected to adapt, first by increasing its EDV to improve CO by Frank Starling forces. Modest myocardial hypertrophy and wall thickening typically follow as an adaptive mechanism to reduce wall stress induced by a chronically elevated afterload. In the pathological state, PAH will eventually cause the hypertrophied RV to stiffen and enter into a pro-fibrotic environment, thereby compromising RV filling and SV (111).
At this stage of PAH pathology, the RV begins to depend almost entirely on right atrial function to maintain CO. Ironically, because of this dependency, RA systolic function is enhanced – with greater RA volume and ejection force (109, 110, 113). Much like what occurs in the RV however, the RA of the untreated PAH patient will eventually stiffen and lose its contractile function over time. Sustained pressure overload can therefore result in end-stage PAH, with heart failure, reduced CO and low organ perfusion (112).

When discussing cardiopulmonary dynamics, it would be premature and irresponsible to equate right-sided pathological adaptations in PAH with what is seen in those ETA with high pressure generation during exercise. PAH remodeling is pressure-induced and occurs at rest regardless of exercise history, whereas the morphological adaptations of the athlete’s heart are a product of cumulative bouts of intensive volume loading induced transiently by exercise. The RV’s thin walled crescent-shaped structure allows it to accommodate such boosts in volume, but not in pressure (112). Dilated RVs and RAs in ETA are therefore considered a healthy stretch-induced adaptation to best accommodate the volume loading of vigorous endurance exercise. However, the RV “mal-adaptations” found in a subset of ETA described previously may be a product of continued exposure to both high-volume, and grossly high-pressure states of exercise. There may therefore be few right-sided cardiac parallels between PAH patients and those athletes who generate a higher-than-‘normal’ range of pulmonary pressures during exercise.

2.12 Assessment of Cardiac Function

Cardiac MRI is the gold standard in measuring cavity dimensions and volumes, however it is only used in a few research studies due to its high expense and low accessibility. 2D Echocardiography – while heavily reliant on sonographer-specific bias and technique (81) – has been commonly used in clinical and research settings due to its lower cost, and high accessibility.

The right side of the heart is especially difficult to study with echo because of its structure. Recently however, the American Society of Echocardiography published new guidelines and standards for the assessment of the right heart (81). The assessment of the right heart in this study adhered to these guidelines.
2.12a Dimensions

Right atrial and ventricular dimensions are best measured in the apical four-chamber view (81). RV maximum (RV max) area is reached at end-diastole, prior to the closing of the tricuspid leaflets. RA maximum (RA max) area is reached at ventricular end-systole, and is measured on echo images just prior to tricuspid opening (initiation of passive filling). A RA max area of > 18 cm² is indicative of RA enlargement. RA approximations of volumes can be done with single plane estimates and a modified Simpson’s method of discs on a four-chamber view(114). Such an approach assumes a spherical structure with a diameter equal to the longitudinal end-ventricular-systolic (or, atrial end-diasole) length parallel to the septum.

2.12b Doppler Imaging

Echo Doppler measures of flow provide reliable and reproducible values of mitral and tricuspid inflow, and of SV. Using pulsed-wave Doppler techniques, a sample volume is selected and captured at the LV outflow track (LVOT) in the apical view, (sometimes called the “5-chamber view” which includes the LVOT as its own “chamber”). The blood flow across the LVOT in systole is calculated by manual tracing called the “Velocity Time Integral” (VTI) which tracks blood-flow of the sample volume (cm/sec) over time (sec). VTI is therefore measured in cm, and when multiplied by the LVOT area (cm²) a volumetric value in cm³ is produced (equivalent to 1 mL). LVOT area can be measured by manually tracing the LVOT diameter in the parasternal long axis view (a 3-chambered view), following the equation: area = ¼(πd²). Because the VTI is generated by one cardiac cycle, the volume calculated is equivalent to SV (mL/beat). Finally, SV can be multiplied by HR (beat/min) to produce a CO (mL/min).

2.12c Tissue Doppler Imaging (TDI)

Whereas Doppler measures blood flow, Tissue Doppler imaging (TDI) measures the velocities of a selected myocardial wall segment in the apical 4-chamber view, in cm/second. The measurement of mitral or tricuspid annular movement on the free walls of the ventricles may provide useful information on ventricular longitudinal systolic and diastolic performance.
Much like Doppler imaging, a sample region is selected within a segment of the ventricular myocardium that will be analyzed offsite. TDI has become a conventional form of assessing RV longitudinal function, where the sample is usually taken at the RV FW tricuspid annulus (23, 81). In the apical 4-chamber view, the echo probe is situated at the apex of the heart; therefore, when contractile movement pulls the annular plane towards the apex, a “positive” (above baseline) displacement will be measured as the myocardium moves towards the probe. The opposite is true during diastole, when the ventricle relaxes and expands, thus pushing the annular plane away from the apex, and generating a “negative” (below baseline) inflection as it moves away from the probe. Tricuspid tissue and flow velocities tend to be lower than mitral values. This is largely because of the increased pressure gradient in the left heart compared to the right (115). As well, septal and FW annular motion will also differ in velocities, with free wall motion typically greater (116).

In a healthy heart, one cardiac cycle will generate 3 waveforms: one positive wave during systole (s’), and the two negative waves during the early and late phases of diastole (117). Systolic waveforms will follow the QRS complex of the corresponding ECG. A RV s’ velocity of less than 10 cm/sec is commonly regarded as systolic dysfunction (81). Early diastole (e’) represents passive filling the ventricle, also characterized as the atrial conduit phasic function. Late diastole (a’) represents the active filling of the ventricle, which occurs during atrial contraction. This corresponds with the p wave of an ECG (64).

2.12d Speckle Tracking Echocardiography (STE)

Two-dimensional speckle tracking echocardiography (STE) has allowed for analysis of the strain and strain rate of selected wall segments. STE-derived strain is a measure of the relative change in length of a wall segment, where the movement of acoustic “speckles” in a selected region of interest is tracked throughout a cardiac cycle. It is expressed as a percent change from the original starting point, usually at end-diastole (onset of the QRS) (118). During contraction, the wall segment shortens and generates a peak negative value at end-systole (%), and during relaxation a positive (or, less negative, %) value represents expansion.
By convention, the more negative the value during systole, the more forceful the contraction. Strain rate – as the name suggests – is a measure of the rate of change in the myocardial speckles being tracked (%/sec), and is used as a representation of the rapidity of myocardial movement. Like TDI, peak strain rates are captured during systole ($s'$) and during early ($e'$) and late ($a'$) diastole.

In strain and strain rate analysis, echo software identifies 6 wall segments within the chamber being measured – 3 on the FW (basal, mid, and apical segments), and 3 on the septal wall (basal, mid and apical). An average of these 6 is often used to represent a “global” strain and strain rate. While these measures have been primarily designed for the LV, the technology has recently been applied to study RV longitudinal systolic function (23, 81, 85, 86, 119).

Because the septal wall is likely more influenced by the LV, RV free wall strain measures (basal, mid and apical) are often looked at in isolation and found to be a more accurate description of RV function (81, 87, 120). Strain and strain rate has also been measured in both left and right atria (38, 76). There is however a lack of a “normal” value for RV and RA strain, which is a common limitation in functional analysis (81).

2.12e Other Echocardiographic measures of Right Heart function

Other commonly used echo-derived measures of right-sided cardiac function can be made in the 2D apical 4-chamber view. These include RV and RA Fractional Area Change (FAC), and Tricuspid Annular Plane Systolic Excursion (TAPSE). Both are common primary outcome measures in exercise and cardiomyopathy studies (24, 81, 89, 106, 121, 122).

- Fractional Area Change (FAC)

RA and RV FAC is used as an accurate determination of systolic efficacy. RV FAC can be calculated with RV maximal (end diastolic) and minimal (end systolic) areas by the following equation:

\[
\text{Equation 5: } \text{RV FAC} = \frac{\text{RVmax} - \text{RVmin}}{\text{RVmax}} \times 100
\]

The same equation is used to calculate RA FAC, using RA chamber areas.
Diminished FAC has been used as a predictor of cardiac outcomes in heart failure and pulmonary diseases (81, 123), with a RV FAC <35% indicating systolic dysfunction.

- *Tricuspid Annular Plane Systolic Excursion (TAPSE)*

From the standard apical 4 chamber view, TAPSE can be measured as the longitudinal displacement of the tricuspid annulus. The distance traveled towards the apex during systole is captured by the echo probe, and can then be measured in centimeters offline using the “motion mode” (MMode) cursor on echo software; a sample wall region is selected and tracked at the tricuspid annulus on the free wall. This will generate a cross-sectional tracing of the selected wall segment, where tissue displacement during systole can be measured. A TAPSE < 16 mm will indicate RV systolic dysfunction (81). As well, in PAH patients, a TAPSE < 18 mm has been associated with an increased risk of mortality (106).

### 2.13 Clinical Relevance

The relationships between right heart remodeling, pulmonary hemodynamics, and the development of adverse cardiac outcomes such as fibrosis and AF are complex and remain poorly understood in a heterogeneous athletic population. With a lack of long-term prospective studies, we are also unable to make a “cause and effect” determination of whether an athlete can exercise “too much” and develop a cardio-toxic effect, or if in a subset of athletes, endurance exercise simply exacerbates an existing propensity to develop these effects. Over a 20 year period from the 1990s into the 2010s, there has been an approximate 300% increase in non-elite, middle-aged endurance exercise participants (124) thus increasing the number of individuals who may require treatment for exercise-induced cardiovascular issues and potentially harmful remodeling. Emerging evidence is suggestive of increased risk of arrhythmias (10-13). Consequently, further research is warranted to fully understand the cardiac responses to exercise in this cohort, particularly given the potential impact of cardiac remodeling and the pulmonary hemodynamic response to acute and chronic exercise.
Chapter 3: Methods

3.1 Subjects

3.1a Endurance Trained Athletes (ETA):

Highly trained endurance male athletes aged 41 – 65 were recruited by advertisements at athletic clubs in the greater Toronto area (See Appendix C). Participants were runners, cyclists or triathletes with a history of ≥ 10 years vigorous year-round training including at least 6hrs (or 35 km for runners) a week. The Lifetime Total Physical Activity Questionnaire was used to confirm exercise history (125) (See Appendix E). Participation in one or more marathons or analogous road races for cyclists (>100 km) a year was also required. Subjects were excluded from the study if they were smokers, diabetic, or had a BMI of < 20kg/m² or > 28kg/m². Athletes with a history of cardiovascular or pulmonary disease, current viral or chronic illness, or prior exposure to chemotherapy or cardio-active drugs were also excluded. The study protocol was reviewed and approved by the Research Ethics Board at Mount Sinai Hospital and the University of Toronto, and written informed consent was obtained from each subject (See Appendix B).

3.1b Controls

Untrained controls were recruited with newspaper and Internet advertisements. The same exclusion criteria as ETA recruits were applied here. Individuals were considered untrained if they engaged in organized physical activity or exercise lasting 20 minutes or less, two or fewer days per week.

