THE INFLUENCE OF FITNESS LEVEL ON THE APPEARANCE OF INTRAPULMONARY ARTERIOVENOUS SHUNTING IN HEALTHY WOMEN

by

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B.Sc., St. Francis Xavier University, 2006

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

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE STUDIES

(Human Kinetics)

THE UNIVERSITY OF BRITISH COLUMBIA
(Vancouver)

June, 2010

ABSTRACT

It was hypothesized that intrapulmonary arteriovenous shunts would be recruited at lower exercise intensities in highly trained individuals, compared to untrained and moderately trained individuals. Twenty-four women with normal lung and cardiac function, completed a maximal exercise test on a semi-supine cycle ergometer, while agitated saline contrast echocardiography was performed. Subjects were considered either untrained (VO_{2peak} < 40ml/kg/min), moderately trained (VO_{2peak} 40-45 ml/kg/min) or highly trained (VO_{2peak} > 45 ml/kg/min), as determined by their performance on the exercise test. One subject did not shunt, four subjects demonstrated shunt pre-exercise, and eleven subjects demonstrated shunt in stage one of exercise. Twenty subjects continued to shunt immediately post-exercise, and seventeen subjects continued to shunt three minutes post exercise. These findings contrast with other studies in the upright cycling position, indicating an effect of body position. Percent of VO_{2peak} at shunt onset was not different between the groups, indicating no influence of training status. Cardiac output was not different between groups, potentially due to the inability of subjects to reach their true maximum on the exercise test. Peripheral oxygen saturation did not drop significantly during exercise and there was no difference in the lowest value reached by each group, indicating no limitations to pulmonary gas exchange.

PREFACE

Collaborators and co-authors are the following:

Dr. William Sheel assisted in developing the research idea and design, coordinated committee members for thesis proposal and defence, assisted in writing of the thesis and ethics document, and provided guidance when needed.

Jill Kennedy performed the literature review, purchased materials, recruited subjects, organized and coordinated data collection days, collected the data (excluding echocardiographic and Doppler measurements), analysed and interpreted the data (excluding contrast echocardiography image analysis), and wrote the ethics documents and thesis document.

Dr. Michael Koehle, Dr. Bill Henderson, and Dr. Kristin Houghton performed saline bubble injections during the data collection sessions.

Dr. James Potts trained Jill Kennedy how to use the lab equipment, assisted in the design of the research study, and helped in writing the ethics documents and methods section pertaining to the Doppler measurements and calculations.

Dr. George Sandor analysed the contrast echocardiography images for appearance of intrapulmonary arteriovenous shunt, as well as for any cardiovascular abnormalities.

Terri Potts collected the contrast echocardiography images of intrapulmonary arteriovenous shunt, as well as additional Doppler measurements.

No publications arising from work presented in this thesis have been published to-date.

The UBC Clinical Research Ethics Board approved this thesis project and the certificate number is: H08-00879.

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LIST OF ABBREVIATIONS

^{99m}Tc = technetium 99m-labelled albumin

σPS = wall stress at peak systole

A-aDO_2 = alveolar-arterial oxygen difference

BMI = body mass index

BSA = body surface area

CI = cardiac index

DBP = diastolic blood pressure

ECG = electrocardiography

E/E' = Doppler mitral valve inflow velocity/tissue Doppler velocity

EIAH = exercise-induced arterial hypoxemia

F_b = breathing frequency

FEV_1 = forced expiratory volume in one second

FIO_2 = fraction of inspired oxygen

FVC = forced vital capacity

FS = fractional shortening

HR = heart rate

HT = highly trained

IPAVS = intrapulmonary arteriovenous shunt

LBPP = lower-body positive pressure

LV = left ventricular

LVIDd = left ventricular internal diameter at end-diastole

LVIDs = left ventricular internal diameter at end-systole

LVOT = left ventricular outflow tract

LVOT Env. Ti. = left ventricular outflow tract envelope time

LVOT V = left ventricular outflow tract peak velocity

LVOT VTI = left ventricular outflow tract velocity-time integral

LVPWs = left ventricular posterior wall thickness at end-systole

MAP = mean arterial pressure

MIGET = multiple inert gas elimination technique

MT = moderately trained

MVCFc = rate-corrected mean velocity of circumferential fiber shortening

MV(E) = mitral value early inflow velocity

MVV = maximal voluntary ventilation

O_2 = oxygen

PAP = pulmonary artery pressure

PAR-Q = Physical Activity Readiness Questionnaire

PAVM = pulmonary arteriovenous malformation

PAWP = pulmonary artery wedge pressure

PFO = patent foramen ovale

Q = cardiac output

RER = respiratory exchange ratio

SaO_2 = arterial oxygen saturation

SBP = systolic blood pressure

SD = standard deviation

SI = stoke index

SpO_2 = saturation of peripheral oxygen

SV = stroke volume

UT = untrained

V_A/Q = alveolar ventilation/perfusion

VCO_2 = carbon dioxide production

V_E = minute ventilation

VO_2 = oxygen consumption

VO_{2max} = maximal oxygen consumption

VO_{2peak} = peak oxygen consumption

V_t = tidal volume

VTI = velocity-time integral

ACKNOWLEDGEMENTS

I would like to express my gratitude to the many individuals who have made the completion of this thesis project possible. Many thanks go to the following:

Dr. William Sheel, my supervisor, for his support, guidance, and for always believing in me.

Dr. James Potts for the use of the exercise physiology lab at BC Children's Hospital and for all of his help.

Terri Potts for her excellent echocardiography skills, dependability, and for answering my many questions.

Dr. George Sandor for the time he has spent reviewing the images and for his insight.

Dr. Mike Koehle, Dr. Bill Henderson, and Dr. Kristin Houghton for their crucial role in data collection.

Naho Kondo for her dedication to the project and unending assistance.

Astrid De Souza for her assistance and guidance around the lab.

Dominik Zbogar and Ashley Charlebois for taking blood pressure measurements.

My lab mates in the Health and Integrative Physiology Lab who have provided me with so much support, insight, guidance, and for sharing their wealth of knowledge.

My friends and loved ones, who have listened and provided endless advice and encouragement that has been crucial to the completion of this thesis. Words cannot express how truly grateful I am to you all.

INTRODUCTION

The cardio-respiratory system is remarkable in its ability to respond to changing environments and physical demands placed on it, whether it be exercise or environmental (i.e. hypoxia) stress. However, this system is not perfect. Recent research suggests there are vessels in the lungs that re-route blood, bypassing the pulmonary capillary bed, thereby, failing to become fully oxygenated. These vessels, termed intrapulmonary arteriovenous shunts (IPAVS), have been reported in a majority of exercising asymptomatic young males (3; 10; 28-30; 32; 50; 51). IPAVS are dormant during rest and are recruited during dynamic exercise, as cardiac output (Q) and pulmonary artery pressure (PAP) increase (10; 50; 51). Stickland et al. (51) observed that IPAVS recruitment was positively correlated to both Q and PAP. They found that if subjects reached an alveolar-arterial oxygen difference ($A\text{-}aDO_2$) that exceeded 12 mmHg and a Q that was greater than 24 litres/min during upright cycling exercise, IPAVS were present, and once the exercise bout was terminated, IPAVS were absent.

It is important to note that IPAVS are different than pulmonary arteriovenous malformations (PAVM) as IPAVS are present in individuals with a healthy cardio-respiratory system. PAVM are rare pulmonary vascular abnormalities, mainly congenital in nature and are often associated with other disorders of the blood vessels (25). PAVM provide direct communication between the pulmonary artery and pulmonary veins, bypassing the capillary bed. The concept is similar to IPAVS, however, PAVM are larger and more severe in their consequences. For example, arterial oxygen saturation (SaO_2) at rest while lying supine in individuals with PAVM is less than 95%, and drops further upon standing, and even further still upon exercise (61). Thus, PAVM can be detected at rest, and have a significant effect on SaO_2, unlike IPAVS.

It is also important to recognize that IPAVS are different than a patent foramen ovale (PFO) and any septal defect that may result in a direct communication between the right and left sides of the heart, also known as an intracardiac shunt. In the developing fetus, there is a small hole between the atria of the heart called the foramen ovale. This hole allows one third of the blood to by-pass the lungs, which are non-functioning in a developing fetus, as the fetus instead relies on the mother's blood for oxygen and nutrients, and to eliminate carbon dioxide and waste. The rest of the blood is pumped to the pulmonary trunk but, again, most is diverted away from

the non-functioning lungs through the ductus arteriosus, a vessel that connects the pulmonary trunk to the aorta. When the baby is born and begins spontaneously breathing, the foramen ovale and ductus arteriosus close. In some infants, however, the foramen ovale does not completely close, potentially allowing blood to move from the ride side of the heart directly to the left side if pressure in the right atrium exceeds pressure in the left atrium (56). Many individuals who have this are not even aware that they do, as this hole is so small it does not significantly affect oxygenation of the blood. However, individuals who have a PFO are excluded from IPAVS studies as the main method of detecting IPAVS, contrast echocardiography, cannot differentiate between contribution due to an intracardiac shunt or IPAVS separately.

It is not completely understood why IPAVS exist or what their consequence, in terms of gas exchange, may be. IPAVS may be remnant fetal vessels that once diverted blood away from the non-functioning alveoli in the fetal lung (29). The functional consequences of these vessels remains unclear, but a small fraction of Q as shunt could widen A-aDO_2 significantly and have an effect on gas exchange (10). Many highly trained athletes exhibit an excessive A-aDO_2 during moderate and high intensity exercise leading to arterial hypoxemia, while others do not (7; 19; 20). Eldridge et al. (10) stated that perhaps these individuals who experience exercise-induced arterial hypoxemia (EIAH) exhibit IPAVS, and those individuals who do not experience EIAH do not exhibit IPAVS (10). Another theory is that IPAVS may protect the pulmonary capillaries from damage by diverting hydrodynamic energy away from them (23). This would mean that athletes who develop exercise-induced pulmonary hemorrhage may be the individuals who do not exhibit IPAVS. Lastly, perhaps individuals who develop pulmonary edema upon rapid ascent to altitude, may also be individuals who do not have IPAVS vessels (47).

Another consideration in the recruitment of IPAVS is the potential effect of biological sex. To date, sex differences have not been found to play a role, however, the majority of studies examining IPAVS have used male subjects. Out of nine studies on IPAVS, 70 subjects have been males and 20 subjects have been females (3; 10; 28-30; 32; 50; 51; 57). As such, it has been difficult to interpret the limited amount of published data. It has been shown that women have smaller lungs, smaller airways, and less surface area for gas exchange, compared to height-matched men (35). A number of studies have concluded that these anatomical differences may render women more susceptible to gas exchange abnormalities during exercise (16; 18; 19; 22; 34; 46; 49). This then leads to the question of whether or not there is a sex difference in the

recruitment of IPAVS. The limited number of studies including women demonstrates the need for more research.

Lastly, the role that fitness level may play in the recruitment of IPAVS has yet to be examined. Vogiatzis et al. (57) studied IPAVS in seven highly trained cyclists (VO_{2max} = 61.3 ± 2.4 ml/kg/min). They hypothesized that while very small IPAVS exist, they make only a minor contribution to the fall in partial pressure of oxygen and increase in A-aDO_2 seen in normoxic and hypoxic exercise in highly trained individuals. Vogiatzis et al. (57) quantified IPAVS as a percent of Q by calculating venous admixture using the Fick equation; arterial oxygen concentrations were measured, mixed venous oxygen concentrations were calculated from oxygen consumption, and PAP was extrapolated from Q measurements and previously published direct measures of PAP and Q during exercise (58). Venous admixture was then expressed as a percent of Q. Vogiatzis et al. (57) did not use contrast echocardiography during a maximal exercise test, the method used by most IPAVS studies, to characterize the onset of IPAVS in these individuals, making it difficult to compare this study to others. Thus the role that fitness level plays in IPAVS recruitment is still unknown. Individuals of a higher fitness level will reach the highest Q compared to those who are of a lower fitness level. If the recruitment of IPAVS is related to Q and PAP, perhaps highly trained individuals experience IPAVS at a lower exercise intensity than those who are not as well-trained. This thesis questions whether or not fitness level affects when IPAVS vessels are recruited in women during semi-supine cycling exercise.

Purpose

To determine the effect of training status on the appearance of IPAVS during exercise in healthy women.

Research Question

Do highly trained women experience early shunt recruitment compared to untrained and moderately trained women?

Hypothesis

Shunting will occur earlier in highly trained women compared to untrained and moderately trained women, as they will reach the highest cardiac outputs. No difference is expected between the untrained and moderately trained women, as cardiac output will not be high enough to generate a difference.

METHODS

Subjects

Twenty-nine healthy, non-smoking, female volunteers, 19-40 years of age were recruited. All subjects were recruited from the University of British Columbia community and Vancouver area through paper and email advertisements. Two subjects were excluded from this study because they had a PFO, two subjects were excluded due to the failure of the intravenous catheter to be inserted, and one subject was excluded due to an insufficient number of images obtained. The remaining 24 subjects had normal pulmonary function (age- and gender-predicted) (26), normal resting blood pressure, were free of any history or symptoms of cardiopulmonary disease (including exercise-induced asthma), and did not have a PFO or PAVM. Nineteen of the 24 subjects had a regular menstrual cycle, 14 of the 24 subjects used contraceptives (oral birth control pills, NuvaRing™, or hormone-eluting intrauterine device), and none of the subjects were pregnant. Subjects were of varying fitness levels, including untrained (n=8), moderately trained (n=6), and highly trained (n=10) as determined by their performance on a maximal exercise test. Subjects who had a peak oxygen consumption (VO_{2peak}) < 40 ml/kg/min were placed in the untrained (UT) group. Subjects who had a VO_{2peak} of 40-45 ml/kg/min were placed in the moderately trained (MT) group and subjects who had a VO_{2peak} > 45 ml/kg/min were placed in the highly trained (HT) group. This maximal exercise test was performed on a semi-supine cycle ergometer, which resulted in lower VO_{2peak} values relative to upright cycling, due to their body position. According to Astrand and Saltin (1), VO_{2max} values in supine cycling are about 15% lower than values attained during upright cycling. VO_{2peak} values for each training group were chosen based on previously published values (24).

Procedure

All subjects underwent the same testing procedures, completed in one testing session in the Exercise Physiology Lab at British Columbia Children's Hospital. Each subject signed a consent form, completed the Physical Activity Readiness Questionnaire (PAR-Q), as well as a medical/menstrual/physical activity history questionnaire. Height and weight were measured, as well as standard spirometry (EasyOne™ Diagnostic Spirometer, Model 2001, ndd Medical Technologies, Chelmsford, MA) according to American Thoracic Society guidelines (37; 41). Perceived Functional Ability and Physical Activity Rating questionnaires, as published by George et al. (12) were completed by the subjects to estimate their VO_{2max} before the test. This

result was used in conjunction with their answers to the physical activity questionnaire, to determine whether to start the subject at 50W or 110W for the exercise test.

To accomplish our objectives, we measured Q using echocardiography-Doppler. IPAVS was determined using contrast echocardiography to detect the appearance of injected saline bubbles in the left ventricle. This method is similar to that performed by Eldridge et al. (10). A highly-skilled pediatric echocardiographer performed all of the echocardiography and Doppler measurements using a Vivid7 ultrasound machine (GE Vingmed Ultrasound AS, Horten, Norway). Presence or absence of a PFO was assessed by visualizing the interatrial septum by 2D echocardiography and using color-flow Doppler to ensure an intact interatrial septum. Spectral Doppler was then used to confirm the presence of a PFO. Heart rate was measured via three-lead electrocardiography (ECG). Arterial oxygen saturation was measured from the index finger continuously via pulse oximetry (Model 920M Plus, Respironics Georgia, Inc., Kennesaw, GA). Absence of a PAVM was determined by observing peripheral oxygen saturation (SpO_2). Subjects did not have an SpO_2 of 95% or lower at rest, and they did not experience a significant drop in SpO_2 during exercise. Blood pressure was measured from the left arm by auscultation. Diastolic blood pressure (DBP) was defined by the muffling of the Korotkoff sounds (phase IV unless the diastolic pressure was heard to zero when phase V was used). After the images were obtained, an experienced pediatric cardiologist reviewed them offline using EchoPac™ 6.2 (GE Medical Systems, Milwaukee, WI) software to determine the presence or absence of IPAVS.

