University of Alberta

CARDIOPULMONARY FUNCTION IN ENDURANCE ATHLETES

by

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TABLE OF CONTENTS

LIST OF TABLES

Chapter Five

LIST OF FIGURES

Chapter Five

LIST OF SYMBOLS

Symbol	Definition
$A\text{-}aDO_2$	- Alveolar – arterial PO_2 difference
$D_{L_{CO}}$	- pulmonary diffusion capacity
D_M	- pulmonary membrane diffusion capacity
EDCA	- End-diastolic cardiac area
EDV	- End-diastolic volume
EIH	- Exercise-induced arterial hypoxemia
ER	- Endurance ride
ESCA	- End-systolic cardiac area
ESTA	- end-systolic total area enclosed by the epicardium
FEV1	- one-second forced expiratory volume
$FEF_{25\text{-}75}$	- forced expiratory flow between 25 and 75% of FVC
FVC	- Forced vital capacity
I-P Shunt	- Intra-pulmonary shunt
LAP	- Left atrial pressure
LV	- Left ventricle
MIGET	- Multiple inert gas elimination technique
PaO_2	- Arterial PO_2
PAO_2	- Alveolar PO_2
PAP	- Pulmonary artery pressure
PAWP	- Pulmonary artery wedge pressure
PVR	- Pulmonary Vascular Resistance
$\dot{Q}$	- Cardiac Output

$\dot{Q}s/\dot{Q}t$	- Fraction of shunt to total cardiac output
SaO_2	- Oxyhemoglobin saturation
RAP	- Right atrial pressure
TT	- 20 km time trial race
$\dot{V}_A$	- Alveloar ventilation
$\dot{V}_A/\dot{Q}$	- Ventilation to perfusion ratio
Vc	- Pulmonary capillary blood volume
$\dot{V}D$	- Deadspace ventilation
$\dot{V}_E$	- Minute ventilation

CHAPTER 1

INTRODUCTION

1.1 Epistomology / Ontology

Recently, the trend in exercise/human physiology and medical research has been towards the application of molecular biology to study cellular and subcellular responses (10). The results from these reductionist experiments may offer explanations for underlying basic relationships within physiology. For example, discovering how the myocardium remodels, or what signals activate phoshorylase, are all important in helping to understand human physiology. However, it is important to acknowledge that the human body, especially during exercise, represents a complex integration of many parts. Chalmers' (1) description of the world seems applicable to human physiology, that "Many kinds of processes are at work in the world around us, and they are all superimposed on, and interact with, each other in complicated ways." The principle of reductionism, which has been used extensively to study physiology, reduces concepts or reality to a more fundamental level. However, it should be noted that with reductionism come assumptions which can be problematic when findings are then re-applied to the whole human being (11). For example, it may be difficult to apply knowledge gained from studying an isolated cardiac muscle cell, to the function of the cardiovascular system, or alternately, the entire exercising human.

Caution towards reductionism in human physiology has been expressed recently by prominent pulmonary physiologists Dr. JB West and Dr. PD Wagner. In a recent article, West and Wagner (14) stated that the movement away from integrated physiology towards reductionism was regrettable, as many problems/questions remain unexplained. They were hopeful that the pendulum would eventually swing back towards studying the body as a whole. Similarly, it has been suggested by Rowell and Shepard in *Handbook of Physiology* that the study of physiology should progress from the molecular level to analysis of the whole animal, with the ultimate goal the understanding of the integrated exercising animal (8). While the reductionist approach to studying physiology is

invaluable, the challenge is for the integrated physiologist to apply this knowledge to the entire exercising human, for as pointed out by Secher and Ludbrook "It is hard to imagine a physiological system that is not affected by, or that does not effect muscular exercise." (10).

This thesis examined pulmonary and cardiovascular function simultaneously during exercise. The theoretical perspective taken could be characterized as a post-positivist, integrated physiologist. As a post-positivist, the limitations of testing and the potential fallibility of conclusions or assumptions are recognized. The subjects predominantly studied in this research were well-trained endurance athletes and therefore, it is acknowledged that the results may not be generalizable beyond this special group. It is the writer's belief that an integrated physiologist should recognize that the greatest advances are made when the knowledge gained by studying phenomena in isolation is then applied to the entire system or person.