3.2 Determination of Maximal Aerobic Power

Prior to the study, peak oxygen consumption (VO₂max) was assessed in the ETA subjects using indirect calorimetry using a metabolic cart (Moxus Modular System, AEI Technonologies Inc., Pittsburgh, PA) during a standard graded exercise test performed on a cycle ergometer (Lode Excalibur, Groningen-Holland Medical Technology). Heart rate was monitored using a Polar Heart Rate Monitor (810i, Polar Inc) throughout the exercise test. Following a 3 minute warm up at 25 Watts (W), workrate was increased every 2 minutes by 50W until 200W was reached (8
minutes), followed by workrate increments every minute by 25W. To determine VO$_2$max, breath-by-breath expired gases were collected and averaged over 20 seconds. VO$_2$max was confirmed when a plateau of oxygen uptake was reached despite an increase in workrate; additional criteria confirmatory measures included a respiratory exchange ratio of >1.15 (The ratio between the CO$_2$ exhaled and O$_2$ consumed in one breath), and achievement of the predicted maximum heart rate [208–(0.7 x age)].

3.3 Cardiac and Hemodynamic Measures

A comprehensive exercise protocol took place at the Cardiac Catheterization Research Lab at Mount Sinai Hospital on a separate day after the VO$_2$max test. Prior to the study, subjects were asked to abstain from training for 48 hours, and from caffeine for 12. At this time, a resting echocardiogram was performed, followed by right heart catheterization and exercise with concurrent hemodynamic monitoring and echocardiography at 3 submaximal workrates targeting specific heart rates. An initial resting 2-dimensional Echocardiography was performed in the supine position. All Echocardiographic images were stored for subsequent off-line analysis.

Right heart catheterization under ultrasound guidance ((Site-Rite 5 Ultrasound System; Bard Access Systems, Salt Lake City, UT) was performed under sterile conditions by a trained cardiologist in a research catheterization suite. In the supine position, the subject’s left arm was sterilized from the axilla to the antecubital fossa and then sterilized for cannulation. Following ultrasonic interrogation, a suitable basilic or cephalic veins was identified, and the least challenging (typically the larger) of the two was chosen to be cannulated with a 21 gauge cannula. After advancement into the lumen of the vein, a 7-Fr venous sheath was inserted, followed by the balloon-tipped, fluid-filled Swan Ganz catheter (CCombo Volumetrics Pulmonary Artery Catheter, Edwards Lifesciences Inc., Irvine, CA) guided into the thorax with fluoroscopy. The balloon was inflated upon the tip’s arrival at the meeting point of the vena cava and right atrium. Inflation of the balloon allowed for the catheter to be floated along the blood flow current towards the pulmonary artery. Pressure waveforms from the pulmonary artery and right atrium were recorded using a Mac-Lab Hemodynamic Recording System (GE Healthcare). Heart rate was also monitored throughout the protocol with a 3 Lead electrocardiogram, and blood pressure with an automated cuff (Tango+, SunTech Medical). After the position of the
catheter was confirmed with fluoroscopy, the subject was carefully transferred on to a purpose-
built cycle ergometer (Ergoselect 1200E, Ergoline GmbH, Germany), with the transducer
positioned at heart level for all measurements. They were adjusted to lie in a semi-upright angled
position with a slight lateral tilt to the left for optional Echocardiographic imaging.

3.4 Exercise Protocol

A sub-maximal exercise protocol was designed to measure various cardiac and hemodynamic
responses to increasing workload and heart rate. Both cohorts (ETA ad controls) were required
to exercise at increasing levels of intensities at target heart rates, with athletes cycling at 100, 130
and then 150 beats per minute (bpm), and untrained controls cycling at 100 and 120 bpm.

After a two minute warm up, workload was manipulated to allow subjects to achieve their target
heart rates. Workloads were increased over a 2-minute period at the start of each stage, after
which a steady state had been reached (maintenance of the target heart rate at the desired
workload), and echo images could be acquired. Hemodynamic measures were taken at the 2 and
7 minute marks of each exercise stage, and we averaged to produce 1 measure from every
variable at each target heart rate.

Untrained controls would exercise at two levels of intensity, while the athletic cohort exercised at
one additional workrate targeting 150 bpm. A 3-minute recovery period at 75W was introduced
in athlete’s protocol before the final stage of exercise at 150bpm, in order to prevent muscle
fatigue. Exercise would be terminated if the subject experienced any chest pain, shortness of
breath, or a drop in systolic blood pressure below the level achieved at the prior workrate.

3.5 Echocardiographic Structural and Functional Measures

Both resting and exercise 2D Echo images were obtained by the same experienced sonographer,
using a commercially available system (GE Vivid 7 Dimension & Imaging System; GE
healthcare, Canada). The images were acquired using a frame rate of 60 – 80 frames per second
to optimize images quality in both the parasternal and apical windows. Off-line post-processing
analysis was performed by the investigator on a proprietary workstation (EchoPAC, Version 11,
GE Healthcare). The following measures were made in accordance with American Society of Echocardiography Guidelines (81, 126) averaged over three cardiac cycles.

3.5a Assessment of Cardiac Structure

RA, RV and LA areas were measured in the apical 4 chamber view. Areas were measured by manual tracing that began at the septal annulus (tricuspid annulus for the right heart chambers, mitral annulus for the left heart chamber), along the intra-atrial/ventricular septum, continuing along the walls of the each chamber until the lateral/free wall annulus was reached. Minimum and maximum areas were measured, with the maximal long axis diameter measured parallel to the septum. Maximal atrial area was achieved at ventricular end-systole, just before the mitral and tricuspid leaflets opened. The same frame was then used to measure RV minimal area. Minimal atrial area was measured at ventricular end-diastole when both atria were emptied and valves begin closure. The same frame was then used to measure RV maximal area.

Chamber areas and RA volumes were measured in both ETA and untrained controls. Chambers were measured in ETA at rest and in all exercise stages, whereas in the untrained population they were only taken at rest.

3.5b Assessment of Cardiac Function

With the data collected above, RA and RV Fractional Area Change (FAC) as defined by \([(\text{Max Area} - \text{Min Area})/ \text{Max Area}]\) could be measured as one determination of contractile function. RA volumes at end-diastole and end-systole were calculated using a single plane modified Simpson method.

Tricuspid annular plane systolic excursion (TAPSE) was assessed using M-Mode, where the total displacement of the tricuspid annulus on the RV free wall was measured in cm on a cross sectional tracing of tricuspid annular movement.

TAPSE was measured throughout all stages in both ETA and untrained controls.
Speckle tracking echocardiography (STE) at rest and during exercise was analyzed to quantify both right atrial and ventricular strain and strain rate measures in the apical 4-chamber view. Much like atrial and ventricular area mapping, speckles on the endocardial border were traced from the tricuspid annulus on the inter-atrial/ventricular septum, towards the corresponding annulus on the free wall. Six wall segments were identified: basal, mid and apical septal wall, and basal, mid and apical lateral wall. They were then averaged to produce a global strain and strain rate. Strain and strain rate measures were taken at rest in both ETA and untrained subjects.

3.5c Functional Measures using Doppler Analysis

Continuous-waved Doppler interrogation of LV outflow tract (LVOT) velocity time integral (VTI) was multiplied by the LVOT area (acquired in the parasternal long axis view) to calculate LV stroke volume. Cardiac Output was then calculated by multiplying stroke volume by heart rate. SV and CO were measured in both ETA and controls at rest and at every stage of exercise.

Tissue Doppler imaging (TDI) of the RV free wall was also assessed from the apical 4-chamber view. A tracer window was placed at the tricuspid annulus where early (e’) and late (a’) diastolic and systolic (s’) tissue velocities (cm/sec) were measured. TDI was assessed in both athletes and controls at rest and at all stages of exercise.

3.6 Invasive Hemodynamic Measurements Using Right Heart Catheter

Right atrial pressure (RAP), PASP and PADP were measured continuously throughout the entire exercise protocol. PCWP was recorded at rest and at each exercise stage when steady-state was reached. Waveforms were recorded by Mac-Lab Hemodynamic Recording System (GE Healthcare) along with heart rate tracings.

3.7 Group Stratification: Characterization of “High” and “Low” Pressure Generators

The Peak PASPs reached throughout the entire protocol were identified in each athlete, and mean, median, and standard deviations were evaluated to determine whether two distinct groups
could be identified. As well, pressure-flow relationships and peak PASPs normalized to resting values were also considered when dichotomizing “high” and “low” pressure generators.

3.8 Statistics

Statistical regression and correlation analyses were performed using Prism software version 6.0 software for Mac OS X. Analysis for each dependent variable for within-subject variables at each stage was done using one-way repeated measures Analysis of Variance (ANOVA). Student unpaired T-Tests were performed first between athletes and controls, and then between subgroups in the athletic cohort. A p value of less than 0.05 was considered significant. All data presented have been reported as mean ± standard deviation (SD) unless otherwise stated.
Chapter 4: Results

4.1 Subjects

21 athletes were recruited and completed the exercise protocol with accompanying echocardiograms at rest and during all stages of exercise. A total of 16 ETA completed the catheterization portion of the protocol and had their pressures recorded with a right heart and pulmonary catheter. These data were used for subgroup analysis. The remaining 5 athletes continued on with the exercise protocol without their pulmonary pressures recorded. Their echo data contributed to ETA characterization.

13 untrained controls were recruited and completed the exercise protocol, with 7 successful catheterizations. The athlete and control baseline characterizations and cardiac morphology and function are presented in Tables 1 and 2. Athletes and controls did not differ in age, height, weight or BSA. As expected, ETA had significantly lower resting heart rates and BMI values. Resting cardiac structure reflected what is commonly shown in the literature, with ETA demonstrating characteristic “athlete’s heart” remodeling. Compared to controls, all resting maximal cardiac dimensions were significantly larger in ETA. Functional systolic Echo measures of TAPSE and Tissue Doppler however were not different between athletes and controls, as demonstrated in Table 2.