Exercise Protocol

The exercise protocol was a progressive, incremental maximal exercise test on an electronically-breaked semi-supine cycle ergometer (Angio Ergometer and Echo Cardiac Stress Table, Lode BV, Groningen, The Netherlands). In this position, the subject's trunk was elevated to a 45º angle with the heart approximately 15 cm above the level of the crank axis of the ergometer. Subjects started at 50W or 110W, increasing by 30W every three minutes until they reached volitional fatigue and were no longer able to maintain a cadence of 60 rpm. During the exercise protocol, subjects breathed through a low-resistance two-way nonrebreathing valve (Hans Rudolph, Inc., Kansas City, MO). Using a MOXUS Modular VO_2 System (AEI Technologies Inc., Naperville, IL), expired gases were analyzed by oxygen and carbon dioxide analyzers (Model S-3A and CD-3A, respectively, AEI Technologies, Inc., Naperville, IL). The system was calibrated before each test with standard gases of known oxygen (20.93% and

15.00%) and carbon dioxide (0.03% and 5.02%) concentrations. The pneumotach was calibrated and verified using a 3-litre syringe (Hans Rudolph, Inc., Kansas City, MO). Echocardiography measurements were taken at rest, during each exercise stage, immediately post-exercise, and three minutes post-exercise. During each exercise stage, imaging started one minute into the stage and bubbles were injected approximately two minutes into the stage. Heart rate, SpO_2 and blood pressure were also recorded at the same time points, as was the rate of perceived exertion (4) for the subjects' legs and breathing.

Contrast Echocardiography

A physician placed a 20-gauge intravenous catheter containing saline solution in the cephalic vein at either the wrist or the antecubital fossa of each subject. A three-way stop-cock was attached, as well as two 10 ml syringes attached to the other two ports. One syringe contained 1 ml of air and the other syringe contained 4 ml of saline. To create the contrast bubbles, the saline solution was flushed from one syringe to another. Immediately following agitation, the saline bubbles were injected and an apical four-chamber view of the heart obtained, showing the presence or absence of the contrast bubbles in the heart chambers. Immediately following injection, contrast bubbles were visible in the right side of the heart.

The timing and appearance of bubbles in the left side of the heart provides important anatomical information (10). In the presence of an atrial septal defect, bubbles will appear in the left side of the heart almost immediately, after one or two heart cycles (15). If the bubbles appear in the left side of the heart after at least three cardiac cycles, an IPAVS is thought to be present (15). This technique is advantageous because it can be used during heavy exercise and can be performed repeatedly within the same exercise test. Pulmonary artery pressure was not assessed during exercise due to the technical difficulties of obtaining tricuspid regurgitation velocity jets while patients are moving.

Echocardiography – Doppler

The pediatric echocardiographer performed the stress echocardiogram using the Vivid 7 System. An M4S transducer (GE Vingmed Ultrasound AS, Horten, Norway) was used for all subjects. An M-mode echocardiogram was performed in the parasternal short axis view to measure the dimensions of the left ventricle at end-systole and end-diastole (LVIDs, LVIDd) and the posterior wall thickness at end-systole (LVPWs). Left ventricular dimensions were indexed

to body surface area (BSA). The diameter of the aortic annulus was measured at the valve using a parasternal long axis view. A left ventricular outflow tract (LVOT) Doppler tracing was done with the sample volume placed at the valve tips from an apical four-chamber view and peak LVOT velocity (LVOT V), the velocity-time integral (VTI), and ejection time (LVOT Env.Ti) were obtained and recorded. Mitral valve early inflow velocities (MV(E)) were obtained from an apical four-chamber view with the sample volume at the tips of the mitral valve leaflets. Tissue Doppler velocities (E') from the basal lateral left ventricular wall, the basal interventricular septum, and the basal right ventricular free wall were obtained from an apical four-chamber view and analyzed off-line using the EchoPac™ 6.2 software. Apical two-chamber and apical long-axis views were also obtained to assess wall motion and was later interpreted by the pediatric cardiologist.

Total work, fractional shortening (FS), rate-corrected mean velocity of circumferential fiber shortening (MVCFc), wall stress at peak systole (σPS), cardiac index (CI), and left ventricular (LV) E/E' were calculated. Heart rate was determined from the R-R interval of the ECG.

Calculations

Work

Total Work ($J \cdot kg^{-1}$) = ($Time_1$ x $Work_1$)/Weight + ($Time_2$ x $Work_2$)/Weight + ($Time_3$ x $Work_3$)/Weight + …

Where $Time_1$ = Time at stage 1(in sec)

$Work_1$ = Work at stage (in Watts)

Contractility

$$FS = \frac{LVIDd - LVIDs}{LVIDd} \times 100\%$$

The following formulas were used to calculate MVCFc and σPS:

$$MVCFc\ (circ/s) = \frac{LVIDd - LVIDs}{(LVOT\ Env.Ti.\ corrected \times LVIDd)}$$

where: LVOT Env.Ti. corrected = LVOT $\frac{\text{Env.Ti. (in sec)}}{\sqrt{\text{R-R interval}}}$

$$\sigma PS\ (g/cm^2) = \frac{SBP \times LVIDs \times 1.36}{4 \times LVPWs\ (1+(LVPWs/LVIDs))}$$

where: 1 mmHg=1333 Dynes/cm^2 =1.36 gm/cm^2

and SBP = systolic blood pressure

Hemodynamics

Stroke volume (SV) was determined from the Doppler signal using the VTI and aortic cross-sectional area (π x aortic diameter^2/4). Cardiac output was calculated as the product of SV and heart rate (HR). Both SV and Q were indexed (cardiac index=CI and stroke volume index=SI) to BSA.

LV E/E' was determined by using the mitral valve E velocities divided by the tissue Doppler E' velocities from the lateral wall and interventricular septum.

Mean arterial pressure (MAP) was calculated as DBP + ⅓ (SBP-DBP).

Data Analysis

Descriptive and physiological data are presented as means ± standard deviations (SD). A one by three way ANOVA was performed on subject characteristics, pulmonary function, expired gases and ventilatory data at peak exercise, cardiovascular data at peak exercise and submaximal exercise, and physiologic data at shunt onset, to determine if group differences existed. If p was < 0.05, a Tukey's post-hoc test was performed to determine which groups were significantly different. To determine if an IPAVS was present, once the injected saline bubbles were visible in the right side of the heart, heart cycles were counted until the saline bubbles were present in the left side of the heart. If saline bubbles were present in the left side of the heart after three or more cardiac cycles, IPAVS was occurring. Thus, shunt recruitment in each group was either a "yes" shunting occurred or "no" shunting did not occur. If shunting did occur during exercise, the stage of exercise was noted. The measurement of shunt is not continuous and shunt

itself is a dichotomous variable, therefore, statistical analysis is limited and mainly qualitative in nature (48). Data was analyzed using STATISTICA 7.0 software (StatSoft, Inc., Tulsa, OK).

RESULTS

Subjects

All subjects had normal resting pulmonary function and blood pressure (range: SBP = 116-121, DBP = 79-83), were free of any history or symptoms of cardiopulmonary disease (including exercise-induced asthma), and did not have a PFO or PAVM. Subject characteristics are shown in Table 1. There was no significant difference in age (p=0.81), height (p=0.34), weight (p=0.42), body-max index (BMI) (p=0.34), and BSA (p=0.50) between the UT, MT and HT groups.

Table 1. Subject Characteristics

	Training Category		
	UT (N=8)	MT (N=6)	HT (N=10)
Age, years	25.6 ± 3.6	26.7 ± 4.7	27.2 ± 6.1
Height, cm	163.0 ± 2.7	166.0 ± 2.8	165.4 ± 5.5
Weight, kg	58.3 ± 6.5	61.1 ± 9.1	56.5 ± 4.6
BMI, kg/m^2	22.0 ± 2.3	22.2 ± 3.6	20.6 ± 1.2
BSA, m^2	1.62 ± 0.10	1.67 ± 0.12	1.61 ± 0.09

Values are means ± SD.
For definitions of abbreviations see text above.

Pulmonary Function

Pulmonary function data are shown in Table 2. Forced vital capacity (FVC) was normal for each group, ranging from 3.9-4.3 litres and there was no difference found between the groups (p=0.30). Maximal voluntary ventilation (MVV) was normal ranging from 115-131 litres/min and there was no difference between the groups (p=0.23). There was a small, but significant difference in forced expiratory volume in one second (FEV_1), with the UT group being significantly lower than the MT and HT groups (p=0.02). However, when expressed as the ratio of FEV_1/FVC all groups were above 80%, thus, considered to have normal pulmonary function. There was no difference in FEV_1/FVC between the groups (p=0.31).

Table 2. Pulmonary Function

	Training Category		
	UT (N=8)	MT (N=6)	HT (N=10)
FVC, litres	3.9 ± 0.4	4.3 ± 0.4	4.1 ± 0.5
FVC % Predicted	106.1 ± 9.3	110.7 ±9.0	106.3 ± 9.9
FEV_1, litres	3.1 ± 0.4	3.6 ± 0.2*	3.5 ± 0.3*
FEV_1 % Predicted	99.6 ± 9.9	107.3 ± 4.8	106.9 ± 6.2
MVV, litres/min	114.9 ± 24.7	130.8 ± 17.2	130.1 ± 17.2
MVV % Predicted	100.2 ± 20.2	112.2 ± 15.4	112.8 ±16.4
FEV_1/FVC	81.0 ± 6.7	82.6 ± 3.4	86.2 ± 7.5

Values are means ± SD. *Statistically significantly different from the UT group.
For definitions of abbreviations see text above.

Cardio-respiratory Responses to Exercise

Expired gases and ventilatory data at peak exercise are shown in Table 3. Peak oxygen uptake (VO_{2peak}) values for each group were significantly different from each other ($p < 0.01$). Absolute VO_{2peak} and carbon dioxide production (VCO_2) in the UT group were significantly less than the MT and HT groups ($p < 0.01$). Minute ventilation (V_E) in the UT group was significantly less than the MT and HT groups ($p=0.01$). V_E/VO_2 ($p=0.41$) and V_E/VCO_2 ($p=0.36$) for each group were not different. Tidal volume (V_t) ($p=0.44$), respiratory exchange ratio (RER) ($p=0.11$), and saturation of peripheral oxygen (SpO_2) ($p=0.06$) were not different between the groups. Breathing frequency (F_b) was significantly lower in the UT group compared to the HT group ($p=0.02$). Power in the UT group was significantly lower than in the MT and HT groups ($p < 0.01$). Only five out of the 24 subjects reached an RER ≥ 1.1, therefore, ventilatory thresholds were not calculated.

Table 3. Expired Gases and Ventilatory Data at Peak Exercise

	Training Category		
	UT (N=8)	MT (N=6)	HT (N=10)
VO_{2peak}, ml/kg/min	35 ± 5†	43 ± 1†	50 ± 3†
VO_{2peak} , litres/min	2.0 ± 0.3	2.5 ± 0.3*	2.7 ± 0.2*
VCO_2, litres/min	2.0 ± 0.3	2.7 ± 0.4*	2.9 ± 0.3*
V_E, litres/min	80.0 ± 18.2	103.8 ± 10.3*	105.2 ± 19.0*
V_E/VO_2	39.8 ± 2.3	41.7 ± 5.0	38.1 ± 4.0
V_E/VCO_2	40.9 ± 10.1	38.6 ± 4.9	36.2 ± 3.5
V_t, litres	1.8 ± 0.3	1.9 ± 0.2	1.8 ± 0.2
F_b, breaths/min	46 ± 7	55 ± 9	60 ± 12*
SpO_2, %	97 ± 1	97 ± 2	96 ± 2
RER	0.99 ± 0.10	1.09 ± 0.12	1.05 ± 0.03
Power, watts	151 ± 22	200 ± 27*	212 ± 21*

Values are means ± SD. *Statistically significantly different from the UT group. †Statistically significantly different from all other groups. For definitions of abbreviations see text above.

Cardiovascular data at peak exercise are shown in Table 4. Heart rate (p=0.21), Q (p=0.43), SV (p= 0.88), SBP (p=0.53), DBP (p=0.43), and MAP (p=0.41) were not different between any of the groups.

Table 4. Cardiovascular Data at Peak Exercise

	Training Category		
	UT (N=8)	MT (N=6)	HT (N=10)
HR (beats/min)	169 ± 17	178 ± 9	179 ± 8
Q (litres/min)	11.2 ± 1.5	11.5 ± 1.5	12.2 ± 1.8
SV (ml)	67.0 ± 13.2	65.2 ± 9.7	67.9 ± 9.2
SBP (mmHg)	168.5 ± 13.6	178.3 ± 23.7	168.1 ± 18.7
DBP (mmHg)	91.3 ± 7.5	90.5 ± 8.7	86.1 ± 9.9
MAP (mmHg)	117 ± 7.9	119.8 ± 10.9	113.4 ± 9.1

Values are means ± SD.

For definitions of abbreviations see text above.

Doppler Measurements

Doppler measurements at submaximal exercise (Stage 3) are presented in Table 5. Stage 3 was chosen as it was the highest submaximal stage with the most complete data set. LVIDd (p=0.25), LVIDs (p=0.27), LVPWs (p=0.21), LVOT V (p=0.56), LVOT VTI (p=0.47), LVOT Env. Ti. (p=0.16), MV(E) (p=0.11), MVCFc (p=0.86), FS (p=0.76), CI (p=0.50), and SI (p=0.36) were not different between the groups. The σPS was significantly lower in the UT group compared to the HT trained group (p=0.03). E/E' was difficult to obtain during exercise due to the increased artefact and high noise-to-signal ratio. Values are not reported as we could only obtain data in less than 50% of the subjects.

Table 5. Doppler Measurements at Submaximal Exercise (Stage 3)

	UT	N	MT	N	HT	N
LVIDd, cm	4.31 ± 0.39	7/8	4.42 ± 0.26	6/6	4.65 ± 0.49	10/10
LVIDs, cm	2.39 ± 0.36	7/8	2.45 ± 0.29	6/6	2.64 ± 0.32	10/10
LVPWs, cm	1.19 ± 0.07	7/8	1.18 ± 0.06	6/6	1.13 ± 0.07	10/10
LVOT V, m/s	1.66 ± 0.26	7/8	1.50 ± 0.25	6/6	1.79 ± 0.29	10/10
LVOT VTI, cm	25.22 ± 3.33	7/8	23.23 ± 2.53	6/6	24.19 ± 3.26	10/10
LVOT Env.Ti, ms	202.57 ± 23.80	7/8	184.67 ± 16.32	6/6	186.5 ± 15.34	10/10
MV(E), m/s	1.37 ± 0.19	7/8	1.53 ± 0.23	6/6	1.6 ± 0.22	10/10
MVCFc, circ/s	1.39 ± 0.25	7/8	1.44 ± 0.16	6/6	1.42 ± 0.12	10/10
σPS, g/cm^2	72.64 ± 9.23	7/8	90.97 ± 12.45	5/6	89.78 ± 15.77*	10/10
FS %	44.78 ± 5.97	7/8	44.58 ± 5.24	6/6	43.27 ± 2.55	10/10
CI, litres/min/m^2	6.76 ± 0.68	8/8	6.76 ± 0.60	6/6	7.29 ± 1.44	10/10
SI, ml/m^2	43.04 ± 5.19	7/8	40.12 ± 4.80	6/6	44.96 ± 7.80	10/10
E/E'	Insufficient Data	3/8	Insufficient Data	2/6	Insufficient Data	4/10

Values are means ± SD. *Statistically significantly different than the UT group.
For definitions of abbreviations see text above.

Doppler measurements at peak exercise are displayed in Table 6. LVIDd (p=0.46), LVIDs (p=0.34), LVPWs (p=0.31), LVOT V (p=0.18), LVOT VTI (p=0.69), LVOT Env. Ti. (p=0.73), MVCFc (p=0.30), σPS (p=0.12), FS (p=0.34), CI (p=0.16), and SI (p=0.28) were not different between the groups. MV(E) was statistically significantly lower in the UT group compared to the HT group (p=0.03). E/E' was difficult to obtain during exercise due to the increased artefact and high noise-to- signal ratio. Values are not reported as we could only obtain data in less than 50% of the subjects.