1.2 General Introduction

The ability of the lungs to oxygenate the blood has not traditionally been considered as a limitation in oxygen transport during exercise (9). Dempsey et al. (2) demonstrated that highly trained athletes ($\dot{V}O_{2max}$ = 72 $ml \cdot kg^{-1} \cdot min^{-1}$) exercising at high workloads exhibited a significant decrease in arterial oxygen tension (PaO_2) due to an impairment in gas exchange, as demonstrated by a widened alveolar-arterial PO_2 difference ($A\text{-}aDO_2$). It is now accepted that most humans develop impaired gas exchange during exercise as demonstrated by an increased $A\text{-}aDO_2$. Depending on $A\text{-}aDO_2$ magnitude and the hyperventilatory response to exercise, a decrease in PaO_2 from rest can occur, reducing hemoglobin saturation (SaO_2). The significant fall in arterial oxygen tension and hemoglobin saturation has been termed exercise-induced arterial hypoxemia (EIH) (3). Mild hyperoxia has been used to return SaO_2 to pre-exercise values and shown to

improve performance and $\dot{V}O_{2max}$, indicating that EIH represents an important pulmonary limitation to exercise (5). Powers et al. (5) suggested that EIH can be observed in 50% of trained athletes capable of exercising at rates close to $\dot{V}O_{2max}$, however recent research has documented EIH at intensities as low as 50% of $\dot{V}O_{2max}$ (7).

Dempsey and Wagner (3) have noted that when examining issues around EIH, it is important to differentiate between the decrease in SaO_2 due to a shift in the oxyhemoglobin dissociation curve, as opposed to a widened A-aDO_2 causing a drop in PaO_2 and SaO_2. Similarly, researchers should differentiate between a decreased PaO_2 due to an inadequate ventilatory response to exercise (either a mechanical constraint, or decreased ventilatory drive) as opposed to a decreased PaO_2 secondary to widening A-aDO_2. This dissertation will focus on pulmonary gas exchange, which is typically evaluated by examining A-aDO_2, however predicted methods such as diffusion capacity have been used previously. Possible causes for the impaired pulmonary gas exchange during exercise include: diffusion limitation; ventilation-perfusion ($\dot{V}_A/\dot{Q}$) inequality; and intra- and extrapulmonary shunt (3).

The reasons behind the impairment in pulmonary gas exchange during exercise have puzzled pulmonary physiologist for many years. Dempsey et al. (2) hypothesized that a diffusion limitation develops during exercise secondary in inadequate pulmonary transit time. Alternately, Wagner et al. (13) proposed that pulmonary edema develops with exercise due to elevated pulmonary vascular pressures, resulting in a $\dot{V}_A/\dot{Q}$ mismatch. It should be noted that there are many different stages of pulmonary edema. Exercise-induced pulmonary edema likely represents a mild 'sub-clinical' form of edema whereby gas exchange is potentially impaired, but full alveolar flooding and froth development in the airways is unlikely (4). A great deal of research has attempted to document exercise-induced edema or damage, however the central theory behind this research is based on

research conducted as part of the Operation Everest research (6, 12, 13) which examined pulmonary artery pressure during exercise (see Chapter 2). Current studies of gas exchange are investigating edema or damage while a clear relationship between pulmonary artery pressure and the impairment in gas-exchange remains to be determined. As well, previous research has examined lung function in isolation, without regard to cardiovascular function, which can affect cardiac filling, pulmonary vascular pressures and, theoretically, pulmonary gas exchange.

1.3 Research Program Purpose

The purpose of this research program was to examine pulmonary and cardiovascular function together in an attempt to evaluate inter-relationships during exercise. It was hypothesized that cardiovascular function may help explain the impairment in pulmonary gas exchange typically observed during exercise. The first investigation examined pulmonary and cardiovascular function before and after 20 kilometers of intense simulated cycle racing. It was hypothesized that diffusion impairment post-exercise may be related to left-ventricular function. The second study was conducted to examine left-ventricular function and pulmonary gas exchange during prolonged exercise to exhaustion. In this study, it was hypothesized that prolonged exercise would result in impaired cardiac function, which would negatively affect pulmonary gas exchange.

The final project took a more mechanistic approach by directly evaluating the effect of pulmonary vascular pressure on pulmonary gas exchange. It was hypothesized that the elevation of pulmonary vascular pressures during incremental exercise via lower-body positive pressure would further impair pulmonary gas exchange. As well, agitated saline contrast echocardiography was used to test the theory that anatomical intra-pulmonary shunts develop with exercise and contribute to the impairment in gas exchange.