Table 1. Athlete and Control Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Athlete</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>21</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>54 ± 6.1</td>
<td>57 ± 8.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>178 ± 3.6</td>
<td>174 ± 7.1</td>
<td>0.15</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76 ± 8.5</td>
<td>77 ± 14</td>
<td>0.72</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24 ± 2.3</td>
<td>25 ± 3.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.9 ± 0.12</td>
<td>1.9 ± 0.21</td>
<td>0.99</td>
</tr>
</tbody>
</table>

BMI, Body Mass Index; BSA, Body Surface Area
Table 2. Athlete and Control Resting Cardiac Structure and Function

<table>
<thead>
<tr>
<th>Resting Structure and Function</th>
<th>Athlete</th>
<th>Control</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA Max (cm²)</td>
<td>26 ± 3.9</td>
<td>20 ± 3.10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RA Max Index (cm²/m²)</td>
<td>13 ± 2.3</td>
<td>10.4 ± 1.8</td>
<td>0.01</td>
</tr>
<tr>
<td>RA FAC (%)</td>
<td>40 ± 8</td>
<td>45 ± 7</td>
<td>0.42</td>
</tr>
<tr>
<td>RV Max (cm²)</td>
<td>30 ± 3.6</td>
<td>24 ± 3.9</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>RV Max Index (cm²/m²)</td>
<td>15.4 ± 1.8</td>
<td>12.4 ± 1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV FAC (%)</td>
<td>39 ± 8</td>
<td>33 ± 8</td>
<td>0.44</td>
</tr>
<tr>
<td>LA Max (cm²)</td>
<td>19.2 ± 3.7</td>
<td>14.3 ± 2.2</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>LA Max Index (cm²/m²)</td>
<td>1 ± 2.1</td>
<td>7.6 ± 1.0</td>
<td>0.007</td>
</tr>
<tr>
<td>LA FAC (%)</td>
<td>48 ± 9</td>
<td>39 ± 1</td>
<td>0.07</td>
</tr>
<tr>
<td>Heart Rate (beat/sec)</td>
<td>50 ± 5.6</td>
<td>65 ± 11</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>VO₂Max (ml/kg/min)</td>
<td>46 ± 7.1</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>3.92 ± 0.61</td>
<td>3.8 ± 0.1</td>
<td>0.7</td>
</tr>
<tr>
<td>TAPSE (cm)</td>
<td>2.3 ± 0.4</td>
<td>2.3 ± 0.5</td>
<td>0.1</td>
</tr>
<tr>
<td>TD E’ (cm/sec)</td>
<td>17 ± 4.6</td>
<td>17 ± 3</td>
<td>0.9</td>
</tr>
<tr>
<td>TD A’ (cm/sec)</td>
<td>18 ± 4.4</td>
<td>19 ± 5.6</td>
<td>0.8</td>
</tr>
<tr>
<td>TD S’ (cm/sec)</td>
<td>16 ± 2.1</td>
<td>16 ± 1.7</td>
<td>0.6</td>
</tr>
</tbody>
</table>

RA, Right Atrial; RA Max represents the largest area of the RA as depicted on an echocardiogram, found during ventricular end-systole. RA FAC, right atrial fractional area change; RV, right ventricle; RV Max represents the largest area of the RV as depicted on an echocardiogram, found during ventricular end-diastole. RV FAC, right ventricular fractional area change. LA, left atrial, LA Max represents the largest area of the LA as depicted on an echocardiogram, measured during on the same frame as RA Max. CO, cardiac output. TAPSE, tricuspid annular plane systolic excursion. TD, tissue Doppler measures of the tricuspid annulus on the RV free (medial) wall, opposite to the intraventricular septum. E’, early diastolic annular velocity; A’ late diastolic annular velocity; S’ systolic annular velocity.
4.2 Pulmonary Pressure in Athletes and Controls

Resting PASP were not significantly different at rest between ETA and untrained controls. With a p value of 0.07, ETA showed only slightly larger PASP (25 ±4.6 mmHg in ETA vs. 21 ± 4.1 mmHg in controls). Because only PASP was recorded in controls, PVR could not be calculated for untrained subjects. There were no significant differences between athletes and controls in their PASPs during exercise either (light exercise, p=0.6; moderate exercise, p=0.4). These data are shown in Figure 3. The average peak PASP reached in ETA was 49 ± 13 mmHg, and 42 ± 6.9 mmHg in controls, with no significant difference between these values (p=0.3). There was a wide range in PASP demonstrated in ETA at the various stages of exercise, however the lack of such a range in untrained controls may be attributed to a smaller sample size.

![Variability in PASP](image)

**Figure 3.** Endurance trained athletes’ and untrained controls’ pulmonary artery systolic pressures (PASP) at rest and during exercise.

Light exercise was established at a heart rate of 100 bpm for both ETA and untrained controls. Moderate exercise was established at 130 bpm in ETA, and at 120 bpm in UC.

4.3 Athlete Heterogeneity in Pulmonary Hemodynamics at Rest and Exercise

4.3a Pressure Flow Relationships

All ETA athletes experienced a uniform rise in CO with little variability. Grouping all the athletes together, the pressure-flow relationship (mPAP/CO slope) fell within the expected
window of $1.2\pm0.5$ mmHg increase for every 1 L of CO. (Similarly, the PASP slope is expectedly higher, with a $1.5\pm0.6$ mmHg increase for every 1 L of CO). However, despite a ‘normal’ average, an expected range of slopes existed with the highly variable pressure generations. (mPAP/CO range: $0.2 – 2.1$; PASP/CO range: $0.3-2.8$) (Figure 4).

![Figure 4](image)

**Figure 4.** Cardiac output and pressure flow relationships of Endurance Trained Athletes.

**4A** A uniformity of CO patterns during exercise is demonstrated. CO was measured using echo Doppler; the sample size was limited to 7 at 150 bpm due to the poor image quality and limited visibility of flow patterns. Resting mean CO = 3.9 \pm 0.6 L/min; 100 bpm mean CO = 10.4 \pm 1.9 L/min; 130 bpm mean CO = 10.4 \pm 1.9 L/min; 150 bpm mean CO = 11.5 \pm 3.5 L/min. *Significant difference from rest (p<0.0001); **significant difference from rest and 100 bpm (p<0.0001, p=0.007); ***significant difference from rest, 100 and 130 bpm (p<0.0001, p=0.006, p=0.03)

**4B** Pressure/Flow relationship between pulmonary artery systolic pressure and cardiac output. PASP coordinates were plotted against CO for each subject at rest, 100, 130 and 150 bpm. PASP/CO slope = $1.5 \pm 0.6$, with the linear equation $y = 1.5x + 26.2$. Slopes at 95% confidence intervals went from $0.3 – 2.8$. **4C** Pressure/Flow relationship between mean pulmonary artery pressure and cardiac output, plotted in the same manner as 2B. mPAP/CO slope = $1.2 \pm 0.5$, with the linear equation $y = 1.2x + 17.5$. Slopes at 95% confidence intervals went from $0.2 – 2.1$.
4.3b Pulmonary Pressures

With the exception of one athlete, ETA experienced an increase in pulmonary pressures during exercise. After an initial, significant rise in pressures, a plateau was generally established from 130 bpm onwards that remained above baseline for the remainder of the exercise protocol. **(Figure 5)**. Much like PASP values during exercise, a wide range in resting pulmonary pressures was recorded from PASPs of 18 – 39 mmHg (Table 3).

**Table 3. Resting Hemodynamic Measures in Endurance Trained Athletes**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>17 ± 4</td>
<td>11 – 26</td>
</tr>
<tr>
<td>PASP (mmHg)</td>
<td>26 ± 6</td>
<td>18 – 39</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>11 ± 3</td>
<td>5 – 18</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>7 ± 2</td>
<td>2 – 11</td>
</tr>
<tr>
<td>PVR (Woods Units)</td>
<td>1.6 ± 0.8</td>
<td>0.4 – 3</td>
</tr>
</tbody>
</table>

Pressure measures were obtained with right heart catheterization. mPAP, mean pulmonary artery pressure; PASP, pulmonary artery systolic pressures; PCWP, pulmonary capillary wedge pressure (surrogate measure of LA pressure); RAP, right atrial pressure. PVR, pulmonary vascular resistance, as calculated by the equation \([\text{mPAP} – \text{PCWP}] / \text{CO}\).
Figure 5. Right heart catheter recording of pulmonary pressures in endurance trained athletes at rest and during 3 stages of exercise

(Light, 100 bpm; moderate, 130 bpm; heavy, 150 bpm) 5A) Pulmonary artery systolic pressure recordings; Resting PASP, 26 ± 5.5 mmHg; 100 bpm PASP 54.7 ± 14.3 mmHg; 130 bpm 46.1 ± 12.0 mmHg; 150 bpm PASP 44.25 ± 14.3 mmHg. 5B) Mean pulmonary artery pressure recordings; Resting mPAP 17 ± 3.7 mmHg; 100 bpm mPAP 33.1 ± 9.6 mmHg; 130 bpm mPAP 32.1 ± 8.6 mmHg; 150 bpm mPAP 29.7 ± 10.4 mmHg.

Peak PASPs were not necessarily reached at peak exercise. We demonstrated not only heterogeneity in the pressures generated, but also in the time it took to reach peak pressures (Figure 6).

Figure 6. Peak PASPs were reached at different times throughout the exercise protocol.

7 athletes reached peak pulmonary artery systolic pressures (PASP) during light exercise (43.75%); 4 athletes reached peak pressures at moderate exercise (25%); 5 athletes reached peak pressures at heavy exercise (31.25%).
Because peak pressures were reached at different exercise stages, peak PASP instead of PASP at peak exercise were investigated further.

Next, we assessed the range in PASP deltas from rest to peak. This athletic cohort experienced an average pressure elevation of 88 ± 43.3 %, with a large range among them of 3.8 – 152.2% (median of 88%) (Figure 7). Importantly, the degree of elevation in PASP was not correlated with resting PASP, implying that an athlete’s propensity of generating high pressures during exercise cannot be predicted with resting hemodynamic values (p=0.37; r = 0.24). Such an observation falls within the accepted definition of (but does not confirm) exercise-induced PAH.

\[ \text{Delta PASP} = \left( \frac{\text{Peak PASP} - \text{Resting PASP}}{\text{Resting PASP}} \right) \times 100 \]

**Figure 7.** Delta PASPs from rest to peak

Deltas are expressed as percentages, calculated for each athlete as: [(Peak PASP – Resting PASP)/Resting PASP] x 100
Delta PASPs were however correlated with resting LA maximal area (p=0.03, r=0.55) and also with height (p=0.05, r=0.5). Correlation values are presented in the Appendix F and G.

4.3c Pulmonary Vascular Resistance and Compliance at Rest and Exercise

Finally, a trend in PVR was not detected among the entire cohort of ETA. This was especially surprising given the uniform increases in CO. As previously described, in the normal healthy individual, an increase in CO is typically met with an average decrease in PVR of 30%.

There were a number of athletes who demonstrated a surprisingly modest decrease in PVR throughout exercise, and, some even experienced significant increases in the PVR. During the first stage of exercise, with no significant variation among ETA in the rise of cardiac output (resting CO 3.9 ± 0.6 L/min, to 8.6 ± 1.9 L/min at 100 bpm) the relative change in PVR ranged from -65.4% from resting value, to 143.8%. Six ETA (37.5%) demonstrated an increase in PVR in response to the initial rise in CO and workload (Figure 8A and 8B). At least 3 of the ETA maintained a higher PVR than resting value throughout the entire exercise protocol (see Figure 8).
Figure 8. PVR (pulmonary vascular resistance) for each athlete.

PVR = (mPAP – PCWP)/CO. **8A)** PVR values for each athlete at rest and at 3 stages of exercise. (rest, 1.6 ± 0.8 WU; 100 bpm, 1.4 ± 1.0 WU; 130 bpm, 1.3 ± 0.7 WU; 150 bpm, 1.0 ± 0.5 WU). The expected decrease in PVR in response to an increased CO is not reflected in this data. **8B)** delta PVR presented in percentages, from rest to the first stage of exercise (100 bpm). Calculated as: [(PVR at 100 bpm – Resting PVR)/Resting PVR] x 100. **8C)** Changes in pulmonary compliance (C) were measured in percentages from and reflect the findings shown in 8B. C = [Stroke Volume/(PASP – PADP)]. Delta C = [(C at 100 bpm – resting C)/resting C] x 100.