Table 6. Doppler Measurements at Peak Exercise

	UT	N	MT	N	HT	N
LVIDd, cm	4.2 ± 0.41	5/8	4.40 ± 0.25	5/6	4.44 ± 0.36	9/10
LVIDs, cm	2.18 ± 0.42	5/8	2.48 ± 0.31	5/6	2.46 ± 0.35	9/10
LVPWs, cm	1.2 ± 0.07	5/8	1.21 ± 0.10	5/6	1.15 ± 0.05	8/10
LVOT V, m/s	1.69 ± 0.23	7/8	1.64 ± 0.27	5/6	1.86 ± 0.19	8/10
LVOT VTI, cm	22.87 ± 4.31	7/8	22.36 ± 2.42	5/6	23.91 ± 2.75	8/10
LVOT Env.Ti, ms	176.43 ± 20.52	7/8	178.8 ± 11.28	5/6	172.25 ± 10.42	8/10
MV(E), m/s	1.38 ± 0.16	7/8	1.54 ± 0.21	5/6	1.68 ± 0.22*	9/10
MVCFc, circ/s	1.65 ± 0.27	5/8	1.44 ± 0.17	5/6	1.56 ± 0.18	7/10
σPS, g/cm^2	74.82 ± 11.82	2/8	95.76 ± 2.81	3/6	85.01 ± 11.24	5/10
FS %	48.36 ± 5.71	5/8	43.72 ± 5.48	5/6	44.90 ± 4.48	9/10
CI, litres/min/m^2	6.86 ± 0.60	8/8	6.91 ± 0.71	6/6	7.56 ± 0.97	10/10
SI, ml/m^2	40.69 ± 7.11	7/8	38.16 ± 3.82	5/6	43.32 ± 4.55	8/10
E/E'	Insufficient Data	2/8	Insufficient Data	2/6	Insufficient Data	1/10

Values are means ± SD. *Statistically significantly different than the UT group.
For definitions of abbreviations see text above.

Intrapulmonary Arteriovenous Shunt

Shunt onset is characterized for each subject in Table 7.

Table 7. Characterizing Shunt Onset for Each Subject

Training Category	% Max Power Shunt Onset	$\%VO_{2peak}$ Shunt Onset	Exercise Stage Shunt Onset	Q (litres/min) Shunt Onset
UT – 5	No shunt	No shunt	No shunt	No shunt
UT – 6	36	42	Stage 1	10.9
UT – 7	45	57	Stage 1	6.4
UT - 10	0	8	Resting	3.5
UT - 13	29	45	Stage 1	9.6
UT - 14	82	81	Stage 2	10.2
UT - 15	29	47	Stage 1	7.2
UT - 19	0	9	Resting	4.2
MT - 3	85	98	Stage 3	11.8
MT - 12	0	9	Resting	2.9
MT - 17	0	7	Resting	3.5
MT - 23	82	85	Stage 2	8.3
MT - 27	55	60	Stage 1	10.9
MT - 29	48	55	Stage 1	9.4
HT – 2	70	82	Stage 2	7.6
HT – 4	74	71	Stage 3	16.4
HT – 8	48	46	Stage 1	12.4
HT – 9	55	52	Stage 1	10.5
HT - 11	55	55	Stage 1	7.3
HT - 18	29	42	Stage 1	6.4
HT - 22	87	90	Stage 4	10.0
HT - 24	61	74	Stage 2	12.0
HT - 25	55	60	Stage 1	10.2
HT - 26	61	59	Stage 2	12.6

Characterizing shunt onset for each group is displayed in Table 8. Percent of max power at shunt onset was not significantly different between the groups (p=0.13). The % of VO_{2peak} at which shunting began to occur was not significantly different between the groups (p=0.26). Cardiac output was not significantly different between the groups (p=0.06). Majority of the subjects began to shunt during stage one of exercise.

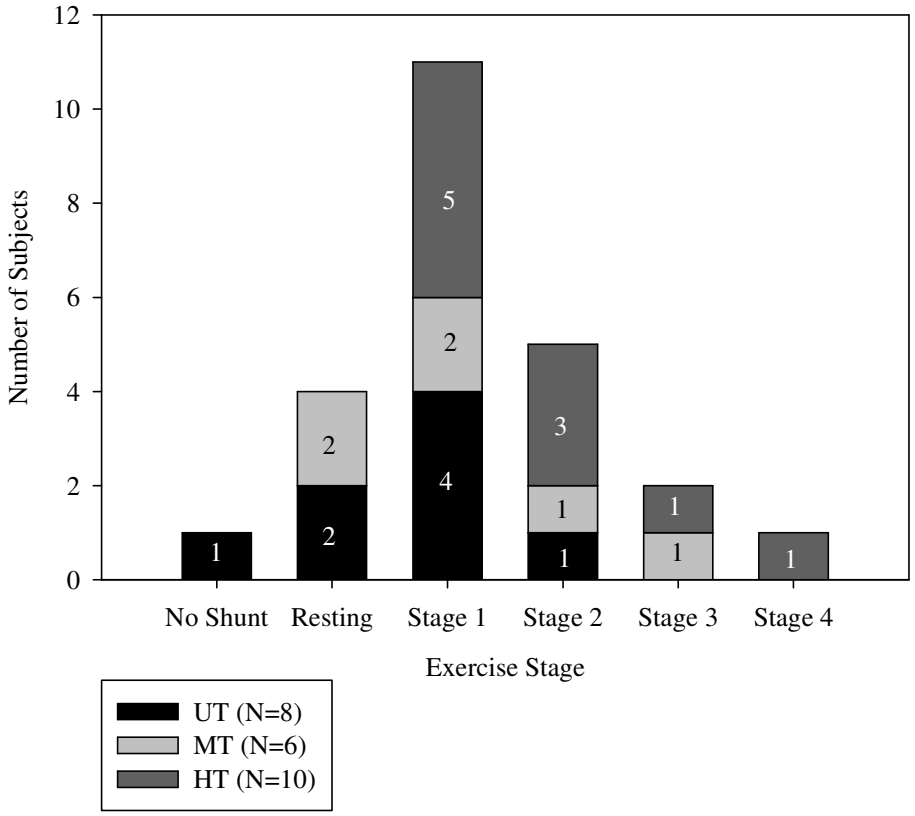
Table 8. Characterizing Shunt Onset for Each Group

	UT (N=8)	MT (N=6)	HT (N=10)
% Max Power at Shunt Onset	32 ± 28 (0-82)	45 ± 38 (0-85)	60 ± 16 (29-87)
% VO_{2peak} at Shunt Onset	41 ± 26 (8-81)	52 ± 38 (7-98)	63 ± 16 (42-90)
Q (litres/min) at Shunt Onset	6.5 ± 3.8 (3.5-12.7)	7.8 ± 3.8 (2.9-11.8)	10.5 ± 3.0 (6.4-16.4)
Stage with Highest Frequency at Shunt Onset	Stage 1	Resting/Stage 1	Stage 1

Values are means ± SD. Values in parentheses are ranges.
For definitions of abbreviations see text above.

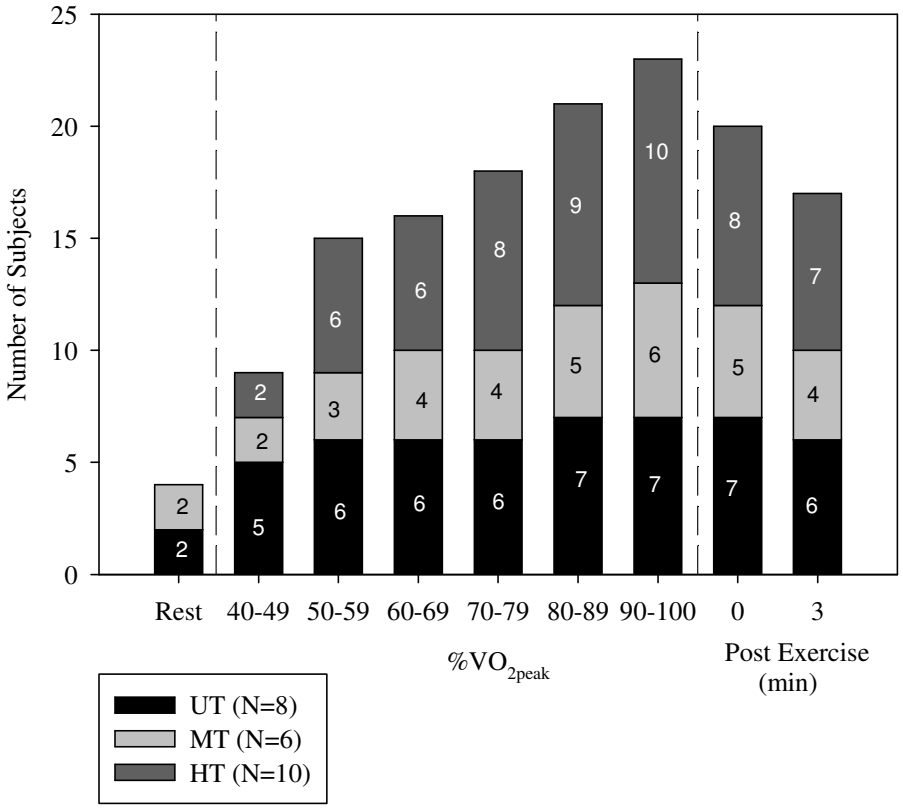
Onset of shunting for each group is displayed in Figure 1. One subject in the UT group did not shunt at all. Two subjects from the UT group and two subjects from the MT group began shunting at rest. Almost half of the remaining subjects started shunting at Stage 1. Five subjects began shunting at Stage 2, while two subjects started shunting at Stage 3 and one subject began shunting at Stage 4.

Figure 1. Onset of Shunt for Each Group



Two subjects from the UT group and two subjects from the MT group started to shunt at rest. Gradually, with increasing exercise intensity more subjects began to shunt and by 90-100% of VO_{2peak} every subject, except for one, demonstrated shunt. Twenty subjects continued to shunt immediately post exercise and 17 subjects continued to shunt three minutes post exercise. Since the subjects were not reaching their true maximum during the exercise test, in the first stage of exercise they were already working around 40% of their VO_{2peak}.

Figure 2. Presence of Shunt in Each Group



Total presence of shunt in all groups combined (n=23) is present in Figure 3. 17% of subjects began shunting at rest and 96% of subjects were shunting by the time they reached 90-100% of VO_{2peak}. Immediately post exercise, 83% were still shunting and by three minutes post exercise 71% were still shunting.

Figure 3. Total Presence of Shunt

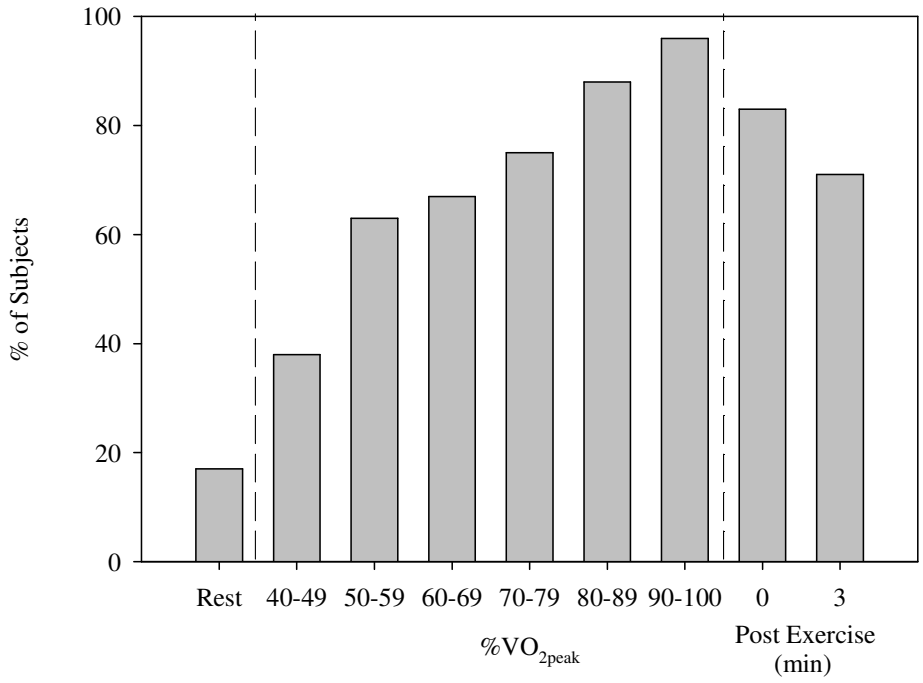


Figure 4 is an apical four-chamber view of subject 17 pre-exercise, and shows the presence of an IPAVS. In the first image, before the saline bubble injection is made, all four chambers of the heart are clear. When the injection is made, the right side of the heart is filled with contrast, as seen in the second image. After the heart has gone through a number of cardiac cycles (more than three), the bubbles are appear in the left side of the heart, depicted in image three.

Figure 4. Apical Four-Chamber View Subject 17 Pre-Exercise

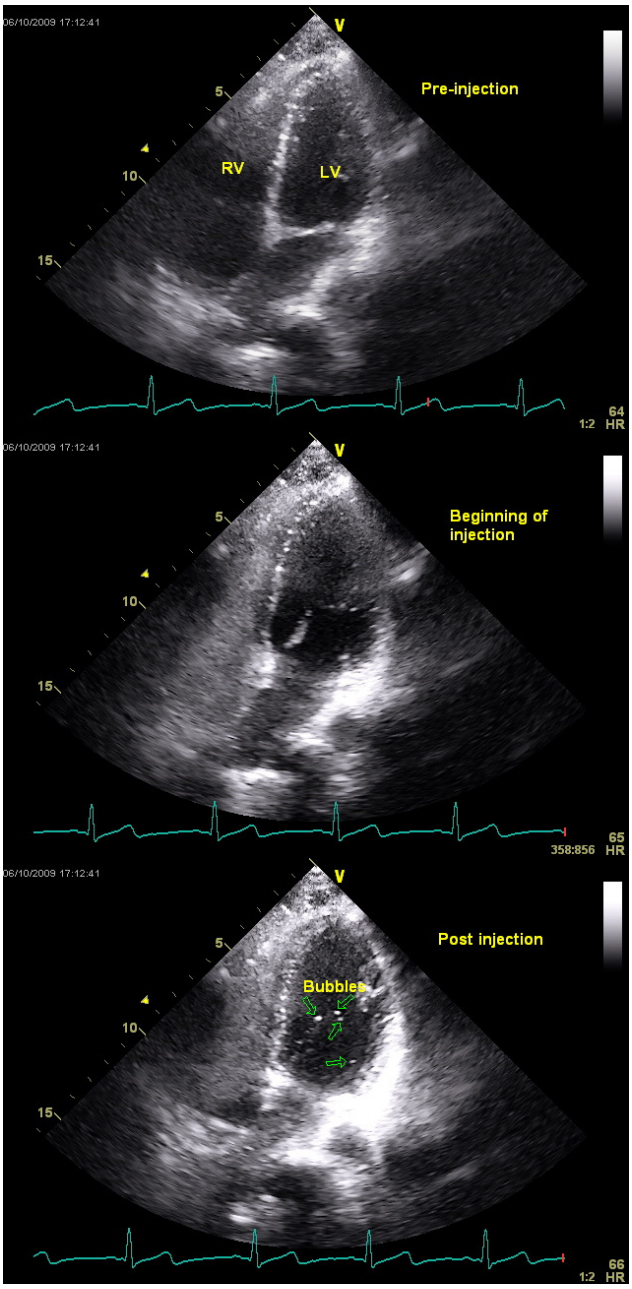


Figure 5 is an apical four-chamber view of subject 11 pre-exercise, during Stage 1 of exercise, and during Stage 2 of exercise. The pre-exercise image demonstrates the absence of bubbles in the left side of the heart, indicating that an IPAVS is not present. The second image taken during Stage 1 of exercise, shows that IPAVS vessels are open as contrast bubbles appear in the left side of the heart after more than three cardiac cycles. The third image taken during Stage 2 of exercise, also shows that IPAVS vessels are open as there are also bubbles in the left side of the heart after more than three cardiac cycles.