4.4 High Pressure Generator and Low Pressure Generator Subgroup Analysis

Dichotomization of groups was determined by peak PASPs generated during exercise. Peak pressures, rather than pressures at peak exercise, were chosen because of the large variability in the exercise stage in which peak pressures were reached. As stated above, 43.75% of our cohort reached their highest pressures at an early and low exercise intensity – therefore, pressures taken
at peak exercise would not accurately reflect the true range of PASPs that can be generated during exercise in our cohort. The mean and median of the peak PASPs reached during exercise are both 49 mmHg. This point was chosen as the cut-off; those athletes with a Peak PASP of over 49 mmHg were labeled “high pressure generators” (HPG), and those with peak PASPs of or below 49 mmHg were labeled “low pressure generators” (LPG)

4.4a Hemodynamic Profiles

Two groups of 8 were analyzed to determine whether “high” and “low” pressure generators could be characterized by right heart systolic and diastolic differences at rest and during exercise. As seen in Figure 9, there was no substantial difference between HPG and LPG athletes regarding their resting PASP values (p=0.1)
Figure 9. Dichotomization of “high” and “low” pressure generators (HPG and LPG). HPG athletes had peak PASPs above 49 mmHg. LPG athletes had peak PASP below.

9A) The data plots represent means with error bars as standard deviations at rest, (HPG, 28.1 ± 5.7 mmHg vs. LPG, 42.1 ± 4.7 mmHg; p=0.1), 100 bpm (HPG, 56.6 ± 10.1 mmHg vs. LPG 35.2 ± 8.6; p=0.0004), 130 bpm (HPG, 55.7 ± 7.2 vs. LPG 36.9 ± 7.3; p=0.0001), and 150 bpm (HPG 54.5 ± 1 vs. 34.4 ± 10.1; p=0.001). The dotted line represents the accepted PASP threshold during exercise beyond which “exercise-induced PAH” is commonly diagnosed.

9B) The degree of elevation in PASP was expectedly significantly higher in HPG athletes, considering the little difference in resting PASP (p=0.01)

* Represents a significant difference between HPG and LPG at that exercise stage

† Represents an intra-group significant difference (p<0.0001) between that exercise stage to rest
Whole-group pressure-flow relationships are presented in Figures 4B and 4C, which show the high degree of variability among pressure-flow plots when looking at the cohort as a whole. Upon dichotomization of HPG and LPG athletes, the heterogeneity in their pulmonary responses to exercise becomes more defined – despite almost equivalent CO at each exercise stage (see Figure 10). The mPAP/CO relationship in HPG athletes fell at the higher-end of normal, with a slope of 2.0 (and 2.8 for PASP/CO slope). The LPG athletes on the other hand generated an average slope of 0.47, falling beyond the lowest cut-off of 0.5.

**Figure 10.** Cardiac output and pressure flow relationships of Endurance Trained Athletes

(HPG, peak PASP ≥ 49 mmHg; LPG, peak PASP < 49 mmHg). **10A** CO measures at rest and each stage of exercise. Data plots represent means, with error bars as standard deviations. No significant difference between HPG and LPG output at any stage: Rest, HPG 4.0 ± 0.6 L/min vs. LPG 3.7 ± 0.7 L/min (p=0.3); 100 bpm, HPG 8.4 ± 2.1 L/min vs. LPG 7.8 ± 1.7 L/min (p=0.6); 130 bpm, HPG 10.9 ± 1.9 L/min vs. LPG 9.7 ± 2.0 L/min (p=0.3); 150 bpm HPG, 10.0 ± 0.9 L/min vs. LPG 10.8 ± 2.7 L/min (p=0.6). **10B** PASP/CO relationship for both HPG (slope = 2.8 ± 0.9; Linear equation: y = 2.8x + 25) and LPG (slope = 0.3 ± 0.5; Linear equation: y = 0.3x + 28). **10C** mPAP/CO relationship for both HPG (slope = 2.0 ± 0.7; Linear equation: y = 2x + 16) and LPG (slope = 0.5 ± 0.4; Linear equation: y = 0.5x + 19).
There was no correlation between time-to-peak pressures and pressure status: at light exercise (100 bpm), 4 HPG and 3 LPG reached peak PASP; at moderate exercise, (130 bpm), 2 athletes in both groups reached peak PASP; and at heavy exercise (150 bpm), 2 HPG athletes and 3 LPG athletes reached peak PASP.

4.5 Baseline and Resting Characteristics of HPG and LPG

Table 4 presents baseline anthropomorphic measures between HPG and LPG athletes, with no differences between them.

Table 4. Baseline characteristics of HPG and LPG athletes

<table>
<thead>
<tr>
<th>Variable</th>
<th>HPG Mean ± SD</th>
<th>LPG Mean ± SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>56 ± 5.8</td>
<td>51 ± 5.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>176 ± 4.24</td>
<td>179 ± 1.5</td>
<td>0.08</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.3 ± 2.1</td>
<td>23.4 ± 2.5</td>
<td>0.45</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.92 ± 0.12</td>
<td>1.93 ± 0.12</td>
<td>0.87</td>
</tr>
<tr>
<td>VO2 max (mL/kg/min)</td>
<td>49.4 ± 9.7</td>
<td>44.0 ± 3.9</td>
<td>0.19</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>4.0 ± 0.6</td>
<td>3.7 ± 0.7</td>
<td>0.3</td>
</tr>
</tbody>
</table>

BMI, body mass index; BSA, body surface area; CO, cardiac output

There were no differences between HPG and LPG resting right heart structure (RA Max: HPG 25.8 ± 5.1 cm² vs. LPG 23.7 ± 4.2 cm²; p=0.38) (RV Max: HPG 30.6 ± 3.5 cm² vs. LPG 29 ± 3.5 cm²)(Table 6). Pulmonary pressure responses were independent of right heart size.

4.5a Functional Difference between HPG and LPG

Strain measures were taken only at rest, due to technological and visual limitations on echocardiograms taken during exercise. While most of these functional measures were similar between HPG and LPG athletes, resting RV systolic strain and early diastolic strain rate were significantly attenuated in the HPG group (p=0.036, p=0.028 respectively) (see Table 5). A reduction in systolic strain (a less negative value in % delta from pre-systolic length) can
represent contractile impairment in these athletes compared to LPG athletes. A reduction in RV early diastolic strain rate reflects a delayed or stiffened relaxation. Importantly, RV systolic strain was significantly correlated with the degree of PASP elevation from rest to peak (p = 0.04, r = 0.53) (see Figure 11).

Table 5. Strain and Strain rate measures for right atrium (RA) and Right Ventricle (RV) in high pressure generating (HPG) and low pressure generating (LPG) athletes

<table>
<thead>
<tr>
<th>Resting Strain Analysis</th>
<th>HPG</th>
<th>LPG</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strain: RA, RV Global and FW</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA Global Systolic Strain</td>
<td>-12.0 ± 5.3</td>
<td>-12.7 ± 4.0</td>
<td>0.78</td>
</tr>
<tr>
<td>RA Global Diastolic Strain</td>
<td>21.2 ± 5.6</td>
<td>20.5 ± 5.1</td>
<td>0.84</td>
</tr>
<tr>
<td>RA Free Wall Systolic Strain</td>
<td>-32.3 ± 13.6</td>
<td>-27.3 ± 5.4</td>
<td>0.42</td>
</tr>
<tr>
<td>RA Free Wall Diastolic Strain</td>
<td>49.7 ± 25.8</td>
<td>45.0 ± 18.3</td>
<td>0.71</td>
</tr>
<tr>
<td>RV Global Systolic Strain</td>
<td>-20.3 ± 4.9</td>
<td>-21.5 ± 1.5</td>
<td>0.55</td>
</tr>
<tr>
<td>RV Free Wall Systolic Strain</td>
<td>-22.8 ± 4.8</td>
<td>-30.3 ± 7.4</td>
<td>0.036</td>
</tr>
</tbody>
</table>

| Strain Rate: RA, RV Global and FW       |              |              |         |
| RA Global Strain Rate A’                | -1.6 ± 0.6   | -1.5 ± 0.5   | 0.77    |
| RA Global Strain Rate S’                | 1.4 ± 0.4    | 1.8 ± 0.3    | 0.08    |
| RA Global Strain Rate E’                | -1.1 ± 0.4   | -1.0 ± 0.7   | 0.85    |
| RA Free Wall Strain Rate A’             | -5.4 ± 2.5   | -4.2 ± 1.1   | 0.32    |
| RA Free Wall Strain Rate S’             | 4.5 ± 1.5    | 4.1 ± 0.7    | 0.52    |
| RA Free Wall Strain Rate E’             | -3.0 ± 0.9   | -3.1 ± 1.1   | 0.86    |
| RV Global Strain Rate S’                | -1.0 ± 0.2   | -1.0 ± 0.1   | 0.83    |
| RV Global Strain Rate E’                | 1.0 ± 0.3    | 1.1 ± 0.1    | 0.89    |
| RV Global Strain Rate A’                | 0.9 ± 0.2    | 0.8 ± 0.3    | 0.46    |
| RV Free Wall Strain Rate S’             | -1.7 ± 0.4   | -2.3 ± 0.8   | 0.1     |
| RV Free Wall Strain Rate E’             | 1.6 ± 0.5    | 2.3 ± 0.4    | 0.028   |
| RV Free Wall Strain Rate A’             | 1.5 ± 0.6    | 1.4 ± 0.5    | 0.79    |

HPG, high pressure generators; LPG, low pressure generators.
Global, average across 6 wall segments; FW, free wall, right (medial) wall opposite to the septum intra-atrial and intra-ventricular septum.
Strain measures are expressed as % (change in cm from original length), with negative measures implying contraction. Strain Rate measures are expressed as %/sec, representing the rapidity of length changes. “RA systolic strain” was measured during atrial contraction (pump function) and corresponded with a P wave on ECG, and ventricular diastole. RA diastolic strain measures were recorded during atrial filling (reservoir function), and corresponded with the QRS wave on ECG, and ventricular systole.
E’, early diastolic annular strain; A’ late diastolic annular strain; S’ systolic annular strain.
Figure 11. Resting right ventricular systolic strain vs. delta PASP from rest to Peak PASP.

Delta PASP is expressed as a percentage. A more positive RV strain reflects a weaker contraction, which is correlated with a greater elevation in PASP from rest. (p=0.04, r=0.53)
4.5b Hemodynamic Differences between High and Low Pressure Generators

As mentioned previously, the degree of elevation from rest to peak pressures were not correlated with resting pulmonary pressure values. It followed then that there were no significant differences between HPG and LPG athletes regarding their resting hemodynamics.

Figure 12. Resting hemodynamic measures for HPG and LPG athletes.

12A) Resting PASP, mPAP, PCWP and RAP in HPG and LPG athletes. No significant differences among them. PASP: HPG 28.1 ± 5.9 mmHg vs. LPG 24.1 ± 4.7 mmHg (p=0.14); mPAP: HPG 17.4 ± 4.0 mmHg vs. LPG 16 ± 3.6 mmHg (p=0.52); PCWP: HPG 12 ± 2.6 mmHg vs. LPG 9.7 ± 2.7 mmHg (p=0.11); RAP: HPG 7 ± 2.8 mmHg vs. LPG 6.9 ± 2.2 mmHg (p=0.92). 12B) Resting pulmonary vascular resistance values for HPG and LPG, with no significant difference between them. HPG 1.4 ± 0.8 WU vs. LPG 1.8 ± 0.7 WU (p=0.32).