Figure 5. Apical Four-Chamber View Subject 11 Pre-Exercise, Stage 1, Stage 2

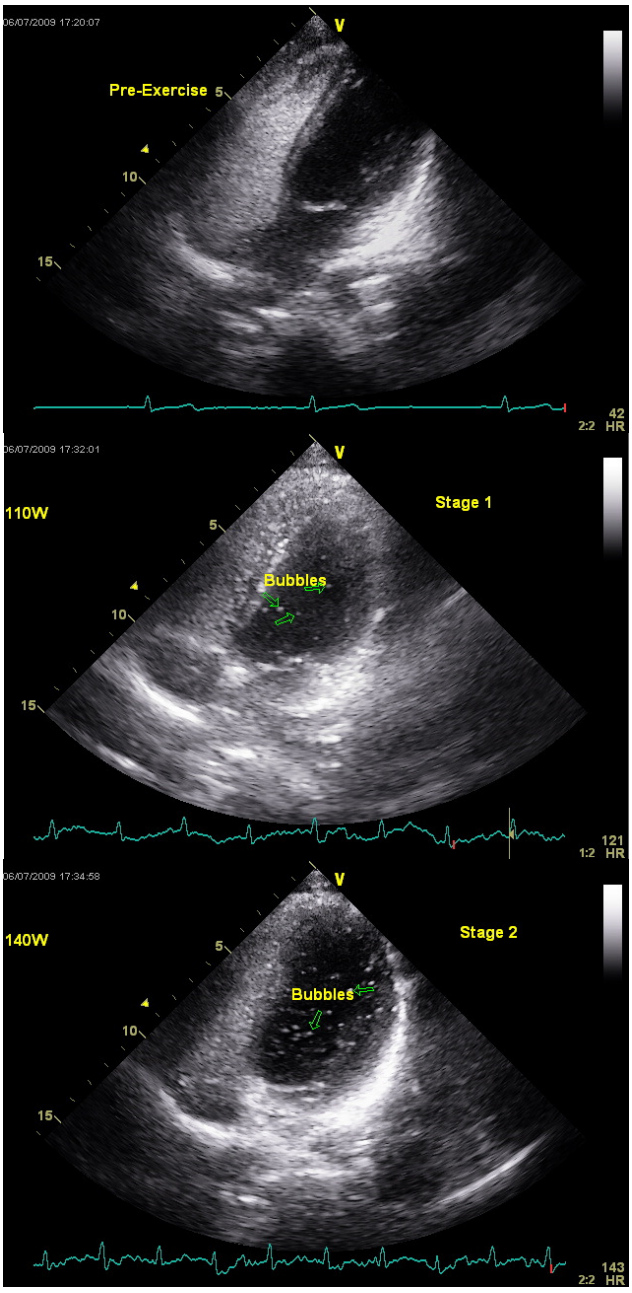
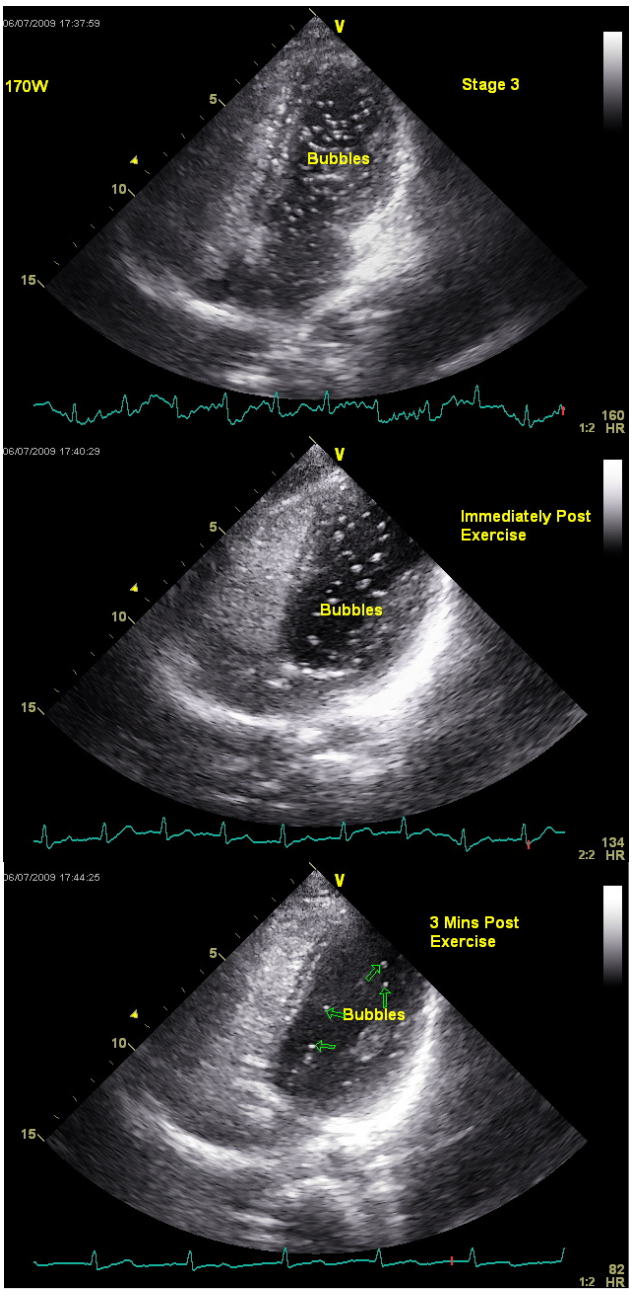


Figure 6 is an apical four-chamber view of subject 11 in Stage 3, immediately post-exercise and three minutes post-exercise. All three images demonstrate that an IPAVS is present as there are contrast bubbles in the left side of the heart after more than three cardiac cycles.

Figure 6. Apical Four-Chamber View Subject 11 Stage 3, Immediately Post, 3 Minutes Post



DISCUSSION

Main Findings

The main findings of this investigation are four-fold. First, four subjects demonstrated shunting under resting conditions and many continued to shunt post-exercise. These observations contrast with other studies where subjects exercised in the upright position, and suggest there may be an effect of body position. Second, the $\%VO_{2peak}$ at shunt onset was not significantly different between the groups and most individuals began shunting during modest levels of exercise intensity. As such, there appears to be no effect of fitness level on shunt onset. Third, Q at peak exercise was highest in the HT group, compared to the MT and UT groups. This difference, however, was not significant and contrary to what we expected to occur. This may be due to body position and the subjects not reaching their true maximum. Lastly, none of the subjects demonstrated EIAH (SpO_2 of 91% or lower) with exercise and the lowest SpO_2 was not significantly different across the groups. This observation suggests that shunt in the semi-supine position does not negatively affect SpO_2. In summary, it appears that IPAVS recruitment can be affected by body position, but not by training status, and does not appear to affect SpO_2.

Shunting Pre- and Post-Exercise

Most studies to-date state that IPAVS vessels are recruited during exercise only, when Q and PAP increase from resting values (10; 30; 50; 51). These studies have been exclusively performed during upright cycling exercise. In the current study, however, subjects exercised in the semi-supine position. Four subjects demonstrated shunt pre-exercise, 20 subjects continued to shunt immediately post-exercise, and 17 subjects continued to shunt three minutes post-exercise. Stickland et al. (51) performed contrast echocardiography in the supine resting position pre-exercise and observed IPAVS in two of eight subjects. When contrast echocardiography was performed again at rest in the upright cycling position, none of these subjects demonstrated IPAVS, indicating an influence of body position. This concept is further supported by preliminary data in subjects seated upright, lying supine, and lying supine with 15º head-down tilt during hypoxia, as more subjects began to shunt when body position changed to supine and supine with head-down tilt (2). Strauss et al. (53) measured IPAVS at rest in the recumbent position through injecting technetium 99m-labelled albumin (^{99m}Tc) microspheres and measuring the radioactivity arriving in a systemic capillary bed. A small amount of shunt (mean of 1.1% ± 1) was found. It was originally understood that shunt vessels do not remain open post-exercise in

normoxia (10). Post-exercise shunting has been demonstrated once previously in normoxia in the upright cycling position by Lovering et al. (29). However, the demonstration of post-exercise shunting is unique to the study by Lovering et al. (29) and the authors do not address this finding in their paper. Post-exercise shunting in our study may be, in part, due to body position, combined with respiratory and cardiovascular variables remaining elevated above resting values post-exercise.

Blood flow in the lung at rest in a standing individual is not uniform due to hydrostatic pressure (17). During standing, blood flow is normally intermittent in the apices and continuous in the lower areas of the lung vasculature. When a person is lying down however, no part of the lung is more than a few centimetres above the level of the heart and blood flow is continuous throughout the entire lung. Tobin and Zariquiey (55) claim that IPAVS vessels are found predominately in the apex of the lung, which would make them more likely to be recruited in the supine position, further supported by the findings of Bates et al. (2) and Stickland et al. (51).

Percent of VO_{2peak} at Shunt Onset

The percent of VO_{2peak} at shunt onset was not significantly different between the groups and most individuals began shunting in Stage 1 of exercise. Shunt onset occurred at 39 ± 30% of VO_{2peak} for the UT group, 50 ± 42% of VO_{2peak} for the MT group, and 63 ± 16% of VO_{2peak} for the HT group. The observed range of $\%VO_{2peak}$ at shunt onset was large, indicating that fitness level is not associated with shunt onset in women during semi-supine exercise. The women (n=10) studied by Eldridge et al. (10), who were comparable in fitness to the MT women in the current study, began shunting at 56 ± 23% of VO_{2max} during upright cycling. This difference may be due to the subjects in the current study not reaching their true maximum on the exercise test in the semi-supine position. Subjects were working at modest workloads when shunting began with the UT group beginning to shunt 49 ± 47W, the MT group beginning to shunt at 88 ± 72W, and the HT group beginning to shunt at 128 ± 40W. Power output at shunt onset was significantly higher in the HT group compared to the UT group, but when expressed as a percent of maximum power output this difference disappeared. Thus each subject, regardless of training status, appeared to start shunting at similar relative workloads, another indication that fitness level does not predict shunt onset.

Cardiac Output

Cardiac output during peak treadmill exercise in young women ranges from 13 - 20 litres/min in UT to HT women respectively (38). In the current study, Q at peak exercise was lower in each group, ranging from 9.42 – 14.63 litres/min for UT to HT subjects respectively. Cycling in the semi-supine position is not an activity that people generally participate in regularly, thus, it requires different muscle recruitment than one is accustomed to. In the semi-supine position, subjects are not able to pedal with the assistance of gravity and body weight to help them push through the resistance as it increases throughout the exercise test, resulting in lower maximum values. The HT group was able to reach a higher average Q at peak exercise when compared to the UT and MT groups however, this difference was not significant. Despite that, Q for each group was low, 23 of the 24 subjects tested demonstrated shunt, unlike the men tested by Stickland et al. (51) who reached a minimum Q of 24 litres/min before beginning to shunt. Cardiac output is the product of SV and HR, both of which are also affected by body position. It was hypothesized that the HT subjects would exhibit a higher Q due to an increased SV compared to the UT subjects, as has been shown previously in upright cycle exercise. Stroke volume at peak upright exercise in young women is typically 68 – 114 ml for UT to HT individuals respectively (38). In the current thesis, SV at peak exercise was below 70 ml for all groups and there was no significant difference between the groups. Typically, during maximal exercise, endurance athletes will exhibit a continual increase in SV while UT individuals will show a SV plateau at 40-50% of VO_{2max} (33). The rate of ventricular filling in trained individuals can be 86% greater than the rate of ventricular emptying contributing to the continual increase in SV (14). In general, SV in the supine position is typically higher when compared to upright exercise (42); Left ventricular end-diastolic volume increases in the supine position, as the role of gravity is reduced increasing venous return, reducing the pooling of blood in the legs, increasing preload. Perhaps all subjects experienced enhanced preload due to their body position, not just the highly trained individuals as is normally the case during upright exercise. There was no difference in peak HR between the groups and peak HR was not as high as the HR during treadmill exercise in the study by Ogawa et al. (38). This difference may also be due to the increased venous return demonstrated while cycling in the semi-supine position (6). No difference in SV or HR between groups coincides with no difference in Q between the groups. If increasing Q with exercise is a reason for IPAVS recruitment, perhaps Q plays less of a role in the semi-supine position.

EIAH and Shunt

If IPAVS is related to gas exchange inefficiencies, it would be plausible that individuals who display an IPAVS would be more likely to experience EIAH, especially in HT subjects. Many HT endurance athletes experience a decrease in the partial pressure of oxygen in arterial blood, resulting in an increased A-aDO_2 with exercise, leading to EIAH. Only a small fraction of Q as shunt may be enough to contribute to this increase in A-aDO_2 with exercise. Gavin and Stager (11) documented that treadmill running resulted in lower SaO_2 values when compared to upright cycle ergometry, due to a higher V_E during cycling exercise. Pedersen et al. (40) concluded that there was no difference in arterial oxygen desaturation in elite cyclists during intense cycle exercise in the upright or supine positions. However, none of the subjects in the current study experienced a notable drop in SpO_2 of 91% or lower (43) and there was no significant difference in the lowest SpO_2 value reached between the groups. The mean drop in saturation from resting to peak exercise reached an average of 3.2 in the HT group, 2.2 in the MT group, and 1.9 in the UT group. Thus, an IPAVS in the semi-supine position does not appear to affect SpO_2.

Doppler Measurements

Additional Doppler measurements were collected to document these values in women during exercise, as published values are limited. These values were not measured to determine their relationship to IPAVS, thus they are not discussed in detail. There was no significant difference between the groups on any of these variables during exercise, except for σPS and MV(E). Peak systolic wall stress in the HT group was significantly higher than in the UT group during submaximal exercise. At peak exercise, mitral valve inflow velocity, was significantly higher in the HT group than in the UT group.

Methodological Considerations

Limitations to Contrast Echocardiography

Contrast echocardiography is a standard technique to image the heart, however, obtaining images during exercise can be difficult due to upper body movement and is echocardiographer-dependent. The subjects in this study were women, thus presenting anatomic constraints in the use of echocardiography. To reduce the imaging difficulty due to exercise and anatomy, subjects exercised on a semi-supine cycle ergometer, and the same experienced echocardiographer performed the imaging for each test.

Contrast echocardiography does not provide a continuous measure of shunt nor does it quantify shunt. It only shows the presence or absence of shunt at certain points in time, but it can be used repeatedly throughout an exercise test. The use of echocardiography has been critiqued due to the inability to follow the path of these saline bubbles to ensure that they are, in-fact, passing through IPAVS and not through dilated pulmonary capillaries (10). However, based on evidence of the size, properties and behaviour of pulmonary vessels and saline contrast bubbles, we can assume this measurement is valid (10). During exercise, when vascular flows and pressures are increased, contrast bubble survival times are likely less than at rest. According to Warren et al. (59), mean pulmonary capillary transit time is approximately 750 ms at rest and decreases during exercise. They estimate that mean pulmonary transit time does not fall below 450 ms even in well-trained athletes at maximal exercise. If this is the case, contrast bubbles 8µm in diameter, small enough to pass through pulmonary microcirculation, would have a life span of < 200ms, not surviving long enough to traverse the pulmonary capillaries (36). True pulmonary transit time measures, however, are not possible in humans. Hopkins et al. (21) performed radionuclide angiography using ^{99m}Tc, and estimated pulmonary transit times based on calculations from the first pass time-activity curves at rest and at maximal exercise in HT endurance athletes. They demonstrated that pulmonary transit times dropped from 9.32 ± 1.41 seconds at rest to 2.91 ± 0.30 seconds during exercise, values that are much higher than those published by Warren et al. (59). Thus, measurements of pulmonary transit time vary considerably as they are not direct in nature, and interpretation of these values must be made with caution. Saline contrast bubbles are typically 60-90µm in diameter, making them too big to pass through pulmonary capillaries (less than 10µm in diameter), even if they survived long enough to pass through (10; 15). Another critique criticism of the method is that the bubbles may be forced through the pulmonary microcirculation. However, this is unlikely because, in humans performing maximal exercise, pulmonary vascular driving pressures remain relatively low, never exceeding 20 mmHg (45). With these low driving pressures, trapped contrast bubbles cannot be forced through pulmonary microcirculation even during high intensity exercise. Finally, the theory that the pulmonary capillaries can distend enough to allow the passage of saline bubbles is refuted by the fact that pulmonary capillary distension does not exceed 20µm, thus, the saline bubbles are unable to pass through (60). Despite the challenges noted above, results from the use of contrast echocardiography have been shown to be reproducible within subjects, therefore, this technique is reliable (10).

Limitations of the Exercise Protocol and Cycle Ergometer

Subjects completed the VO_{2max} test once, thus choosing the correct protocol was difficult in some cases. The prediction equation (12) used was based on running, resulting in some participants unsure how to score themselves because they did not participate in regular run training. Subjects who scored a high predicted VO_{2max} according to the prediction equation, and who stated they currently cycled or cycled in the more recent past at a moderate intensity or higher, and/or weight trained, started the exercise test at 110W. This method was successful in most cases, only a couple of circumstances existed where choosing the other protocol would have been better, resulting in the subject exercising for a more appropriate length of time.