4.6 High Pressure Generator and Low Pressure Generator characterizations during Exercise

Structural, functional and hemodynamic data for rest and exercise are listed in Table 6.
## Table 6: HPC and LPC athletes cardiopulmonary characteristics at rest and during exercise

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rest</th>
<th>100 bpm</th>
<th>150 bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPC</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

*Data unavailable or not provided.*
HPG and LPG athletes did not differ in their intensity levels at any stage of exercise (Figure 13)

![Workrate-vs-Exercise-Stage](image)

**Figure 13.** Workrates of HPG and LPG athletes at each exercise stage

Workrates were measured in power outputs (W) and were not significantly different between HPG and LPG athletes at any stage of exercise.

Right-sided structure was fairly uniform throughout exercise in and among HPG and LPG groups. RA areas seemed to significantly decrease from rest in LPG athletes (p=0.05), and RV areas decreased from rest in HPG athletes (p=0.04) – both during heavy exercise. However, these findings may have been skewed based on the limited visibility. HPG athletes also maintained a larger LA at rest and throughout exercise, reaching significance at 130 bpm (p=0.05). HPG and LPG athletes differed slightly but significantly with regards to their RA FAC, with the LPG exercising with greater RA contractile performance at 100 bpm (HPG 40 ± 8% vs. LPG 55 ± 13%; p=0.02). **(Figure 14)** RA FAC was the only available measure to be used as a surrogate for RA contractile performance. Further investigation is warranted on RA function during exercise in high-pressure generating athletes.
Figure 14. Right atrial fractional area change (FAC) in ‘high’ and ‘low pressure generator athletes at rest and during exercise.

FAC expressed as a fraction of RA diastolic area. FAC = [(RA maximum area — RA minimum area)/RA maximum area]. Multiply by 100 for percentage. ¶ represents a significant difference between HPG and LPG athletes at 100 bpm

HPG and LPG athletes showed similar TAPSE and TD outcomes at rest and throughout the exercise protocol, with the expected increases from rest at all stages of exercise. There were no significant differences between them regarding all TD measurements, TAPSE however was different between groups during exercise (at 130 bpm, HPG 2.5 ± 0.7 cm vs. LPG 2.4 ± 0.1 cm; p = 0.01).

4.6a Pulmonary and Systemic Pressures, and Pulmonary Vascular Resistance

All pulmonary pressures measured with the right heart catheter were significantly elevated in both groups compared to resting conditions. Despite uniform elevation, HPG athletes experienced a greater relative rise in pressures (Table 6).

Additionally, HPG and LPG athletes did not differ regarding their systolic blood pressures throughout any exercise stage (Figure 15)
Figure 15. Systemic blood pressure responses in HPG and LPG at rest and during exercise

15A) Systolic Blood Pressure measures in HPG and LPG athletes, with no significant differences between them at rest or at any stage of exercise; 15B) Mean arterial pressure measures in HPG and LPG athletes, with no significant differences between them at rest or at any stage of exercise.

HPG and LPG differed greatly however regarding their pulmonary vascular accommodation to the initial increase in workload and CO.

A healthy athlete is expected to lower his or her vascular resistance in response to increases in CO. LPG athletes respond this way, with a significant decrease in vascular resistance during the first stage of exercise by 34.6% from rest (LPG resting PVR 1.46 Woods Units vs LPG 100 bpm PVR 1.0 Woods Units; p=0.03). A decrease by 34.6% is within the expected average for a normal response to increases in CO (96). HPG athletes however respond in an unusual way, with an average increase in PVR of 43.6% (see Figure 16). The increase in PVR in the HPG group was not correlated with any anthropomorphic measures, and cannot be predicted by our echo-derived measures of resting cardiac characteristics.

Additionally, compliance calculations showed that HPG athletes experienced declining compliance throughout exercise, which further points to abnormal responses to increases in CO (p=0.04 in HPG between 130 bpm and rest; p=0.01 in HPG between 150 bpm and rest) (Table 6 and Figure 16 B).
Figure 16. Pulmonary vascular resistance (PVR) and pulmonary compliance trends throughout exercise in HPG and LPG.

16A) PVR measures in HPG and LPG athletes. 16B) Compliance measures in HPG and LPG athletes

¶ represents a significant difference (p<0.05) between HPG and LPG athletes within a specified exercise stage

* represents a significant difference (p<0.05) between rest and a specified exercise stage within a group
Chapter 5: Discussion, Limitations, Conclusions and Future Directions

To the best of our knowledge, this study is among the first to describe the heterogeneity of pulmonary pressure generation in endurance-trained athletes, and to characterize right heart function in the context of such heterogeneity. A wide range of PASPs was demonstrated despite almost equivalent CO and workload values among our cohort. We were therefore able to stratify athletes into 2 groups based on their peak PASPs generated during exercise. Those athletes who responded to increases in CO with higher pulmonary pressures also demonstrated impaired RV systolic performance at rest. Athletes with higher peak PASPs also responded to light exercise with increases in pulmonary vascular resistance, which is suggestive of inherent or genetic differences (compared to lower-pressure generators) that govern their response patterns. Furthermore, right-sided structural remodeling trends were uniform across all athletes regardless of their pulmonary features.

With the growing number of aging ETA over the past decade, the clinical significance of exercise-induced adverse cardiac remodeling has become more acute; for example, its potential contribution to the pathogenesis of AF has been previously discussed, with a is 5-10 fold more common rate in ETA compared to untrained healthy adults (10-13). It is our hope that this study will advance the screening for endurance athletes who go on to develop RV pathologies.

5.1 Comparisons between Endurance Trained Athletes and Untrained Controls

5.1a Baseline Characteristics of Athletes and Controls

Compared to the control groups, ETA demonstrated the expected features of the Athlete’s Heart (see Table 2). Additionally, this study is among the very few to look at RA morphology and function in athletes. Our echo-derived functional measures complied with the published athlete’s heart guidelines, and those obtained from the control population fall within the range of normal as calculated by the American Society of Echocardiography (81), and other studies using control groups (105).
5.1b Range of Pulmonary Pressures in Athletes and Controls

Because only PASP was recorded in controls, PVR could not be calculated for untrained subjects. Interestingly, there were no significant differences between ETA and controls in their PASPs during exercise. This further confirms that the generation of higher pulmonary pressures is not a characteristic found in athletes alone.

5.2 Endurance Trained Athletes’ Hemodynamics in Response to Exercise

With the exception of one athlete, ETA experienced an increase in pulmonary pressures during exercise. After an initial, significant rise in pressures, a plateau was generally established (see Figure 5). We recorded a wide range in resting pulmonary pressures and PVR (see Table 3), with a similar range seen at each exercise stage, with individuals reaching peak PASPs at different stages of the exercise protocol. Peak PASPs normalized to resting values were presented as percent deltas, where a large range was also evident, demonstrating PASP increases of 3.8 – 152 % of resting values (see Figure 7).

Finally, a common trend in PVR was not detected among the entire cohort of ETA. This was especially surprising given the uniform increases in CO. There were a number of athletes who demonstrated a surprisingly modest decrease in PVR throughout exercise, and, some actually experienced significant increases in the PVR. At least 3 ETA maintained a higher PVR than resting value throughout the entire exercise protocol; such a phenomenon has been previously shown in athletes living and training in high altitudes (127-130). Because of the difficulty of Doppler flow echocardiography at vigorous stages of exercise, certain measures of CO could not be confirmed, making our PVR measurements limited and at the higher stages of exercise.

5.3 Dichotomization of Athletes

Considerable heterogeneity was observed in the pulmonary response to exercise, evidenced by the wide PASP range, the different peak times, and the vastly different PVR response. In fact, the majority of athletes (11 out of 16, 69%) generated PASPs that reached far above the “exercise-induced PAH” cut off of 40 mmHg (26). Additionally, the pressure-flow relationships of our athletic subjects showed a high degree of variability. Grouping all the athletes together, the mPAP/CO slope fell within the expected window of 1.2±0.5 mmHg increase for every 1 L of
CO. Similarly, the PASP slope is higher, with a 1.5±0.6 mmHg increase for every 1 L of CO. However, upon analysis of the range of slopes, it became clear that the “normal” average was mainly a result of two exaggerated extremes (See Figure 4). These data challenge our understanding of what a “normal” pulmonary response to exercise is. We therefore performed subgroup analyses based on Peak PASPs generated during exercise.

Dichotomizing “high” and “low” pressure generators was done previously in our lab (131) and by others (95). This approach was used in the present cohort to better understand the factors involved in determining or characterizing the different responses to exercise among our cohort.

5.4 Subgroup Analysis: High Pressure vs Low Pressure Generators at Rest

5.4a Baseline and Athlete’s Heart Characteristics

Baseline characteristics and resting cardiac structural morphologies were not significantly different between HPG and LPG, with the exception of LA maximal area (p<0.0005). This tells us that an endurance athlete’s age, height, BMI, and resting right heart structural adaptation cannot generally predict his pulmonary pressure response to exercise. While HPG athletes were slightly but not significantly older, their corresponding VO$_2$max and resting PVR values were well within range of a healthy trained athlete, and perhaps more so than LPG athletes (See Table 4). HPG athletes showed larger VO$_2$max values than their LPG counterparts (HPG 49.4 ± 0.6 ml/kg/min vs. LPG 44 ± 3.9 ml/kg/min; p=0.19), and contrary to what is known of the older untrained individual, the older HPG athletes demonstrated lower resting PVR values than the younger LPG athletes. We therefore cannot fairly attribute the higher-than-“normal” PASP values to the slightly older age range in the HPG group.

Resting right heart structural morphologies were not significantly different between HPG and LPG groups; both experienced the typical, within-normal, dilatory adaptations of the Athlete’s Heart. These data suggest that RV and RA sizes are unrelated to the pulmonary pressure response to exercise. On the other hand, LA max size correlated positively with peak pulmonary pressures, which is echoed by the positive correlation between PCWP and peak PASPs. This may suggest that the LA may be more adaptable to higher-pressure loading conditions.
5.4b Resting Functional Differences:

While most measures of systolic function (TAPSE, FAC, Tissue Doppler waves) were similar between HPG and LPG, a marked attenuation in resting RV free wall systolic strain was detected in the HPG group. In a meta-analysis on RV echocardiographic measurements, Rudski et al referenced a mean strain of -28% (range 25 – 32%) in the basal free wall segment of the healthy RV(81). The LPG group fell within the upper limits of this range (-30.3 ± 7.4).

The HPG group however did not fit this trend, demonstrating diminished strain values compared to LPG counterparts (see Table 5). Importantly, RV systolic strain correlated significantly with the degree of PASP elevation, from rest to peak pressure (see Figure 12). This suggests that a diminished resting contractile performance is associated with a steeper or exaggerated elevation of pulmonary pressures during exercise. Additionally, there was a marked reduction in RV early diastolic (e’) strain rate, implying a “slowing” of relaxation in those athletes in the HPG group. It remains unknown if recurrent exposures to high pulmonary pressures over a rigorous exercise history directly causes RV strain impairments.

5.5c. Inferences from Pulmonary Arterial Hypertension Literature

A reduction in resting RV strain in elite athletes has been noted previously, especially in the basal FW segment as we have shown in our study (85, 120). Additionally, a reduction in RV function was previously recorded in athletes with higher vascular resistance (95). However, most exercise studies in healthy athletes do not examine athletes on a continuum of pulmonary pressure responses during exercise. We may then draw inferences from the PAH literature, which also demonstrates significant reductions in RV functional measurements like strain and strain rate(105, 112, 132, 133). For example, Sachdev et al calculated a RV free wall strain of -20±7% in patients with mPAP greater than 25 mmHg (or 30 mmHg during exercise)(132). Similarly, Viteralli et al calculated a strain of -23.2 ± 6.7%, and -19.9 ± 7.9% in those with mPAP over 35 mmHg, compared to a control group with strain values of -32.5 ±10.2 (105). PAH strain values in these publications are not dissimilar to our measured HPG strain values of – 23 ± 4.8. RV function has long been accepted as an adequate prognostic measure of PAH disease progression, so much so that BNP screening has been suggested in patients with primary PAH(104). BNP is a known marker of acute RV dysfunction or fatigue, and is up-regulated in
PAH. Its elevation in primary PAH patients was previously correlated with exercise intolerance, PVR, mPAP, and a worsening World Health Organization Class of PAH (104). This information may be relevant to our study, as BNP has also been shown to be elevated in a number of athletes during exercise (106, 108, 110-112), and especially in athletes who generated higher pulmonary pressures (95), reflecting a significant load on the RV and pulmonary vasculature.

These connections however remain speculative at this time. There have been reports showing that a reduced myocardial strain is not necessarily representative of cardiac damage or dysfunction, as it bared no effect on the isovolemic acceleration of the RV (85).

5.4c Resting Hemodynamic Differences:

At rest, all pressure recordings in HPG athletes were slightly greater than LPG participants – albeit not significantly (see Figure 12). Only 1 athlete, at 26 mmHg, had a resting mPAP greater than the accepted cut-off of 25 mmHg. His peak mPAP during exercise was 50 mmHg, with a corresponding peak PASP of 72 mmHg. At 54 years old (vs. average age of 54.8 years), this athlete was among the heaviest in the cohort, with a weight of 91.5 kg (vs. average of 76.2±8 kg) and a BMI of 28.6 kg/m² (vs. average of 24±2.1 kg/m²). Other than this particular athlete (who only exceeded the accepted cut-off by 1 mmHg), all ETA in our study demonstrated pulmonary and RA pressures that fell within the established healthy range with no substantial differences between the two groups.

5.5 Differences Between High and Low Pressure Generators During Exercise

The 2 groups were tracked throughout the exercise protocol to compare their response to increased CO and exercise intensity. CO did not differ between the two groups, as both experienced almost identical increases in flow (see Figure 10). Similarly, the workloads between HPG and LPG athletes were not substantially different – although, HPG athletes exercised at slightly higher workloads.

5.5a Right Sided Morphological Differences in Response to Exercise

Visibility on echocardiograms was limited at higher stages of exercise, which may have impacted chamber quantification, despite the low intra-class variability. There were no
substantial differences both between and within HPG and LPG groups with regard to their right atrial and ventricular maximal area and volume patterns during exercise, with the exception of 150 bpm (See Table 6). The echo-derived measurements at this time point however (heavy exercise) remain dubious.

5.5b Functional Differences in Response to Exercise

Due to methodological limitations on echoPAC, strain and strain rate analysis could not be assessed during exercise. Instead, other measures of right-sided performance were used, including TAPSE, TDI, and FAC.

RV FAC did not differ between the two groups, however HPG athletes experienced a more pronounced TAPSE during the first two stages of exercise (See Table 6). This is perhaps expected due to the slightly larger RV end-diastolic areas of HPG athletes. While the distance traveled by the annular plane was greater in HPG, TDI measures of the rate of movement (cm/sec), and RV FAC were almost identical in both groups. Considering the similar CO achieved by both groups, it must be concluded that RV of both groups responded to exercise similarly in accommodating elevated loading conditions.

While there are fewer validated measures of RA function, RA FAC was significantly attenuated in HPG athletes at the first stage of exercise (see Figure 13). This finding is in concert with other exercise studies that show a subset of athletes responding to exercise with diminished RA performance (77). Sudden rises in pulmonary and RV pressures during exercise may “stun” the RA, as elevated RV and pulmonary pressures come at a high-energy expense, causing the RA to work with increased wall stress. RA strain measures and analyses of pro-fibrotic or arrhythmogenic factors should be quantified in HPG athletes to understand RA response to elevated pressures during exercise.

5.5c Hemodynamic Differences during Exercise

Perhaps the most significant finding during exercise was the sudden increase in PVR in the HPG group during the first stage of exercise. Both groups experienced the same increases in CO with little to no differences between them in both value and degree of elevation (Calculated from
Table 6: delta CO from rest, HPG 111% vs. LPG 122.5%; p=0.62). LPG athletes respond as expected, with a significant decrease in vascular resistance during the first stage of exercise by 34.6% from rest (p=0.03). HPG athletes however respond in an unusual way, with an average increase in PVR of 43.6%.

The increase in PVR in the HPG group was not correlated with any anthropomorphic measures, and cannot be predicted by our echo-derived measures of resting cardiac characteristics. We therefore believe that there may be inherent differences (not measured in our study) between these two athletic groups that account for this abnormal response pattern. An increase in PVR in response to exercise has been shown previously in athletes native to high altitudes. These pulmonary vaso-constrictive responses however are speculated to consequences of hypoxemic environments and acid-base imbalances (127-130), but our subjects remained fully saturated during exercise.

The differences in PVR, and the exaggerated compliance of LPG athletes may be phenotypic manifestations of genetic or inherent differences between two different groups of athletes.

5.6 Potential Causes for High Pressure Generators

HPG athletes demonstrated significantly larger LA sizes than LPG counterparts. Additionally, their PCWP measure were elevated at rest (albeit not-significantly), and reached significantly higher values during exercise at 100 and 150 bpm. Additionally, the relative increase in pressure from rest to peak PASP was correlated significantly with resting LA size (Appendix G). These data may be indicative of a “back-pressure” effect, where higher pressures affecting the left heart exert additional stress on pulmonary function, thereby increasing its pressures during a high-flow state of exercise. Potential contributions to this back-pressure could be a greater left-sided afterload. We measured systemic blood pressures at rest and during exercise, which can represent minor indices of afterload. However, they were not different from one another, and both experienced the same trends in pressure responses (Figure 15). Another potential contribution could be left-sided diastolic dysfunction, where ventricular relaxation is stiffened and exerts added downstream pressure against left atrial function. Measures of LV diastolic function was
out of the scope of this study, but warrants further investigation in order to better understand how why some athletes may generate greater pressures than others during exercise.

A genetic link may also explain high pulmonary pressure generation during exercise, which has been previously investigated in untrained individuals. While this discussion remains speculative in nature, it fosters important questions regarding a possible predisposition to developing high pulmonary pressures during exercise, which warrants further characterization in this athletic cohort. In 1997, approximately 6% of documented primary PAH was found to be inherited (137). Although the specific gene responsible for the disease has not yet been identified, a genome-wide association search found significant linkage between two chromosome markers that was highly prevalent in the disease population, and in related asymptomatic family members compared to the genetic make-up of non-PAH or related controls (137-139). A brief explanation of genetic linkage is provided in Appendix I. In 2000, Grunig et al investigated the prevalence of this linkage in non-PAH family members of PAH patients. 14 out of 52 blood relatives of PAH patients (27%) with normal resting PASP values (21± 12 mmHg) demonstrated an “abnormal” PASP response to exercise (51±12 mmHg). All 14 members shared the same chromosomal 2q haplotype (therefore the same linkage patterns) as their PAH family members. It was concluded that such a genetic pattern may likely be an early sign of PAH, and – importantly – that an exaggerated increase in PASP during exercise may be an early phenotypic expression of this genetic make-up (138). While it is still too early to suggest that our HPG athletes may be among those who later develop PAH, such information could be considered when designing further exercise studies.

5.7 Potential Cause for LowPressure Generators

While PASPs and mPAPs in HPG athletes in most studies are characterized as “abnormal” or indicative of exercise-induced PAH, it cannot be denied that LPG athletes in our study experienced an exaggerated compliance that can also be viewed as “abnormal”. With a pressure-flow slope of 0.47, these athletes are apparently capable of accommodating huge increases in volume at an extraordinarily low pulmonary cost. This however is not reflected in their PVR response to increased CO, as we see the appropriate dilatory response. The idea that some endurance athletes have ‘adapted’ pulmonary vasculatures has been postulated previously: increases in capillary reserve and the opening of intra-pulmonary shunts in endurance-trained
athletes have been investigated and suggested to be protective adaptations against an exaggerated rise in pulmonary pressures (28, 140, 141). Further exercise studies using contrast echocardiography should be conducted to further elucidate potential mechanisms behind such pulmonary compliance in LPG athletes, which are clearly absent in HPG athletes.

5.8 Exercise-induced Pulmonary Arterial Hypertension?

The diagnosis of “exercise-induced PAH” was first introduced in a normal, untrained population. It was meant to describe individuals who had normal pulmonary pressures at rest, but exaggerated pressure responses to exercise, with mPAP reaching over 30 mmHg, and PASP over 40 mmHg (26, 138). Applying this diagnosis to an athletic population however may be premature. We suggest here that in order to truly identify a cut-off beyond which a diagnosis can be made, we must have a working understanding of a “normal” response to exercise. Our study questions the accepted definition of normal, especially with the majority of our ETA (68.75%) generating PASPs far above the cut off of 40 mmHg, with a total median of 49 mmHg. Instead, we propose a reevaluation of “normal”, and suggest viewing the athletic population as a heterogeneous group. But, while we cannot call it “exercise-induced PAH”, our study results are in concert with previous reports, where elevations in pulmonary pressures during exercise may be associated with RV dysfunction (18, 83, 95).

5.9 Limitations and Future Directions

There are a number of limitations in our study. Our inclusion of a control group was intended to describe the range in their hemodynamic profiles compared to ETA, and to provide confirmation that our athletes demonstrated the athletic heart’s adaptations compared to an untrained cohort. However, our interpretation of structural and functional differences between HPG and LPG athletes would have been more robust with comparative measures from a control group at each exercise stage. Despite this limitation, we drew from a wide range of resources to characterize a generalized untrained “control” population, including small exercise studies and consensus guidelines.
This study was part of a larger investigation examining the influence of high-volume, long-standing endurance exercise in middle-aged men where cardiac remodeling was more likely to be detected. Consequently, our study participants were between the ages of 45 and 60, and therefore represented an older population. As such, an older age may have impacted our outcomes. Even though age was not correlated with peak pressures during exercise or the relative increase in PASP, nor was there a significant difference between HPG and LPG ages, measures of vascular quality are often reduced in an older population (34, 95). We may expect different results in a younger cohort of athletes. Additionally, familial history of cardiovascular or pulmonary diseases was not collected, which may have given further insights in the characterization of our athletes. Visibility on echocardiograms presented several limitations during heavier stages of exercise. Already at rest, the RV FW is thin and often out of focus. These visual drawbacks were exacerbated in the turbulent images captured during exercise. Additionally, echo-derived measurements tend to under-estimate structural quantifications such as chamber area and wall thickness when compared to MRI (142, 143). CO values are also typically underestimated with echo analysis in part because they rely on a spherical LVOT, which anatomically is not always the case (See Review of Literature, Section 2.12b). Therefore, MRI still remains the gold-standard for cardiac measurements, but despite the stated limitations, our Echocardiographic measures fell within healthy characterizations previously described by our lab, other authors and accepted guidelines.