Cycling in the semi-supine position is unnatural for most individuals. This position makes it impossible for the subject to use gravity or their body weight to help them cycle. An RER $\geq$ 1.1 indicates excess carbon dioxide production from buffering lactate and, hence, an increase in pulmonary ventilation, which occurs with high intensity exercise. One criterion for a VO_{2max} test is that RER is $\geq$ 1.1. Average RER for each group in this study was not $\geq$ 1.1, thus, one can assume that leg fatigue was the limiting factor, not the cardio-respiratory system. The demand of Q to the working muscles did not exceed the capacity of the respiratory system in the current study, thus EIAH did not occur. When VO_2 at each exercise stage was expressed as a percent of VO_{2peak}, subjects were working at higher percentages of their peak earlier in the exercise test because their peak was lower. This created some difficulties when interpreting the data. However, all subjects encountered the same difficulties during the exercise test, thus the comparison between groups is valid.

Limitations of Viewing the Contrast Images Offline

An experienced cardiologist viewed the images offline to determine whether or not an IPAVS was occurring. However, the images were not presented in a blinded fashion. The contrast of the images was sometimes dull, making distinguishing structures difficult. As some individuals breathed, their lungs slid over the image obstructing the heart. The contrast of the images and the movement of the lungs made the determination of bubbles in the left side of the heart difficult in some subjects. Despite these difficulties, care was taken to ensure the data obtained from these images was valid and interpreted in the best way possible given the circumstances.

Conclusion

The results from this study indicate that an IPAVS is present in a majority of healthy, young, women and shunt vessels can be recruited at rest in the semi-supine position. This is interpreted to occur because blood flow is redirected apically in the lung in this position. Fitness level does not appear to result in earlier shunt onset in HT individuals, perhaps in part due to the HT group not reaching significantly higher Q. The demand of Q to the working muscles did not exceed the capacity of the respiratory system in the semi-supine position, thus an IPAVS in the semi-supine position does not appear to affect EIAH in women. While the exact behaviour of IPAVS vessels remains unclear, these findings bring us a step closer to a more complete understanding of an IPAVS and its properties.

REFERENCE LIST

1. **Astrand PO and Saltin B**. Maximal oxygen uptake and heart rate in various types of muscular activity. *J Appl Physiol* 16: 977-981, 1961.

2. Bates, M. L., Schrage, W. G., and Eldridge, M. W. Intrapulmonary Shunt Vessels are Recruited with Hypoxia and Postural Changes. International Hypoxia Symposia. 2009. Ref Type: Conference Proceeding

3. **Beasley KM**. *Image Analysis and Segmentation in Adobe Photoshop for Quantification of Intrapulmonary Arteriovenous Shunting at Various Levels of Acute Hypoxic Exposure* (Dissertation). 2009.

4. **Borg G**. *Borg's Perceived Exertion and Pain Scales*. Champaign, IL: Human Kinetics, 1998.

5. **Chilvers ER, Peters AM, George P, Hughes JM and Allison DJ**. Quantification of right-to-left shunt through pulmonary arteriovenous malformations using 99m Tc albumin microspheres. *Clin Radiol* 39: 611-614, 1988.

6. **Currie PJ, Kelly MJ and Pitt A**. Comparison of supine and erect bicycle exercise electrocardiography in coronary heart disease: accentuation of exercise-induced ischemic ST depression by supine posture. *Am J Cardiol* 52: 1167-1173, 1983.

7. **Dempsey JA, Hanson PG and Henderson KS**. Exercise-induced arterial hypoxaemia in healthy human subjects at sea level. *J Physiol* 355: 161-175, 1984.

8. **Dempsey JA and Wagner PD**. Exercise-induced arterial hypoxemia. *J Appl Physiol* 87: 1997-2006, 1999.

9. **Di B, V, Santoro G, Talarico L, Di MC, Caputo MT, Giorgi D, Bertini A, Bianchi M and Giusti C**. Left ventricular function during exercise in athletes and in sedentary men. *Med Sci Sports Exerc* 28: 190-196, 1996.

10. **Eldridge MW, Dempsey JA, Haverkamp HC, Lovering AT and Hokanson JS**. Exercise-induced intrapulmonary arteriovenous shunting in healthy humans. *J Appl Physiol* 97: 797-805, 2004.

11. **Gavin TP and Stager JM**. The effect of exercise modality on exercise-induced hypoxemia. *Respir Physiol* 115: 317-323, 1999.

12. **George JD, Stone WJ and Burkett LN**. Non-exercise VO_2max estimation for physically active college students. *Med Sci Sports Exerc* 29: 415-423, 1997.

13. **Gershon AS, Faughnan ME, Chon KS, Pugash RA, Clark JA, Bohan MJ, Henderson KJ, Hyland RH and White RI, Jr.** Transcatheter embolotherapy of maternal pulmonary arteriovenous malformations during pregnancy. *Chest* 119: 470-477, 2001.

14. **Gledhill N, Cox D and Jamnik R**. Endurance athletes' stroke volume does not plateau: major advantage is diastolic function. *Med Sci Sports Exerc* 26: 1116-1121, 1994.

15. **Gudavalli A, Kalaria VG, Chen X and Schwarz KQ**. Intrapulmonary arteriovenous shunt: diagnosis by saline contrast bubbles in the pulmonary veins. *J Am Soc Echocardiogr* 15: 1012-1014, 2002.

16. **Guenette JA and Sheel AW**. Exercise-induced arterial hypoxaemia in active young women. *Appl Physiol Nutr Metab* 32: 1263-1273, 2007.

17. **Guyton AC and Hall JE**. *Textbook of Medical Physiology*. Philadelphia, PA: W.B. Saunders Company, 1996.

18. **Harms CA, McClaran SR, Nickele GA, Pegelow DF, Nelson WB and Dempsey JA**. Effect of exercise-induced arterial O_2 desaturation on VO_2max in women. *Med Sci Sports Exerc* 32: 1101-1108, 2000.

19. **Harms CA, McClaran SR, Nickele GA, Pegelow DF, Nelson WB and Dempsey JA**. Exercise-induced arterial hypoxaemia in healthy young women. *J Physiol* 507 (Pt 2): 619-628, 1998.

20. **Hopkins SR, Barker RC, Brutsaert TD, Gavin TP, Entin P, Olfert IM, Veisel S and Wagner PD**. Pulmonary gas exchange during exercise in women: effects of exercise type and work increment. *J Appl Physiol* 89: 721-730, 2000.

21. **Hopkins SR, Belzberg AS, Wiggs BR and McKenzie DC**. Pulmonary transit time and diffusion limitation during heavy exercise in athletes. *Respir Physiol* 103: 67-73, 1996.

22. **Hopkins SR and Harms CA**. Gender and pulmonary gas exchange during exercise. *Exerc Sport Sci Rev* 32: 50-56, 2004.

23. **Hopkins SR, Schoene RB, Henderson WR, Spragg RG, Martin TR and West JB**. Intense exercise impairs the integrity of the pulmonary blood-gas barrier in elite athletes. *Am J Respir Crit Care Med* 155: 1090-1094, 1997.

24. **Katch FI and McArdle WD**. *Nutrition, Weight Control, and Exercise*. Philadelphia: Lea and Febriger, 1983.

25. **Khurshid I and Downie GH**. Pulmonary arteriovenous malformation. *Postgrad Med J* 78: 191-197, 2002.

26. **Knudson RJ, Lebowitz MD, Holberg CJ and Burrows B**. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis* 127: 725-734, 1983.

27. **Lee WL, Graham AF, Pugash RA, Hutchison SJ, Grande P, Hyland RH and Faughnan ME**. Contrast echocardiography remains positive after treatment of pulmonary arteriovenous malformations. *Chest* 123: 351-358, 2003.

28. **Lovering AT, Haverkamp HC, Romer LM, Hokanson JS and Eldridge MW**. Transpulmonary passage of 99m Tc macroaggregated albumin in healthy humans at rest and during maximal exercise. *J Appl Physiol* 106: 1986-1992, 2009.

29. **Lovering AT, Romer LM, Haverkamp HC, Pegelow DF, Hokanson JS and Eldridge MW**. Intrapulmonary shunting and pulmonary gas exchange during normoxic and hypoxic exercise in healthy humans. *J Appl Physiol* 104: 1418-1425, 2008.

30. **Lovering AT, Stickland MK, Amann M, Murphy JC, O'Brien MJ, Hokanson JS and Eldridge MW**. Hyperoxia prevents exercise-induced intrapulmonary arteriovenous shunt in healthy humans. *J Physiol* 586: 4559-4565, 2008.

31. **Lovering AT, Stickland MK and Eldridge MW**. Intrapulmonary shunt during normoxic and hypoxic exercise in healthy humans. *Adv Exp Med Biol* 588: 31-45, 2006.

32. **Lovering AT, Stickland MK, Kelso AJ and Eldridge MW**. Direct demonstration of 25- and 50-micron arteriovenous pathways in healthy human and baboon lungs. *Am J Physiol Heart Circ Physiol* 292: H1777-H1781, 2007.

33. **McArdle WD, Katch FI and Katch VL**. *Exercise Physiology: Energy, Nutrition, and Human Performance*. Baltimore, MD: Lippincott Williams & Wilkins, 2007.

34. **McClaran SR, Harms CA, Pegelow DF and Dempsey JA**. Smaller lungs in women affect exercise hyperpnea. *J Appl Physiol* 84: 1872-1881, 1998.

35. **Mead J**. Dysanapsis in normal lungs assessed by the relationship between maximal flow, static recoil, and vital capacity. *Am Rev Respir Dis* 121: 339-342, 1980.

36. **Meltzer RS, Tickner EG and Popp RL**. Why do the lungs clear ultrasonic contrast? *Ultrasound Med Biol* 6: 263-269, 1980.

37. **Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G and Wanger J**. Standardisation of spirometry. *Eur Respir J* 26: 319-338, 2005.

38. **Ogawa T, Spina RJ, Martin WH, III, Kohrt WM, Schechtman KB, Holloszy JO and Ehsani AA**. Effects of aging, sex, and physical training on cardiovascular responses to exercise. *Circulation* 86: 494-503, 1992.

39. **Olfert IM, Balouch J, Kleinsasser A, Knapp A, Wagner H, Wagner PD and Hopkins SR**. Does gender affect human pulmonary gas exchange during exercise? *J Physiol* 557: 529-541, 2004.

40. **Pedersen PK, Mandoe H, Jensen K, Andersen C and Madsen K**. Reduced arterial O_2 saturation during supine exercise in highly trained cyclists. *Acta Physiol Scand* 158: 325-331, 1996.

41. **Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson DC, MacIntyre N, McKay R, Miller MR, Navajas D, Pedersen OF and Wanger J**. Interpretative strategies for lung function tests. *Eur Respir J* 26: 948-968, 2005.

42. **Poliner LR, Dehmer GJ, Lewis SE, Parkey RW, Blomqvist CG and Willerson JT**. Left ventricular performance in normal subjects: a comparison of the responses to exercise in the upright and supine positions. *Circulation* 62: 528-534, 1980.

43. **Powers SK, Dodd S, Lawler J, Landry G, Kirtley M, McKnight T and Grinton S**. Incidence of exercise induced hypoxemia in elite endurance athletes at sea level. *Eur J Appl Physiol Occup Physiol* 58: 298-302, 1988.

44. **Proctor DN, Beck KC, Shen PH, Eickhoff TJ, Halliwill JR and Joyner MJ**. Influence of age and gender on cardiac output-VO2 relationships during submaximal cycle ergometry. *J Appl Physiol* 84: 599-605, 1998.

45. **Reeves JT, Moon RE, Grover RF and Groves BM**. Increased wedge pressure facilitates decreased lung vascular resistance during upright exercise. *Chest* 93: 97S-99S, 1988.

46. **Richards JC, McKenzie DC, Warburton DE, Road JD and Sheel AW**. Prevalence of exercise-induced arterial hypoxemia in healthy women. *Med Sci Sports Exerc* 36: 1514-1521, 2004.

47. **Schoene RB, Swenson ER, Pizzo CJ, Hackett PH, Roach RC, Mills WJ, Jr., Henderson WR, Jr. and Martin TR**. The lung at high altitude: bronchoalveolar lavage in acute mountain sickness and pulmonary edema. *J Appl Physiol* 64: 2605-2613, 1988.

48. Schutz, R. Stats Question for my Thesis Project. 7-20-2008.
Ref Type: Personal Communication

49. **Sheel AW, Richards JC, Foster GE and Guenette JA**. Sex differences in respiratory exercise physiology. *Sports Med* 34: 567-579, 2004.

50. **Stickland MK, Welsh RC, Haykowsky MJ, Petersen SR, Anderson WD, Taylor DA, Bouffard M and Jones RL**. Effect of acute increases in pulmonary vascular pressures on exercise pulmonary gas exchange. *J Appl Physiol* 100: 1910-1917, 2006.

51. **Stickland MK, Welsh RC, Haykowsky MJ, Petersen SR, Anderson WD, Taylor DA, Bouffard M and Jones RL**. Intra-pulmonary shunt and pulmonary gas exchange during exercise in humans. *J Physiol* 561: 321-329, 2004.

52. **Stickland MK, Welsh RC, Petersen SR, Tyberg JV, Anderson WD, Jones RL, Taylor DA, Bouffard M and Haykowsky MJ**. Does fitness level modulate the cardiovascular hemodynamic response to exercise? *J Appl Physiol* 100: 1895-1901, 2006.

53. **Strauss HW, Hurley PJ, Rhodes BA and Wagner HN, Jr.** Quantification of right-to-left transpulmonary shunts in man. *J Lab Clin Med* 74: 597-607, 1969.

54. **Tobin CE**. Arteriovenous shunts in the peripheral pulmonary circulation in the human lung. *Thorax* 21: 197-204, 1966.

55. **Tobin CE and ZARIQUIEY MO**. Arteriovenous shunts in the human lung. *Proc Soc Exp Biol Med* 75: 827-829, 1950.

56. **Tortora GJ and Grabowski SR**. *Principles of Anatomy and Physiology*. Hoboken, NJ: John Wiley & Sons, Inc., 2003.

57. **Vogiatzis I, Zakynthinos S, Boushel R, Athanasopoulos D, Guenette JA, Wagner H, Roussos C and Wagner PD**. The contribution of intrapulmonary shunts to the alveolar-

to-arterial oxygen difference during exercise is very small. *J Physiol* 586: 2381-2391, 2008.

58. **Wagner PD, Gale GE, Moon RE, Torre-Bueno JR, Stolp BW and Saltzman HA**. Pulmonary gas exchange in humans exercising at sea level and simulated altitude. *J Appl Physiol* 61: 260-270, 1986.

59. **Warren GL, Cureton KJ, Middendorf WF, Ray CA and Warren JA**. Red blood cell pulmonary capillary transit time during exercise in athletes. *Med Sci Sports Exerc* 23: 1353-1361, 1991.

60. **West JB**. Left ventricular filling pressures during exercise: a cardiological blind spot? *Chest* 113: 1695-1697, 1998.

61. **Whyte MK, Hughes JM, Jackson JE, Peters AM, Hempleman SC, Moore DP and Jones HA**. Cardiopulmonary response to exercise in patients with intrapulmonary vascular shunts. *J Appl Physiol* 75: 321-328, 1993.

62. **Whyte MK, Peters AM, Hughes JM, Henderson BL, Bellingan GJ, Jackson JE and Chilvers ER**. Quantification of right-to-left shunt at rest and during exercise in patients with pulmonary arteriovenous malformations. *Thorax* 47: 790-796, 1992.

63. **Wilkinson MJ and Fagan DG**. Postmortem demonstration of intrapulmonary arteriovenous shunting. *Arch Dis Child* 65: 435-437, 1990.

APPENDIX A – LITERATURE REVIEW

Introduction

The cardio-respiratory system is remarkable in its ability to respond to changing environments and physical demands placed on it, whether it be exercise or environmental (i.e. hypoxia) stress. However, this system is not perfect. Recent research suggests there are vessels in the lungs that re-route blood, bypassing the pulmonary capillary bed, failing to become fully oxygenated. These vessels, termed intrapulmonary arteriovenous shunts (IPAVS), have been reported to occur in a majority of exercising, asymptomatic young males (3; 10; 28-30; 32; 50; 51). IPAVS are dormant at rest and are recruited during dynamic exercise, as cardiac output (Q) and pulmonary artery pressure (PAP) increase (10; 50; 51). Stickland et al. (51) observed that IPAVS recruitment was significantly related to both Q and PAP. They found that if subjects reached an alveolar-arterial oxygen difference ($A\text{-}aDO_2$) that exceeded 12 mmHg and a Q that was greater than 24 litres/min during upright cycling exercise, IPAVS were present, and once the exercise bout was terminated, IPAVS vessels were absent.

It is important to note that IPAVS are different than pulmonary arteriovenous malformations (PAVM) as IPAVS are present in individuals with a healthy cardio-respiratory system. PAVMs are rare pulmonary vascular abnormalities, mainly congenital in nature and are often associated with other disorders of the blood vessels (25). PAVMs provide direct communication between the pulmonary artery and pulmonary veins, bypassing the capillary bed. The concept is similar to IPAVS, however, PAVMs are larger and more severe in their consequences. For example, arterial oxygen saturation (SaO_2) at rest while lying supine in individuals with PAVM is less than 95%, and drops further upon standing, and even further still upon exercise (61). Thus, PAVMs can be detected at rest, and have a significant effect on SaO_2, unlike IPAVS.

It is also important to recognize that IPAVS are different than a patent foramen ovale (PFO) and any septal defect that may result in a direct communication between the right and left sides of the heart, also known as intracardiac shunts. In the developing fetus, there is a small hole between the atria of the heart called the foramen ovale. This hole allows one third of the blood to by-pass the lungs, which are non-functioning in a developing fetus, as the fetus instead relies on the mother's blood for oxygen and nutrients, and to eliminate carbon dioxide and waste. The rest

of the blood is pumped to the pulmonary trunk but again, most is diverted away from the non-functioning lungs through the ductus arteriosus, a vessel that connects the pulmonary trunk to the aorta. When the baby is born and begins spontaneously breathing, the foramen ovale and ductus arteriosus close. In some individuals, however, the foramen ovale does not completely close, potentially allowing blood to move from the ride side of the heart directly to the left side if pressure in the right atrium exceeds pressure in the left atrium (56). Many individuals who have this are not even aware that they do, as this hole is so small it does not significantly affect oxygenation of the blood. However, individuals who have a PFO are excluded from IPAVS studies as the main method of detecting IPAVS, contrast echocardiography, cannot differentiate between contribution due to intracardiac shunt and IPAVS separately.

It is not completely understood why IPAVS exist or what their consequence, in terms of gas exchange, may be. IPAVS may be remnant fetal vessels that once diverted blood away from the non-functioning alveoli in the fetal lung (29). The functional consequences of these vessels remains unclear but a small fraction of Q as shunt could widen A-aDO_2 significantly and have an effect on gas exchange (10). Many highly trained athletes exhibit an excessive A-aDO_2 during moderate and high intensity exercise leading to arterial hypoxemia, while others do not (7; 19; 20). Eldridge et al. (10) stated that perhaps these individuals who experience exercise-induced arterial hypoxemia (EIAH) exhibit IPAVS, and those individuals who do not experience EIAH do not exhibit IPAVS (10). Another theory is that IPAVS may protect the pulmonary capillaries from damage by diverting hydrodynamic energy away from them (23). This would mean that athletes who develop exercise-induced pulmonary hemorrhage may be the individuals who do not exhibit IPAVS. Lastly, perhaps individuals who develop pulmonary edema upon rapid ascent to altitude, may also be individuals who do not have IPAVS vessels (47).

Direct Anatomical Evidence for IPAVS

Anatomical evidence for IPAVS in humans is not new. In 1966, Tobin (54) examined the pulmonary microcirculation of whole human lungs by infusing glass or resin beads (50-100µm in diameter) into the pulmonary artery or inferior vena cava. They observed IPAVS in the peripheral section of the second lobule, bypassing alveolar circulation in 47% of the lobules. Wilkinson and Fagan (63) also demonstrated IPAVS in post-mortem infants (n=49) who had no previous cardio-respiratory abnormalities. A gelatin mixture containing polymethylmethacrylate beads was injected into the pulmonary arteries. The mixture was collected in the left atrium

demonstrating that they had either passed through the normal pulmonary circulation or through IPAVS. Injected beads were 64µm in diameter and the diameter of the pulmonary capillaries only about 7µm, therefore, the capillaries would have had to stretch 2000% in order for the beads to pass through. Thus, these authors suggest that the gelatin and beads bypassed the pulmonary capillary bed through IPAVS.

A more recent study by Lovering et al. (32) aimed to determine whether large diameter (> 25-50µm) IPAVS are functional in human (n=6) and baboon lungs (n=4) under physiological perfusion and ventilation pressures. Isolated lung preparations were ventilated with room air by using a peak inflation pressure of 15 cmH_2O and a positive end-expiratory pressure of 5 cmH_2O. They infused a mixture of 25- and 50-µm microspheres into the pulmonary artery and collected the entire venous outflow. In the lungs that demonstrated IPAVS, 50µm microspheres always traversed the pulmonary circulation. Therefore, the data showed that IPAVS > 50µm in diameter are functional under physiologic ventilation and perfusion pressures in the isolated lung.

Evidence for IPAVS in Humans

All of the previously mentioned studies support that IPAVS exist in the isolated lung. Technological advances have permitted the investigation of this phenomenon in vivo under physiologically relevant conditions. Whyte et al. (62) measured right-to-left pulmonary shunt during rest in 19 patients with a PAVM and six normal subjects by intravenously injecting albumin microspheres labelled with ^{99m}Tc, a gamma emitting isotope used as a radioactive tracer. This technique reflects shunt fraction as these microspheres do not normally traverse the pulmonary capillary bed (5). In this study, subjects exercised at 50% of their previously determined maximum workload for five minutes. At the end of five minutes, subjects continued to cycle at that intensity and the microspheres were injected into an antecubital vein. After the injection, subjects then stopped exercising and rested supine in order for the images of the upper abdomen and lungs to be taken with a gamma camera. Microspheres were counted before injection and then counted as they appeared in the right kidney. A correction was made for the physical decay according to the timing of each image. This technique is reliable and valid in quantifying shunt, but it cannot be performed during a VO_{2max} test, as the subject must be lying supine in order to take the images with the gamma camera, thus, the exact intensity at which these vessels are recruited cannot be determined. In the healthy controls, shunt was 2.7% of Q at rest and in five of the normal subjects mean shunt increased from 2.9% to 5.1% of Q during

exercise at 50% of their maximal workload. These findings support the existence of IPAVS in people who have a healthy cardio-respiratory system, and demonstrates the fraction of Q as shunt, which may affect gas exchange. They did show that arterial desaturation was correlated with the change in the size of the shunt during exercise (r=0.80) in the PAVM subjects, however, not in the normal subjects, as they did not desaturate.

Saline injection contrast echocardiography has become the standard clinical technique used to diagnose intracardiac and intrapulmonary shunting. Lee et al. (27) used contrast echocardiography, before and after treatment of the PAVM by transcatheter embolotherapy, a procedure that occludes the artery feeding the PAVM with a detachable balloon or metal coils (13). The study results showed that contrast echocardiography remains positive after treatment of PAVM in >90% of patients, despite the pulmonary angiography being negative. The presence of IPAVS may explain the positive contrast echocardiography result after the treatment of PAVM.

Eldridge et al. (10) was the first to specifically examine IPAVS with contrast echocardiography. They hypothesized that increasing exercise intensity recruits dormant IPAVS and that these vessels may contribute to the widening A-aDO_2 seen with exercise. Twenty-three subjects (13 men and 10 women) who had normal lung function and varying fitness levels (average 126% of predicted VO_{2max}) performed a progressive, incremental exercise test to exhaustion on a cycle ergometer. The test started at 65W and increased by 30W every two minutes. Saline injections and contrast images were conducted at rest, during the last minute of each exercise stage, and at three minutes post-exercise. As these subjects presented with a normal cardio-respiratory system and a normal response to exercise, it would be expected that the contrast echocardiography would be negative for any shunting. However, in 21 of the 23 subjects, this was not the case, demonstrating that IPAVS may occur in healthy, asymptomatic individuals.

Stickland et al. (51) also used contrast echocardiography to determine if IPAVS develop with exercise, and see if there was a relationship to the increased A-aDO_2 also seen with exercise. The participants were males who performed graded cycling to 90% VO_{2max} while PAP and pulmonary artery wedge pressure (PAWP) were measured directly from pressure catheters, and Q was measured via the Fick method. Subjects exercised five minutes at each of the following workloads: 75W, 150W, power output at ventilatory threshold, 25W above power at

ventilatory threshold, and 90% VO_{2max}. At each exercise stage, saline injections and subsequent images were taken during the third minute of each five minute workload. Stickland et al. (51) found that IPAVS was related to Q (r=0.76) and PAP (r=0.73), and to a lesser extent A-aDO_2 (r=0.68), but the relationship to A-aDO_2 was not consistent among subjects. The authors stated that perhaps this variability was due to the contribution of diffusion limitation and alveolar ventilation-perfusion (V_A/Q) mismatching to A-aDO_2. Another finding was that IPAVS was always recruited when A-aDO_2 exceeded 12 mmHg and when Q exceeded 24 litres/min. Normal values for A-aDO_2 at rest are 5-10 mmHg and for Q 5-6 litres/min. This finding was supported by the finding that the only subject who did not demonstrate IPAVS during exercise had the lowest VO_{2max}, had a Q of 20 litres/min, and had a PAP that was 10mmHg higher than the average PAP for the other subjects at the same Q.

Lovering et al. (30) questioned whether breathing 100% oxygen affected IPAVS recruitment during exercise. Seven subjects (four male and three female) performed two different exercise protocols; The first protocol was an incremental exercise test on a cycle ergometer, that started at 60W, increasing by 30W every two minutes, breathing room air to start. Once significant shunting was present, the workload was held constant and the fraction of inspired oxygen (FIO_2) was alternated between hyperoxia (100% O_2) for three minutes and normoxia (20.9% O_2) for two minutes, then hyperoxia for two minutes, and normoxia for two minutes, then hyperoxia for one minute and normoxia for two minutes. In the second protocol, subjects performed an incremental cycle test until exhaustion while breathing 100% O_2 continuously. All subjects demonstrated IPAVS in the first protocol during submaximal exercise intensities, however, once hyperoxia was applied shunting was reduced or eliminated in all subjects. The degree to which shunting was eliminated depended on the length of the hyperoxia bout, where it was partially eliminated after one minute and then fully eliminated after two minutes. Once back in normoxia IPAVS returned. In the second protocol, hyperoxia substantially decreased or eliminated IPAVS during exercise in all subjects at submaximal intensities, and in four out of the seven subjects at maximal exercise. Therefore, it appears that IPAVS behave more like systemic vessels in response to hyperoxia (vasoconstricting), unlike the pulmonary circulation (dilating).

Another study by Lovering et al. (29) studied the effect of hypoxia on IPAVS recruitment. They hypothesized that, despite Q and pulmonary pressure being higher in hypoxia, the pulmonary vasoconstrictor effect of hypoxia would actually reduce IPAVS during exercise.

Nine healthy men exercised to exhaustion on a cycle ergometer starting at 65W and increasing by 30W every two minutes. Contrast echocardiography was performed at rest, at the end of each exercise stage, and three to five minutes post exercise. One test was in normoxia, while a second test was conducted in hypoxia (12% O_2). At rest during the normoxic trial, no subjects exhibited IPAVS, where three out of the nine subjects exhibited IPAVS at rest in hypoxia. During exercise, eight out of the nine subjects demonstrated IPAVS in normoxia, while four out of the nine subjects shunted at a lower workload during hypoxia. All subjects continued to shunt post-exercise in hypoxia, unlike in normoxia. Thus, it appears that hypoxia induces IPAVS recruitment at rest and during exercise, and keeps these vessels open post-exercise. Once again, it appears that IPAVS behave more like systemic vessels than pulmonary vessels, dilating in response to hypoxia.

Limitations to Gas Exchange

Inefficient gas exchange is defined by an excessive increase of the A-aDO_2 and/or insufficient alveolar hyperventilation during exercise (8). Normal A-aDO_2 values at rest are 5-10 mmHg (31). At VO_{2max}, A-aDO_2 values of 15-25 mmHg are common and in elite athletes A-aDO_2 can reach 24-40 mmHg. If A-aDO_2 exceeds 35-40 mmHg, severe inefficiencies in gas exchange are present (8). Efficiency of gas exchange is a major determinant of SaO_2 (20). EIAH is defined as a reduction in arterial oxygen saturation to 91% or lower during exercise (43). This happens mainly at high exercise intensities (> 80% VO_{2max}), therefore, gas exchange limitations are more common in those individuals capable of achieving high levels of aerobic work.

Powers et al. (43) was one of the first to determine the incidence of EIAH during exercise in healthy males of different fitness levels. Sixty-eight subjects were divided into three groups based on their fitness level: untrained, moderately trained, and elite highly-trained endurance athletes. Subjects performed an incremental VO_{2max} test on a cycle ergometer, while respiratory data and SaO_2 (via pulse oximetry) was measured. The subjects in the highly trained group tended to have lower end-tidal partial pressures of oxygen and higher end-tidal partial pressures of carbon dioxide at VO_{2max} compared to the other groups. All of the subjects had normal pulmonary function and no resting diffusion limitation. Powers et al. (43) reported that 52% of their highly trained endurance subjects (VO_{2max} >68 ml/kg/min) experienced EIAH during work rates greater than 90%VO_{2max}. It was unclear why some highly trained subjects in this study experienced EIAH and why some did not. Perhaps the presence or absence of IPAVS contributes

to the difference seen among athletes, with those who do experience this hypoxemia also exhibiting IPAVS (10).

Fitness Level and Limitations to Gas Exchange

Proctor et al. (44) studied the influence of age and gender on the relationship between Q and VO_2 during submaximal exercise. The purpose of this study was to generate a greater understanding of how gender, age, and physical activity status interact to determine the magnitude of the increase in Q during submaximal exercise. Four groups were studied: younger and older men, and younger and older women, all chronically endurance trained. The primary finding of this study was that the relationship between Q and a given VO_2 does not differ among the groups. Older men and women did show a reduced ability to maintain stroke volume (SV) at exercise intensities above 70% VO_{2peak} when compared to their younger counterparts. This effect was most prominent in the older women. These results suggest that neither age nor gender, per se, significantly modify the Q response to submaximal dynamic exercise in these individuals (44). It is interesting to note that because of these findings, there may not be any difference in IPAVS recruitment between endurance trained men and women. It would be interesting to see the results if the study had included an untrained group.

Stickland et al. (52) examined the effects of fitness on exercise cardiac compliance and cardiac filling pressures as subjects with greater aerobic fitness demonstrate greater diastolic compliance at rest. They also examined the application of lower-body positive pressure (LBPP) to see if acute changes in pulmonary pressure affect pulmonary gas exchange. All subjects were male and were divided into low and high aerobic capacity groups. Each subject performed a discontinuous maximal exercise test staged according to power output. Additional workloads were conducted with the application of LBPP. Traditionally, it has been accepted that SV plateaus during aerobic exercise and that the increase Q seen from submaximal to maximal exercise is due solely to increases in heart rate. However, more recent studies have shown that endurance-trained athletes do not demonstrate a plateau in SV during exercise, therefore, they are better able to use the Frank-Starling mechanism (9; 14). There were no differences between the low and high groups on any measure at rest. Subjects with greater aerobic fitness demonstrated low left-ventricular filling pressures during exercise, whereas SV and end-diastolic volume were either similar (submaximal exercise) or higher (peak exercise), suggesting superior diastolic compliance and function. These findings suggest that enhanced exercise SV in

endurance trained athletes was due to favorable changes in diastolic function. Mean PAP was not different at rest or during submaximal exercise in either group, however, at maximal exercise, there was a trend for PAP to be higher in the lower fitness group.

Stickland et al. (50) studied the effect of acute increases in pulmonary vascular pressures, via the application of LBPP, on exercise A-aDO_2, anatomic IPAVS recruitment, and ventilation. Eight men (VO_{2max} of 54.7 ± 9 ml/kg/min) cycled at 90% VO_{2max} under normal conditions with the application of 52 mmHg of LBPP. PAP, PWAP, Q, A-aDO_2, mean right atrial pressure, and IPAVS were measured. The elevated PAP increased shunt frequency slightly at rest and during low intensity exercise, but LBPP did not affect IPAVS recruitment during moderate to very heavy exercise. The data showed that IPAVS recruitment typically develops with increasing Q, and not consistently with increasing PAP. It is likely that shunt vessels are sensitive to very specific opening pressures upon increasing driving pressure and Q with exercise. This opening pressure appears to be consistent within subjects, but extremely variable between subjects. These two factors, along with the relatively small increase in PAP via LBPP, likely explain why LBPP failed to substantially affect IPAVS recruitment. Lastly, it was found that ventilation was not affected by acute increases in pulmonary vascular pressures. This investigation showed that acute increases (4-5mmHg) in pulmonary vascular pressures via LBPP do not impair pulmonary gas exchange, and do not affect A-aDO_2 or ventilation. The subjects in this study were of average fitness level and the investigators report that their results may have been different had their subjects been athletes of a higher fitness level, who experience significant impairment in pulmonary gas exchange during exercise. Stickland et al. (50) reason that previous research suggests that athletes would have greater PAP pressures during exercise because of their elevated Q and, therefore, would be more likely to develop a larger impairment in gas exchange. The results from the current experiment indicate that to achieve greater pulmonary flow rates, subjects who are more fit accomplish this not through high PAP, but by having better cardiac compliance and, therefore, lower pulmonary venous pressures compared with less-fit subjects.