While echo-derived PASP measures have been well correlated with catheter-derived recordings (144), visualization of Doppler flow waves can be greatly degraded at heavier stages of exercise, where the line between artifact and signal is increasingly blurred. We therefore decided to only include catheter-derived hemodynamic measures, which were recorded in 16 out of the 21 athletes recruited (76%), and in 7 out of the 13 untrained controls (54%). Despite this, we were still capable of dichotomizing high vs. low generators in our ETA cohort. This study did not acquire molecular or genetic endpoints, nor were cardiac biomarkers stress such as Troponin and BNP at rest or during exercise obtained, which have been correlated with RV dysfunction and pulmonary hypertension (15, 24, 95, 104). Future exercise studies may focus on creating a more complete characterization of high-pressure generating athletes that includes
their genetic and biochemical profiles, compared to lower-pressure generating athletes and a healthy untrained control population.

The dichotomization of HPG and LPG athletes was based on the median peak PASP generation during exercise. There are a number of reasons behind this analysis. Because of our small sample size, multiple linear regression models would not have been accurate in determining differentiating features correlated with pressure response. There were also no outliers in peak-pressure data, which reassured us of limited bias that may have skewed our results. Additionally, a similar technique was done previously in differentiating “high” and “low” athletic responders (95). Despite these considerations, it is of no doubt that the cut-off point of a median value of 49 mmHg can be seen as arbitrary, as a median value of another sample may be higher or lower than the value calculated in this study. This study however would hopefully generate greater interest among researchers to study pulmonary pressures during exercise as a continuum rather than in a dichotomized fashion.

5.10 Conclusion

Our results report heterogeneity in the pulmonary hemodynamic response to exercise, despite similar CO and cardiac structure amongst long-standing, middle-aged male endurance athletes. In contrast to ‘low’ pulmonary pressure generators, individuals who were ‘high’ pulmonary pressure generators demonstrated reduced RV strain and diastolic strain rate at rest – which are indices of RV function. Both these findings have been documented previously in human and animal studies of PAH. Moreover, this cohort also demonstrated an abnormal increase in PVR despite identical CO levels seen in their LPG counterparts. Further study is required to elucidate whether repeated exposures to intensive exercise in those who have exaggerated pulmonary pressure responses may contribute to long-term mal-adaptations. Additionally, the mechanisms governing the pulmonary response to exercise remain poorly understood. Genetic and hemodynamic differences among athletes warrant further investigations, as our data suggests phenotypic features that may contribute to abnormal responses to exercise in those athletes who generate higher pulmonary pressures.
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Appendix

Appendix A: Frank Starling Forces

The Frank-Starling relationship explains an adaptive response in cardiac tissue that allows for adjustments in stroke volume (SV) to match cardiac inflow (and ventricular end-diastolic volume, EDV); the larger the cardiac inflow, the greater the stroke volume. This accommodation is established by increasing the myocardial force of contraction, which in turn is correlated with muscle fiber length. In healthy ETA, increases in preload and CO causes elevations in EDV. These volume boosts promote healthy myocardial stretching, which then translates to an increase in contractile force. Over time, healthy long-term ETA will develop adaptive cardiac muscle fibers that are longer in order to generate larger contractile responses. This then allows the heart to adapt to increases in preload by maintaining appropriate SV responses, thereby promoting faster and effective systemic distribution of oxygen to high-demand tissues.
Appendix B: 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 sided pumping chamber of the 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 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></td>
<td>X</td>
<td></td>
<td></td>
<td>1 hour</td>
</tr>
<tr>
<td>Cardiac Assessment</td>
<td>X</td>
<td>X</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 (ie. 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 C: Study Recruitment Ad

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 D: Par-Q+: The Physical Activity Readiness Questionnaire for Everyone

**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.

### SECTION 1 - GENERAL HEALTH

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

1. Has your doctor ever said that you have a heart condition OR high blood pressure?
   - [ ] YES
   - [ ] NO

2. Do you feel pain in your chest at rest, during your daily activities of living, OR when you do physical activity?
   - [ ] YES
   - [ ] NO

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).
   - [ ] YES
   - [ ] NO

4. Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)?
   - [ ] YES
   - [ ] NO

5. Are you currently taking prescribed medications for a chronic medical condition?
   - [ ] YES
   - [ ] NO

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.
   - [ ] YES
   - [ ] NO

7. Has your doctor ever said that you should only do medically supervised physical activity?
   - [ ] YES
   - [ ] NO

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

- ✔️ Start becoming much more physically active – start slowly and build up gradually.
- ✔️ Follow the Canadian 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 CSEP Certified Exercise Physiologist® (CSEP-CEP) or CSEP Certified Personal Trainer® (CSEP-CPT).
- ✔️ If you are over the age of 45 yrs. and NOT accustomed to regular vigorous physical activity, please consult a qualified exercise professional (CSEP-CEP) before engaging in maximal effort exercise.

If you answered YES to one or more of the questions above, please GO TO SECTION 2.

- ✗ 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 PARmed-X for Pregnancy before becoming more physically active OR
  - Your health changes – please answer the questions on Section 2 of this document and/or talk to your doctor or qualified exercise professional (CSEP-CEP or CSEP-CPT) before continuing with any physical activity programme.
## SECTION 2 - CHRONIC MEDICAL CONDITIONS

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

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have Arthritis, Osteoporosis, or Back Problems?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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 spondylolysis/pars defect (a crack in the bony ring on the back of the spinal column)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1c. Have you had steroid injections or taken steroid tablets regularly for more than 3 months?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Do you have Cancer of any kind?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2a. Does your cancer diagnosis include any of the following types: lung/bronchogenic, multiple myeloma (cancer of plasma cells), head, and neck?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2b. Are you currently receiving cancer therapy (such as chemotherapy or radiotherapy)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you have Heart Disease or Cardiovascular Disease?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. This includes Coronary Artery Disease, High Blood Pressure, Heart Failure, Diagnosed Abnormality of Heart Rhythm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3a. 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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3b. Do you have an irregular heart beat that requires medical management? (e.g. atrial fibrillation, premature ventricular contraction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3c. Do you have chronic heart failure?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3e. Do you have diagnosed coronary artery (cardiovascular) disease and have not participated in regular physical activity in the last 2 months?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Do you have any Metabolic Conditions? This includes Type 1 Diabetes, Type 2 Diabetes, Pre-Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4a. Is your blood sugar often above 13.0 mmol/L? (Answer YES if you are not sure)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4c. Do you have other metabolic conditions (such as thyroid disorders, pregnancy-related diabetes, chronic kidney disease, liver problems)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. If yes, answer questions 5a-5b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5b. Do you also have back problems affecting nerves or muscles?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Question</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>-----</td>
<td>----</td>
</tr>
<tr>
<td>Please read the questions below carefully and answer each one honestly: check YES or NO.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Do you have a Respiratory Disease? This includes Chronic Obstructive Pulmonary Disease, Asthma, Pulmonary High Blood Pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6b. Has your doctor ever said your blood oxygen level is low at rest or during exercise and/or that you require supplemental oxygen therapy?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6d. Has your doctor ever said you have high blood pressure in the blood vessels of your lungs?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Do you have a Spinal Cord Injury? This includes Tetraplegia and Paraplegia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7b. Do you commonly exhibit low resting blood pressure significant enough to cause dizziness, light-headedness, and/or fainting?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7c. Has your physician indicated that you exhibit sudden bouts of high blood pressure (known as Autonomic Dysreflexia)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Have you had a Stroke? This includes Transient Ischemic Attack (TIA) or Cerebrovascular Event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8b. Do you have any impairment in walking or mobility?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8c. Have you experienced a stroke or impairment in nerves or muscles in the past 6 months?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Do you have any other medical condition not listed above or do you live with two chronic conditions?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9b. Do you have a medical condition that is not listed (such as epilepsy, neurological conditions, kidney problems)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9c. Do you currently live with two chronic conditions?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please proceed to Page 4 for recommendations for your current medical condition and sign this document.

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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:

- 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 yrs. and NOT accustomed to regular vigorous physical activity, please consult a qualified exercise professional (CSEP-CEP) before engaging in maximal effort exercise.

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

- You should seek further information from a licensed health care professional before becoming more physically active or engaging in a fitness appraisal and/or visit a qualified exercise professional (CSEP-CEP) 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 PARmed-X for Pregnancy before becoming more physically active OR
- Your health changes - please talk to your doctor or qualified exercise professional (CSEP-CEP) before continuing with any physical activity programme.

SECTION 3 - DECLARATION

- You are encouraged to photocopy the PAR-Q+. You must use the entire questionnaire and NO changes are permitted.
- The Canadian Society for Exercise Physiology, the PAR-Q+ Collaboration, 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.
- 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.
- Please read and sign the declaration below:

  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 Trustee (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 Trustee 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 ____________________________ DATE ____________________________

SIGNATURE ____________________________ WITNESS ____________________________

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER ____________________________

For more information, please contact:
Canadian Society for Exercise Physiology
www.csep.ca

KEY REFERENCES

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 Gledhill, Dr. Veronica Jamnik, 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 BC Ministry of Health Services.
Appendix E: 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></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></td>
<td>Hours</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>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2  3  4</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:

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

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

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

Number of years

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

\[
\sum \frac{((\text{Age finished} - \text{Age started}) \times 365 \text{ d/yr} \times (\text{No. of times/day}) \times (\text{Hr/exercise session}))}{52} \]

Number of years
If respondent reported per week: Equation 1D

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

If respondent reported per month: Equation 1E

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

If respondent reported per year: Equation 1F

\[
\sum \frac{[(\text{Age finished} - \text{Age started}) \times \text{(No. of times/yr)} \times (\text{Hr/exercise session})]}{52} \text{ Number of years}
\]
## Appendix F: Correlations with Peak PASP