Vogiatzis et al. (57) studied IPAVS in seven highly trained cyclists (VO_{2max} = 61.3 ± 2.4 ml/kg/min). They hypothesized that very small IPAVS exist, only making a minor contribution to the fall in partial pressure of oxygen and increase in A-aDO_2 seen in normoxic and hypoxic exercise in highly trained individuals. Vogiatzis et al. (57) quantified IPAVS as a percent of Q by calculating venous admixture using the Fick equation; Arterial oxygen concentrations were

measured, mixed venous oxygen concentrations were calculated from oxygen consumption, and PAP was extrapolated from Q measurements and previously published direct measures of PAP and Q during exercise (58). Venous admixture was then expressed as a percent of Q. Vogiatzis et al. (57) did not use contrast echocardiography during a maximal exercise test, the method used by most IPAVS studies, to characterize the onset of IPAVS in these individuals, making it difficult to compare this study to others. Thus, the role that fitness level plays in IPAVS recruitment is still unknown. Individuals of a higher fitness level will reach the highest Q compared to those who are of a lower fitness level. If the recruitment of IPAVS is related to Q and PAP, perhaps highly trained individuals experience IPAVS at a lower exercise intensity than those who are not as well-trained.

Biological Sex Differences

A majority of the studies examining IPAVS to-date have used male subjects, however, it has been shown that women have smaller lungs, smaller airways, and less surface area for gas exchange, compared to height-matched men (35). A number of studies since then have concluded that these anatomical differences may render women more susceptible to inefficient gas exchange during exercise (16; 18; 19; 22; 34; 46; 49). This leads to the question of whether or not there is a biological sex difference in the recruitment of IPAVS. Sex differences have not yet been found, however, the limited number of studies on women demonstrates the need for more research. The prevalence of EIAH in a large female population with a wide range of VO_{2max} values was studied by Richards et al. (46). Fifty-two young women performed a VO_{2max} test on a cycle ergometer and SaO_2 was measured via pulse oximetry. After the test, subjects were placed into either the non-EIAH group, the mild EIAH group, or the moderate EIAH group. They found that EIAH was present in 67% of their women, thus occurring at a slightly higher prevalence and at a relatively lower fitness level (VO_{2max} values 15-20% of predicted) than that previously reported for highly fit men (VO_{2max} values > 150% predicted) (19). Except for end-exercise SaO_2, there was no difference between the groups on any physiological variables and they found no relationship between EIAH and aerobic capacity. The finding of EIAH in untrained women is unusual, as it is typically reported only in highly trained males. Women, regardless of fitness level, may experience gas exchange difficulties compared to men simply because of their smaller lungs, smaller airways, and less surface area available for gas exchange.

Harms et al. (19) questioned whether EIAH occurs in healthy active women compared to age- and height-matched men. Twenty-nine healthy, young women of varying fitness levels completed a VO_{2max} test measuring respiratory data, and taking arterial blood samples at rest and near the end of each workload. Subjects either fell into the no EIAH group, the mild EIAH group, or the severe EIAH group. In this study, almost half of the women with significant EIAH had a VO_{2max} within 15% of predicted, and it occurred at VO_2 values ranging from 43-70 ml/kg/min. This is different from the EIAH reported in men who have a VO_{2max} greater than 150% of their predicted VO_{2max} and when exercising at near maximal intensity. Subjects who experienced the greatest widening in A-aDO_2 (46-52 mmHg) at VO_{2max} were the most hypoxemic and the prevalence of hypoxemia was distinctly higher in subjects with a higher VO_{2max}. The group that did not show hypoxemia had a significantly lower VO_{2max} values compared to the mild and severe hypoxemia groups. Therefore, fitness level plays an important role in EIAH severity and EIAH appears to also occur in women who are not as highly trained, and at a lower percent of their maximal exercising intensity. This raises the question of whether or not fitness level plays a role in IPAVS recruitment.

In a similar study, Harms et al. (18) questioned whether EIAH affected VO_{2max} in healthy, habitually active women and whether the effect was similar to that reported in men. Twenty-five healthy, young women of varying fitness levels performed two randomized incremental treadmill VO_{2max} tests, one with an FIO_2 of 21% administered and another with an FIO_2 of 26%. The researchers found that when desaturation was prevented via the administration of 26% O_2, VO_{2max} increased in proportion to the degree of desaturation in 22 of the 25 women. Even small amounts of EIAH (approximately a 3% decrease) were shown to have a significant detrimental effect on VO_{2max} in these women. This demonstrated that desaturation limits VO_{2max} in women, by altering O_2 content, hence, O_2 delivery.

Olfert et al. (39) used a multiple inert gas elimination technique (MIGET) to determine whether women would develop greater V_A/Q mismatching and/or diffusion limitation during exercise compared to men, and to compare the effects of biological sex, independent of the effects of lung size, on pulmonary gas exchange. Women and men were matched for age, height, aerobic capacity, and lung size. This study differs from most studies because men and women often are age- and height-matched only. Both sexes performed light, moderate, and heavy exercise in normoxia and hypoxia in order to give the best evaluation of the contribution of V_A/Q

mismatching and diffusion limitation to pulmonary gas exchange. They determined that active women do not experience greater exercise-induced abnormalities in gas exchange than men, in normoxia and hypoxia. V_A/Q mismatching and diffusion limitation were not higher in women. Olfert et al. (39) suggested that perhaps fitness level and lung size are more important than sex, in determining whether or not pulmonary gas exchange impairments occur during exercise. However, these subjects were reasonably fit and may not be representative of the population at large. This may reflect a population bias to athletic women with large lungs. If fitness level does play a more important role in gas exchange impairment and it is important to look at the effect of fitness level on IPAVS recruitment.

Conclusion

IPAVS appear to be present in most individuals who have a healthy cardio-respiratory system. Why these vessels exist and their consequences are not completely known. They appear to be remnant fetal vessels and may contribute to the EIAH experienced in athletes, the exercise-induced pulmonary hemorrhage also seen in athletes, or to pulmonary edema experienced by those who ascend to altitude quickly. A common trend is that the resulting cardio-respiratory limitations seem to be worse in those who are more highly trained. The limited number of studies on IPAVS in highly trained individuals warrants further investigation into the role that fitness level may play in the recruitment of IPAVS. Although there appears to be no difference between sexes, the number of studies examining IPAVS in women is limited. The existing literature demonstrates that women are more susceptible to gas exchange limitations than men, suggesting that a difference in IPAVS recruitment may exist.

APPENDIX B – INDIVIDUAL DATA

Note that subjects 1, 16, 20, 21, and 28 have been excluded from analyses.

Subject Characteristics

Subject #	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	BSA (m^2)
UT – 5	22	158.4	56.5	22.5	1.58
UT – 6	25	166.8	56.7	20.4	1.62
UT – 7	23	163.7	56.3	21.0	1.60
UT – 10	28	162.2	47.9	18.2	1.47
UT – 13	24	164.3	68.7	25.5	1.77
UT – 14	23	165.5	62.8	23.1	1.70
UT – 15	27	160.4	53.9	21.0	1.55
UT – 19	33	162.3	63.9	24.3	1.70
MT – 3	24	169.2	61.3	21.4	1.70
MT – 12	32	161.9	72.4	27.6	1.80
MT – 17	26	168.4	55.3	19.4	1.60
MT – 23	32	165.1	52.4	19.2	1.55
MT – 27	26	163.9	53.1	19.8	1.55
MT – 29	20	167.4	71.9	25.7	1.83
HT – 2	25	155.0	51.6	21.5	1.49
HT – 4	25	172.1	65.4	22.1	1.77
HT – 8	24	168.0	53.0	18.6	1.57
HT – 9	22	165.9	57.5	20.9	1.63
HT – 11	21	159.0	52.2	20.6	1.52
HT – 18	22	161.0	52.9	20.4	1.54
HT – 22	30	166.0	61.7	22.4	1.69
HT – 24	38	167.0	54.4	19.5	1.59
HT – 25	37	168.2	56.8	20.1	1.63
HT – 26	28	171.9	59.4	20.1	1.68

Pulmonary Function

Subject #	FVC (litres)	FEV_1 (litres)	MVV (litres)	FEV_1/FVC
UT – 5	3.63	2.86	128.9	78.79
UT – 6	4.38	3.48	123.8	79.45
UT – 7	3.84	2.77	77.2	72.14
UT - 10	3.69	2.80	95.1	75.88
UT - 13	3.70	3.06	130.4	82.70
UT - 14	4.48	3.84	150.6	85.71
UT - 15	3.34	3.15	122.9	94.31
UT - 19	4.02	3.19	90.2	79.35
MT - 3	4.28	3.65	128.1	85.28
MT - 12	3.95	3.43	134.8	86.84
MT - 17	3.79	3.50	162.7	92.35
MT - 23	4.45	3.55	116.7	79.78
MT - 27	4.07	3.34	127.1	82.06
MT - 29	4.97	3.87	115.6	77.87
HT – 2	3.60	3.04	134.3	84.44
HT – 4	3.73	3.68	137.5	98.66
HT – 8	3.73	3.28	138.5	87.94
HT – 9	4.81	3.52	100.5	73.18
HT - 11	3.75	3.39	102.3	90.40
HT - 18	3.65	3.52	124.9	96.44
HT - 22	4.52	3.77	131.8	83.41
HT - 24	4.18	3.26	131.8	77.99
HT - 25	4.41	3.90	155.9	88.44
HT - 26	4.76	3.88	143.7	81.51

Expired Gases and Ventilatory Data at Peak Exercise

Subject #	VO_{2peak} (ml/kg/min)	VO_2 (l/min)	VCO_2 (l/min)	V_E (l/min)	V_E/VO_2	V_E/VCO_2	V_t (litres)	F_b (br/min)	RER
UT – 5	29.8	1.67	1.77	66.93	41.49	38.34	1.44	47	1.07
UT – 6	39.6	2.16	2.2	88.55	30.22	30.42	1.97	46	1.02
UT – 7	27.6	1.54	1.53	46.54	41.00	40.25	1.42	33	1.00
UT – 10	38.9	1.82	1.97	75.52	40.08	37.81	1.51	50	1.09
UT – 13	32.7	2.21	2.32	84.44	38.21	36.40	1.76	49	1.05
UT – 14	36.8	2.12	1.85	106.50	50.23	57.56	2.06	52	0.88
UT – 15	39.6	2.11	1.72	94.48	44.78	54.93	1.84	52	0.81
UT – 19	37.7	2.40	2.46	76.93	32.05	31.27	2.11	37	1.03
MT – 3	43.3	2.60	2.54	108.60	50.39	41.26	1.52	71	0.98
MT – 12	42.9	2.85	2.84	102.90	43.40	43.98	2.05	51	1.00
MT – 17	42.4	2.26	2.23	98.08	41.76	42.75	2.05	48	0.99
MT – 23	40.7	2.08	2.54	104.80	36.09	36.22	1.91	55	1.23
MT – 27	44.3	2.34	2.87	88.77	37.94	30.93	1.92	46	1.23
MT – 29	41.2	2.94	3.28	119.60	40.67	36.45	2.04	59	1.12
HT – 2	48.4	2.50	2.55	80.74	41.23	39.02	1.85	44	1.02
HT – 4	49.1	3.18	3.36	131.10	32.30	31.66	1.77	74	1.06
HT – 8	56.3	2.96	3.09	113.40	38.32	36.71	1.54	74	1.04
HT – 9	49.5	2.63	2.88	99.32	37.76	34.49	2.11	47	1.10
HT – 11	48.6	2.53	2.65	81.91	32.38	30.91	1.39	60	1.05
HT – 18	48.3	2.50	2.52	85.16	34.06	33.79	2.02	43	1.01
HT – 22	48.37	2.99	3.24	129.50	43.30	39.96	1.92	68	1.09
HT – 24	47.3	2.55	2.75	97.49	38.23	35.45	1.75	56	1.08
HT – 25	50.2	2.80	2.76	114.00	40.71	41.30	1.65	69	0.99
HT – 26	49.0	2.80	3.07	119.20	42.59	38.84	1.76	68	1.10

Cardiovascular Data at Peak Exercise

Subject #	HR (beats/min)	Q (l/min)	SV (ml)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	S_pO_2 (%)	Power (Watts)
UT – 5	189	9.42	49.85	190	92	124.7	97	140
UT – 6	168	11.87	70.65	180	102	128.0	98	140
UT – 7	143	10.18	71.22	166	86	112.7	99	110
UT - 10	173	9.61	55.58	154	98	116.7	97	140
UT - 13	182	12.38	68.01	152	84	106.7	97	170
UT - 14	169	12.73	75.33	180	92	121.3	99	170
UT - 15	184	10.17	55.26	166	96	119.3	95	170
UT - 19	144	13.02	90.43	160	80	106.7	97	170
MT - 3	179	11.01	61.49	162	88	112.7	99	200
MT - 12	164	13.44	81.95	218	90	132.7	98	230
MT - 17	175	9.62	54.98	160	95	116.7	98	170
MT - 23	177	10.17	57.48	160	75	103.3	95	170
MT - 27	192	12.66	65.94	175	100	125.0	96	200
MT - 29	179	12.37	69.08	195	95	128.3	97	230
HT – 2	177	9.12	51.53	165	100	121.7	98	200
HT – 4	182	14.63	80.38	160	80	106.7	95	230
HT – 8	184	14.62	79.44	154	92	112.7	93	230
HT – 9	197	12.98	65.89	160	82	108.0	97	200
HT - 11	173	11.11	64.20	132	80	97.3	95	200
HT - 18	168	11.76	70.00	175	85	115.0	97	170
HT - 22	175	10.88	62.17	190	70	110.0	93	230
HT - 24	179	10.65	59.51	190	80	116.7	94	230
HT - 25	173	12.11	70.02	190	102	131.3	98	200
HT - 26	184	14.04	76.30	165	90	115.0	96	230

Stress Echo Calculations at Submaximal Exercise (Stage 3)

Subject #	LVIDd cm	LVIDs cm	LVPWs cm	LVOT V m/s	LVOT VTI cm	LVOT Env.Ti ms	MV (E) m/s
UT – 5	3.9	1.8	1.1	1.7	22.6	179	1.40
UT – 6	4.5	2.7	1.2	1.8	26.0	201	1.60
UT – 7	4.5	2.2	1.2	2	28.0	196	1.40
UT - 10	4.3	2.3	1.1	1.2	18.5	205	1.28
UT - 13	4.0	2.5	1.2	1.8	25.4	201	1.50
UT - 14	N/A	N/A	N/A	N/A	N/A	N/A	N/A
UT - 15	4.0	2.3	1.2	1.7	22.2	184	1.40
UT - 19	5.0	2.9	1.3	1.44	26.6	252	1.00
MT - 3	4.5	2.7	1.1	1.6	21.7	166	1.60
MT - 12	4.8	2.5	1.2	1.8	26.2	205	1.70
MT - 17	4.0	2.0	1.25	1.3	19.4	192	1.70
MT - 23	4.4	2.8	1.1	1.5	22.6	184	1.20
MT - 27	4.3	2.3	1.2	2.0	24.0	165	1.70
MT - 29	4.5	2.4	1.2	1.8	25.5	196	1.30
HT – 2	4.1	2.5	1.0	1.9	21.5	165	1.60
HT – 4	5.1	2.9	1.1	2.3	31.2	183	1.70
HT – 8	5.7	3.3	1.2	2.1	28.6	184	2.00
HT – 9	4.4	2.6	1.2	1.8	23.5	166	1.40
HT - 11	4.5	2.4	1.1	2.0	27.5	188	1.90
HT - 18	4.1	2.2	1.1	1.6	22.7	188	1.50
HT - 22	4.9	2.9	1.1	1.3	22.4	218	1.40
HT - 24	4.4	2.4	1.2	1.7	23.0	188	1.30
HT - 25	4.5	2.5	1.1	1.6	23.6	184	1.60
HT - 26	4.8	2.7	1.2	1.6	28.2	201	1.60