<table>
<thead>
<tr>
<th>Correlations with Peak PASP</th>
<th>R</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthropomorphic Measures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.27</td>
<td>0.30</td>
</tr>
<tr>
<td>Height</td>
<td>0.42</td>
<td>0.11</td>
</tr>
<tr>
<td>Weight</td>
<td>0.17</td>
<td>0.52</td>
</tr>
<tr>
<td>BMI</td>
<td>0.37</td>
<td>0.15</td>
</tr>
<tr>
<td>VO2</td>
<td>0.31</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Resting Dimensions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA Max</td>
<td>0.02</td>
<td>0.95</td>
</tr>
<tr>
<td>RA Max Index</td>
<td>0.01</td>
<td>0.96</td>
</tr>
<tr>
<td>RA Max Volume</td>
<td>0.07</td>
<td>0.80</td>
</tr>
<tr>
<td>RA Max Volume Index</td>
<td>0.06</td>
<td>0.83</td>
</tr>
<tr>
<td>RV Max</td>
<td>0.03</td>
<td>0.91</td>
</tr>
<tr>
<td>RV Max Index</td>
<td>0.00</td>
<td>1.00</td>
</tr>
<tr>
<td>LA Max</td>
<td>0.80</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>LA Max Index</td>
<td>0.81</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td><strong>Resting Functional Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA FAC</td>
<td>0.48</td>
<td>0.06</td>
</tr>
<tr>
<td>RV FAC</td>
<td>0.30</td>
<td>0.26</td>
</tr>
<tr>
<td>LA FAC</td>
<td>0.62</td>
<td>0.06</td>
</tr>
<tr>
<td>TAPSE</td>
<td>0.45</td>
<td>0.07</td>
</tr>
<tr>
<td>TD E'</td>
<td>0.04</td>
<td>0.88</td>
</tr>
<tr>
<td>TD A'</td>
<td>0.96</td>
<td>0.25</td>
</tr>
<tr>
<td>TD S'</td>
<td>0.02</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>Resting Strain and Strain Rate Measures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RA Global Strain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA Global Peak Negative</td>
<td>0.11</td>
<td>0.71</td>
</tr>
<tr>
<td>RA Global Peak Positive</td>
<td>0.92</td>
<td>0.80</td>
</tr>
<tr>
<td><strong>RA Free Wall Strain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA Free Wall Peak Negative</td>
<td>0.16</td>
<td>0.59</td>
</tr>
<tr>
<td>RA Free Wall Peak Positive</td>
<td>0.05</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>RA Global Strain Rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA Global SR A' (pump)</td>
<td>0.09</td>
<td>0.76</td>
</tr>
<tr>
<td>RA Global SR S (reservoir)</td>
<td>0.31</td>
<td>0.29</td>
</tr>
<tr>
<td>RA Global SR E (early cont)</td>
<td>0.24</td>
<td>0.41</td>
</tr>
<tr>
<td><strong>RA Free Wall Strain Rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA Free Wall SR A (pump)</td>
<td>0.12</td>
<td>0.71</td>
</tr>
<tr>
<td>RA Free Wall SR S (reservoir)</td>
<td>0.06</td>
<td>0.84</td>
</tr>
<tr>
<td>Parameter</td>
<td>Value1</td>
<td>Value2</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>RA Free Wall SR E (early cont)</td>
<td>0.20</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>RV Global and Free Wall Strain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV Global Peak Negative</td>
<td>0.18</td>
<td>0.52</td>
</tr>
<tr>
<td>RV Free Wall Peak Negative</td>
<td>0.38</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>RV Global Strain Rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV Global SR S</td>
<td>0.16</td>
<td>0.58</td>
</tr>
<tr>
<td>RV Global SR E</td>
<td>0.07</td>
<td>0.80</td>
</tr>
<tr>
<td>RV Global SR A</td>
<td>0.22</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>RV Free Wall Strain Rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV Free Wall SR S</td>
<td>0.44</td>
<td>0.13</td>
</tr>
<tr>
<td>RV Free Wall SR E</td>
<td>0.43</td>
<td>0.15</td>
</tr>
<tr>
<td>RV Free Wall SR A</td>
<td>0.13</td>
<td>0.68</td>
</tr>
<tr>
<td><strong>Resting Hemodynamics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SV at Rest</td>
<td>0.22</td>
<td>0.40</td>
</tr>
<tr>
<td>RAP at Rest</td>
<td>0.37</td>
<td>0.15</td>
</tr>
<tr>
<td>mPAP at Rest</td>
<td>0.50</td>
<td>0.05</td>
</tr>
<tr>
<td>PASP at Rest</td>
<td>0.59</td>
<td>0.02</td>
</tr>
<tr>
<td>PCWP at Rest</td>
<td>0.50</td>
<td>0.05</td>
</tr>
<tr>
<td>Resting Heart Rate</td>
<td>0.26</td>
<td>0.33</td>
</tr>
<tr>
<td>Resting PVR</td>
<td>0.15</td>
<td>0.59</td>
</tr>
<tr>
<td><strong>Correlations with PASP During Exercise</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delta PASP (rest to peak)</td>
<td>0.64</td>
<td>0.01</td>
</tr>
<tr>
<td>Delta mPAP (rest to peak)</td>
<td>0.63</td>
<td>0.01</td>
</tr>
<tr>
<td>Delta PCWP (rest to peak)</td>
<td>0.30</td>
<td>0.28</td>
</tr>
<tr>
<td>Delta PVR (rest to 100bpm)</td>
<td>0.68</td>
<td>0.01</td>
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<tr>
<td>Workload at 100bpm</td>
<td>0.05</td>
<td>0.86</td>
</tr>
<tr>
<td>Workload at 130 bpm</td>
<td>0.41</td>
<td>0.14</td>
</tr>
</tbody>
</table>
### Appendix G: Correlations with % Rise in PASP (from Rest to Peak)

<table>
<thead>
<tr>
<th>Correlations with % Rise in PASP</th>
<th>R</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthropomorphic Measures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.14</td>
<td>0.60</td>
</tr>
<tr>
<td>Height</td>
<td>0.50</td>
<td>0.05</td>
</tr>
<tr>
<td>Weight</td>
<td>0.51</td>
<td>0.04</td>
</tr>
<tr>
<td>BMI</td>
<td>0.39</td>
<td>0.14</td>
</tr>
<tr>
<td>VO2</td>
<td>0.51</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Resting Dimensions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA Max</td>
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<td>0.50</td>
</tr>
<tr>
<td>RA Max Index</td>
<td>0.35</td>
<td>0.19</td>
</tr>
<tr>
<td>RA Max Volume</td>
<td>0.15</td>
<td>0.58</td>
</tr>
<tr>
<td>RA Max Volume Index</td>
<td>0.25</td>
<td>0.34</td>
</tr>
<tr>
<td>RV Max</td>
<td>0.16</td>
<td>0.54</td>
</tr>
<tr>
<td>RV Max Index</td>
<td>0.11</td>
<td>0.70</td>
</tr>
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Appendix H: Catheterization Technical Protocol

**Right Heart Hemodynamics and Left Atrial Phasic Function During Exercise: The Influence of Chronic Endurance Training**

**Purpose:** To examine the hemodynamic and echocardiographic response to incremental semi-supine cycling exercise.

**Hypotheses:** Exercise will elicit an increase in pulmonary artery pressure associated with right heart cardiac output. Atrial filling will be acutely improved related to atrioventricular plane displacement.

**Equipment:**
- Ergoselect table
- 5-lead ECG
- Non-invasive BP monitor
- 8-Fr venous sheath
- 0.035-145 cm Long J-wire with 1.5mm J
- 18g X 1 1/2” Seldinger needle (Argon)
- Tourniquet (Sarstedt)
- 1x Swan sleeve, omit if patient very tall
- 2x Right Heart kits
- 2x COBE stopcocks
- 1x 500cc heparin flush bags
- 2x fluid administration sets
- 2x flush devices
- 4x NICOM stickers
- Swan-Ganz CCOMbo Volumetrics PA catheter (CO, SvO2, RAP, PAP)
- Vigilance II SvO2/CCO monitor
- Sterile towel drapes for left antecubital fossa
- Site-rite portable ultrasound (Site-rite 5, Bard)
- NICOM Non-invasive cardiac output monitor
- Tango BP monitor
- Non-invasive pulse oximetry finger probe or disposable finger sensor
- Blood tubes: 2 Lavender top

**Preparation:**
- Prepare flush line/pressure bag for the RA and PA ports
- Synchronize clocks (GE/Vigilance/NICOM/Tango)
- Cover Ergo Select with sheet
- Place handle on left side to drive table
- Prepare blood tubes for the following conditions:
  - baseline Hgb/Hct
**Measures:**
- Hematocrit (Hct)
- Hemoglobin (Hb)
- Plasma volume (PV)
- Blood pressure (Systolic, Diastolic, MAP)
- RA, PA (Systolic, Diastolic, Mean), PAWP (a-wave, v-wave)
- CO (CCombo continuous thermo; NICOM)
- SV/SvO2/RV EF (CCombo)
- SpO2 (Non-invasive pulse oximetry - finger probe)
- Echocardiographic Images

**In Cath Lab Bay**
- Subject arrives at cath lab following 12hr fasting
- 12 lead ECG completed
- Subject weighed
- Start IV
- Baseline Echo in the Bay

**Procedure:**
- Subject lies supine on cath table
- Fully drape subject
- Use good technique to apply ECG electrodes, prepping with sandpaper and alcohol swab
- Apply electrodes anteriorly with (2) RA (2) LA (2) LL (1) RL and (1) ground
- BP cuff around patient’s right arm
- Place Site-Rite on right side of table and Vigilance II on left side of table (will need to be moved after subject is transferred to Ergoselect)
- Clip transducers on Right side of table
- Place Ergoselect out of the way on right side of table
- Notify Joan to come to cath lab in 15min
  - Prep and drape left anticubital access
  - Apply tourniquet loosely
  - Tighten tourniquet
  - Anesthetize site with local anesthesia
  - Prep ultrasound head with transducer jelly
  - Cannulate vein and advance 8-Fr sheath as per routine
- Position Swan-Ganz catheter and connect PA line to transducer
- Monitor PA port while subject is transferred from bed to Ergoselect
- Bring Ergoselect adjacent to cath table
- Transfer subject to Ergoselect
- Move the Ergoselect away from cath table
- Move the Vigilance II monitor and place the Vivid machine beside the Ergoselect
- Attach electrical ports to Vigilance II monitor and calibrate using in vivo instructions.
  - If Unit fails to calibrate, use baseline PA Sat and Hgb from sample sent pre-procedure
  - Slave ECG into Vigilance using phono to phono cable from back of Vigilance to top of Defibrillator
• Place BP Tango cuff on opposite arm from Swan. Import ECG by slaving from T connector beneath cath lab table
• Move arm-table and board to left side of Ergoselect
• Connect RA and PA to transducers and set up flush
• Secure RA/PA ports to medial side of black arm board
• Electrodes for NICOM placed anteriorly - make sure left inferior doesn’t obstruct apical window
• Assign someone to annotate NICOM machine
Appendix I: Genetic Linkage

Genetic linkage refers to the high probability of 2 alleles being inherited together from one parent. Put briefly, after conception, maternal and paternal chromatids pair with one another and exchange genetic information, thereby creating complete chromosomes with a unique combination of alleles from both parents. When 2 alleles are “linked”, this means that there is a higher chance that they will be inherited together from one parent.
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La Gerche A, Connelly KA, Mooney DJ, MacIsaac AI, Prior DL. Biochemical and functional abnormalities of left and right ventricular function after ultra-endurance exercise. *Heart.* 2008; 94(7): 860-866.