Stress Echo Calculations at Submaximal Exercise (Stage 3) – Continued

Subject #	MVCFc circ/s	σPS g/cm^2	FS %	CI $l/min/m^2$	SI Ml	E/E'
UT – 5	1.75	65.13	53.85	6.45	36.46	0.10
UT – 6	1.22	92.53	40.00	8.01	50.38	N/A
UT – 7	1.69	66.46	51.11	6.36	44.51	0.10
UT - 10	1.38	73.52	46.51	6.43	39.45	0.10
UT - 13	1.11	69.36	37.50	6.83	40.66	N/A
UT - 14	N/A	N/A	N/A	7.49	N/A	N/A
UT - 15	1.40	69.71	42.50	6.66	40.60	N/A
UT - 19	1.18	71.74	42.00	5.86	49.21	0.07
MT - 3	1.40	95.35	40.00	6.49	36.23	N/A
MT - 12	1.48	104.52	47.92	6.79	45.59	0.12
MT - 17	1.52	N/A	50.00	6.00	34.27	0.13
MT - 23	1.15	98.69	36.36	6.56	37.08	N/A
MT - 27	1.64	74.39	46.51	7.79	43.74	N/A
MT - 29	1.47	81.90	46.67	6.92	43.79	N/A
HT – 2	1.43	96.43	39.02	5.37	32.27	0.11
HT – 4	1.41	101.92	43.14	9.26	55.42	0.11
HT – 8	1.38	98.01	42.11	9.51	57.29	N/A
HT – 9	1.41	80.05	40.91	7.53	40.91	N/A
HT - 11	1.50	66.65	46.67	6.78	41.08	0.16
HT - 18	1.66	71.10	46.34	5.52	41.82	N/A
HT - 22	1.20	119.34	40.82	6.13	41.70	0.09
HT - 24	1.44	83.25	45.45	6.98	41.03	N/A
HT - 25	1.47	96.95	44.44	7.41	45.49	N/A
HT - 26	1.34	84.12	43.75	8.36	52.58	N/A

Stress Echo Calculations at Peak Exercise

Subject #	LVIDd cm	LVIDs cm	LVPWs cm	LVOT V m/s	LVOT VTI cm	LVOT Env.Ti ms	MV (E) m/s
UT – 5	3.8	1.9	1.1	1.7	19.6	158	1.50
UT – 6	N/A	N/A	N/A	1.7	22.5	171	1.50
UT – 7	4.5	2.2	1.2	2.0	28.0	196	1.40
UT - 10	4.2	2.0	1.2	1.3	17.7	188	1.30
UT - 13	N/A	N/A	N/A	1.8	24.0	168	1.50
UT - 14	N/A	N/A	N/A	N/A	N/A	N/A	N/A
UT - 15	3.8	1.9	1.2	1.5	19.5	149	1.40
UT - 19	4.7	2.9	1.3	1.8	28.8	205	1.07
MT - 3	4.5	2.7	1.1	1.6	21.7	166	1.60
MT - 12	4.7	2.5	1.3	2.0	26.1	184	1.70
MT - 17	4.0	2.0	1.25	1.3	19.4	192	1.70
MT - 23	4.4	2.8	1.1	1.5	22.6	184	1.20
MT - 27	N/A	N/A	N/A	N/A	N/A	N/A	N/A
MT - 29	4.4	2.4	1.3	1.8	22.0	168	1.50
HT – 2	4.2	2.6	N/A	N/A	N/A	N/A	1.70
HT – 4	4.9	2.8	1.1	2.2	25.6	175	1.90
HT – 8	5.2	3.2	1.2	2.0	25.3	166	2.00
HT – 9	4.3	2.2	1.2	N/A	N/A	N/A	1.50
HT - 11	4.4	2.3	1.1	2.0	28.3	179	N/A
HT - 18	4.2	2.2	1.1	1.8	24.7	179	1.80
HT - 22	4.4	2.2	1.2	1.6	19.8	154	1.80
HT - 24	4.2	2.4	1.1	1.8	21.0	162	1.30
HT - 25	4.2	2.2	1.2	1.7	22.3	179	1.50
HT - 26	N/A	N/A	N/A	1.8	24.3	184	1.60

Stress Echo Calculations at Peak Exercise - Continued

Subject #	MVCFc circ/s	σPS g/cm^2	FS %	CI $l/min/m^2$	SI ml	E/E'
UT – 5	1.78	N/A	50.00	5.98	31.62	N/A
UT – 6	N/A	N/A	N/A	7.33	43.60	N/A
UT – 7	1.69	66.46	51.11	6.36	44.51	0.10
UT – 10	1.64	N/A	52.38	6.53	37.75	0.09
UT – 13	N/A	N/A	N/A	6.99	38.42	N/A
UT – 14	N/A	N/A	N/A	7.49	N/A	N/A
UT – 15	1.92	N/A	50.00	6.56	35.66	N/A
UT – 19	1.21	83.18	38.30	7.67	53.28	N/A
MT – 3	1.40	95.50	40.00	6.49	36.23	N/A
MT – 12	1.54	93.09	46.81	7.45	45.42	0.12
MT – 17	1.52	N/A	50.00	6.00	34.27	0.13
MT – 23	1.15	98.69	36.36	6.56	37.08	N/A
MT – 27	N/A	N/A	N/A	8.17	N/A	N/A
MT – 29	1.57	N/A	45.45	6.76	37.78	N/A
HT – 2	N/A	N/A	38.10	6.12	N/A	N/A
HT – 4	1.41	98.69	42.86	8.28	45.47	0.13
HT – 8	1.32	N/A	38.46	9.32	50.68	N/A
HT – 9	N/A	N/A	48.84	7.96	N/A	N/A
HT – 11	1.57	N/A	47.73	7.31	42.27	N/A
HT – 18	1.59	78.75	47.62	7.65	45.51	N/A
HT – 22	1.90	76.07	50.00	6.45	36.86	N/A
HT – 24	1.53	95.94	42.86	6.71	37.46	N/A
HT – 25	1.57	76.07	47.62	7.44	42.98	N/A
HT – 26	N/A	N/A	N/A	8.34	45.31	N/A

Characterizing Shunt Onset for Each Subject

Training Category	% Max Power Shunt Onset	$\%VO_{2peak}$ Shunt Onset	Exercise Stage Shunt Onset	Q (litres/min) Shunt Onset
UT – 5	No shunt	No shunt	No shunt	No shunt
UT – 6	36	42	Stage 1	10.9
UT – 7	45	57	Stage 1	6.4
UT – 10	0	8	Resting	3.5
UT – 13	29	45	Stage 1	9.6
UT – 14	82	81	Stage 2	10.2
UT – 15	29	47	Stage 1	7.2
UT – 19	0	9	Resting	4.2
MT – 3	85	98	Stage 3	11.8
MT – 12	0	9	Resting	2.9
MT – 17	0	7	Resting	3.5
MT – 23	82	85	Stage 2	8.3
MT – 27	55	60	Stage 1	10.9
MT – 29	48	55	Stage 1	9.4
HT – 2	70	82	Stage 2	7.6
HT – 4	74	71	Stage 3	16.4
HT – 8	48	46	Stage 1	12.4
HT – 9	55	52	Stage 1	10.5
HT – 11	55	55	Stage 1	7.3
HT – 18	29	42	Stage 1	6.4
HT – 22	87	90	Stage 4	10.0
HT – 24	61	74	Stage 2	12.0
HT – 25	55	60	Stage 1	10.2
HT – 26	61	59	Stage 2	12.6

APPENDIX C – MEDICAL/MENSTRUAL/PHYSICAL ACTIVITY QUESTIONNAIRE

Age:
Subject Code:
Date/Time:

Menstrual History

1. Are you having regular periods? YES/NO

2. How long is your cycle length? _____ (days)

3. How many days long is your flow? _____ (days)

4. Can you usually tell, by the way you feel, that your period is coming? YES/NO

5. Do you usually experience the following symptoms?

Breast tenderness YES/NO
Appetite changes YES/NO
Mood changes YES/NO
Fluid retention YES/NO

6. How many times did you menstruate in the past year? _____

7. How many periods have you missed in the last five years? _____

8. Are you currently taking oral contraceptives? YES/NO

If yes, for how long? _____

What is the name of the oral contraceptive pill which you are taking? _____

9. When was the last start of your period (DAY 1)? _____

Medical History

1. Are you currently taking any medications (excluding oral contraceptives)?

Please List: _____

2. Do you currently smoke? YES/NO

3. Are you a past smoker? YES/NO

4. When was the last time you had a cold? _____

5. Do you have asthma, other lung problems or significant illness? Please List:
_____

Physical Activity History

Activity #1:_____
Average Duration: _____
Average Frequency: _____
Average Intensity (state heart rate if known):_____
Do you compete? If so, at what level, how often a year, and for how many years?_____
_____
_____

Activity #2:_____
Average Duration: _____
Average Frequency: _____
Average Intensity (state heart rate if known):_____
Do you compete? If so, at what level, how often a year, and for how many years?_____
_____
_____

Activity #3:_____
Average Duration: _____
Average Frequency: _____
Average Intensity (state heart rate if known):_____
Do you compete? If so, at what level, how often a year, and for how many years?_____
_____
_____

Activity #4:_____
Average Duration: _____
Average Frequency: _____
Average Intensity (state heart rate if known): _____
Do you compete? If so, at what level, how often a year, and for how many years? _____
_____
_____

All other activities:_____
_____
Average Duration: _____
Average Frequency:_____
Average Intensity:_____
_____

Have you had a VO_{2max} test done before? If so, what was your score previously?_____
_____

APPENDIX D – VO_{2max} PREDICTION EQUATION

Part 1:
Perceived Functional Ability (PFA)

Suppose you were going to exercise continuously on an indoor track for 1 mile. Which exercise pace is just right for you – not too easy and not too hard?

Circle the appropriate number (any number, 1-13):

1 Walking at a *slow* pace (18 minutes per mile or more)
2
3 Walking at a *medium* pace (16 minutes per mile)
4
5 Walking at a *fast* pace (14 minutes per mile)
6
7 Jogging at a *slow* pace (12 minutes per mile)
8
9 Jogging at a *medium* pace (10 minutes per mile)
10
11 Jogging at a *fast* pace (8 minutes per mile)
12
13 Running at a *fast* pace (7 minutes per mile or less)

How fast could you cover a distance of 3-miles and NOT become breathless or overly fatigued? Be realistic.

Circle the appropriate number (any number, 1-13):

1 I could walk the entire distance at a *slow* pace (18 minutes per mile or more)
2
3 I could walk the entire distance at a *medium* pace (16 minutes per mile)
4
5 I could walk the entire distance at a *fast* pace (14 minutes per mile)
6
7 I could jog the entire distance at a *slow* pace (12 minutes per mile)
8
9 I could jog the entire distance at a *medium* pace (10 minutes per mile)
10
11 I could jog the entire distance at a *fast* pace (8 minutes per mile)
12
13 I could jog the entire distance at a *fast* pace (7 minutes per mile or less)

George et al. (12)

Part 2:
Physical Activity Rating (PA-R)

Select the number that best describes your overall level of physical activity for the previous 6 months:

0 = avoid walking or exertion; eg. always use the elevator and drive instead of walking

1 = light activity: walk for pleasure, routinely use stairs, occasionally exercise sufficiently to cause heavy breathing

2 = moderate activity: 10 to 60 minutes per week of moderate activity; such as golf, aerobics, tennis, bowling, weight lifting, yard work, walking.

3 = moderate activity: over 1 hour per week of moderate activity described above

4 = vigorous activity; run less than one mile per week or spend less than 30 minutes in comparable activity such as running or jogging, swimming, cycling, rowing, aerobics, soccer, basketball, tennis, racquetball, squash.

5 = vigorous activity: run one mile or less than 5 miles per week or spend 30 minutes to less than 60 minutes per week in comparable activity.

6 = vigorous activity: run 5 miles to less than 10 miles per week or spend one hour to less than 3 hours per week in comparable activity.

7 = vigorous activity: run 10 miles to less than 15 miles per week or spend 3 hours to less than 6 hours per week in comparable activity.

8 = vigorous activity: run 15 miles to less than 20 miles per week or spend 6 hours to less than 7 hours per week in comparable activity

9 = vigorous activity: run 20 to 25 miles per week or spend 7 to 8 hours per week in comparable activity.

10 = vigorous activity: run over 25 miles per week or spend 8 hours per week in comparable activity.

Equation:
VO_{2max} (ml/kg/min) prediction equation = 45.513 + (6.564 * gender) – (0.749 * BMI) + (0.724 * PFA) + (0.788 * PA-R)

Gender (0 = females, 1 = males)
R = 0.86, SEE = 3.44 ml/kg/min

George et al. (12)

APPENDIX E - ETHICS CERTIFICATE OF FULL BOARD APPROVAL

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

ETHICS CERTIFICATE OF FULL BOARD APPROVAL

PRINCIPAL INVESTIGATOR:	**INSTITUTION / DEPARTMENT:**	**UBC CREB NUMBER:**
William Sheel	UBC/Education/Human Kinetics	H08-00879

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

Institution	Site
UBC	Vancouver (excludes UBC Hospital)
Children's and Women's Health Centre of BC (incl. Sunny Hill)	Children's and Women's Health Centre of BC (incl. Sunny Hill)

Other locations where the research will be conducted:
N/A

CO-INVESTIGATOR(S):
Jill M. Kennedy
Michael S. Koehle
James E. Potts

SPONSORING AGENCIES:
- Michael Smith Foundation for Health Research - "Can intrapulmonary arteriovenous shunting explain exercise-induced arterial hypoxemia in women?"
- Natural Sciences and Engineering Research Council of Canada (NSERC) - "Respiratory and neurovascular adaptation to physiological stress"

PROJECT TITLE:
The Influence of Fitness Level on the Appearance of Intrapulmonary Arteriovenous Shunting in Healthy Women

THE CURRENT UBC CREB APPROVAL FOR THIS STUDY EXPIRES: September 9, 2009

The full UBC Clinical Research Ethics Board has reviewed the above described research project, including associated documentation noted below, and finds the research project acceptable on ethical grounds for research involving human subjects and hereby grants approval.

REB FULL BOARD MEETING REVIEW DATE:
September 9, 2008

DOCUMENTS INCLUDED IN THIS APPROVAL:

DATE DOCUMENTS APPROVED:

Document Name	Version	Date
Protocol:		
Fitness and I-P Shunt Recruitment in Healthy Women	3	October 3, 2008
Consent Forms:		
Main Study Consent Form	2	October 3, 2008
Advertisements:		
Subject Recruitment	2	October 3, 2008
Questionnaire, Questionnaire Cover Letter, Tests:		
PAR Q	2	October 3, 2008
Menstrual, Medical, and Physical Activity History	1	July 15, 2008

October 7, 2008

Other Documents:	

CERTIFICATION:

In respect of clinical trials:

1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.

2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.

3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

The documentation included for the above-named project has been reviewed by the UBC CREB, and the research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved by the UBC CREB.

Approval of the Clinical Research Ethics Board by one of:

Dr. Gail Bellward, Chair

APPENDIX F - ETHICS CERTIFICATE OF EXPEDITED APPROVAL: RENEWAL

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

ETHICS CERTIFICATE OF EXPEDITED APPROVAL: RENEWAL

PRINCIPAL INVESTIGATOR:	**DEPARTMENT:**	**UBC CREB NUMBER:**
William Sheel	UBC/Education/Human Kinetics	H08-00879

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

Institution	Site
UBC	Vancouver (excludes UBC Hospital)
Children's and Women's Health Centre of BC (incl. Sunny Hill)	Child & Family Research Institute

Other locations where the research will be conducted:
N/A

CO-INVESTIGATOR(S):
Jill M. Kennedy
Michael S. Koehle
James E. Potts

SPONSORING AGENCIES:
- Michael Smith Foundation for Health Research - "Can intrapulmonary arteriovenous shunting explain exercise-induced arterial hypoxemia in women?"
- Natural Sciences and Engineering Research Council of Canada (NSERC) - "Respiratory and neurovascular adaptation to physiological stress"

PROJECT TITLE:
The Influence of Fitness Level on the Appearance of Intrapulmonary Arteriovenous Shunting in Healthy Women

EXPIRY DATE OF THIS APPROVAL: July 31, 2010

APPROVAL DATE: July 31, 2009

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

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

Approval of the Clinical Research Ethics Board by one of:
Dr. Peter Loewen, Chair
Dr. James McCormack, Associate Chair