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CHAPTER 2

REVIEW OF LITERATURE

2.1 Pulmonary Gas Exchange During Exercise

Determinants of pulmonary gas exchange include extra-pulmonary: and intra-pulmonary (I-P) shunt; ventilation-perfusion ($\dot{V}_A/\dot{Q}$) inequality; and pulmonary oxygen diffusion limitation (8). These proposed mechanisms as they relate to exercise will be reviewed, with specific reference to I –P shunt and diffusion limitation. A large body of research in gas exchange and exercise has been driven by a theory that pulmonary edema / damage develops with exercise due to high pulmonary artery pressures (PAP) (58, 60). Pulmonary artery pressure is dependent on LV function, most specifically diastolic function and therefore, cardiovascular function and exercise will be briefly discussed.

2.2 Extra-Pulmonary Shunt

A portion of oxygenated blood leaving the left ventricle is directed through the bronchial circulation, returning to the left atrium through the thebesian veins. This less oxygenated blood is then combined with the newly oxygenated blood from the pulmonary circulation, decreasing PO_2 in the left atrium. Determination of extrapulmonary shunt is possible by breathing 100% O_2 and examining the change in arterial PO_2. Using this procedure, Torre-Buone et al. (53) calculated that extrapulmonary shunt was less than 0.18% of cardiac output during exercise, accounting for under 1% of the total exercise-induced arterial hypoxemia (EIH), suggesting that extrapulmonary shunt does not contribute to the widened A-aDO_2 during exercise.

2.3 Intra-Pulmonary Shunt

An alternate explanation for the increased alveolar arterial pressure difference (A-aDO_2) during exercise may be anatomical I-P shunting. Tobin (51) documented arteriovenous shunts within the secondary pulmonary lobules of normal human lungs. His findings were made from making casts of the pulmonary vasculature and with the injection of small glass spheres into the pulmonary arteries of isolated, perfused whole lung

preparations. These 200μm spheres are much larger than the pulmonary capillaries (10 μm) yet many were found in the pulmonary veins, indicating direct large artery to vein connections. It should be noted that the integrity of the pulmonary capillaries was maintained during perfusion. In an earlier study, Tobin and Zariquiey (52) injected glass beads of various diameters to demonstrate A-V shunts within different sections of the lung including: at the apex of the lobular subdivision of the bronchopulmonary segments (500μm), smaller bronchi and respiratory bronchioles (50-100μm) and near the alveolar sacs and alveoli (20-25μm). Cheney et al. (4) perfused isolated dog lungs with 50 μm beads and found that as pulmonary artery pressure was increased, more beads were recovered on the venous side, suggesting recruitment of shunt vessels with increased pressure. Through microscopic observation Irwin et al. (24) documented AV-shunts in the lungs of guinea pigs, while Rahn et al.(41) demonstrated A-V shunts with cinefluorography in dogs.

Shunt, as measured by the $\dot{Q}s/\dot{Q}T$ equation, has been shown to increase with increasing cardiac output (2, 37). Berk et al. (2) suggested that the increased shunt from high output states is the result of opening of anatomic arteriovenous shunts which may act as "pop-off valves" in response to increased vascular pressure. This mechanism is supported by Sykes et al. (49) who demonstrated an increase in $A\text{-}aDO_2$ with increasing pulmonary artery pressure in dogs, while as mentioned above, Cheney et al. (4) found more 50μm beads within the pulmonary veins as perfusion pressure was increased.

Intra-pulmonary shunt has been previously dismissed as a mechanism for the increased $A\text{-}aDO_2$ with exercise. Dempsey et al. found that arterial PO_2 increased with hyperoxia and suggested that the proportional increase in alveolar and arterial PO_2 does not suggest shunt as a mechanism. Wagner et al.(58) examined shunt during sea level cycling and found that with oxygen breathing PaO_2 increased to 570 mmHg, which equates to a

physiological shunt of approximately 6%. However, neither Wagner et al. (58) or Hopkins et al.(19), nor Rice et al. (43) have documented physiological shunt during exercise using the multiple-inert gas elimination technique (MIGET), leading them to conclude that I-P shunt does not contribute to A-aDO_2.

Precapillary pulmonary arterial oxygenation occurs in the small arteries of isolated cat lungs(6). Small pulmonary arteries (100μm) were found to take up oxygen from the alveoli during ventilation with room air, while blood in larger diameter arteries (400-500μm) was completely oxygenated during 100% O_2 ventilation. Similarly, rapid increases in oxygen and hydrogen in the pulmonary artery have been detected with increasing F_IO_2 and F_IH_2 in humans via the distal port of the Swan-Ganz catheter (25, 26, 46). These changes are detected rapidly (0.4-0.7 sec) following a change in FiO_2 and precede the elevation of O_2 in the descending aorta, arguing against the possibility of a bronchial arterial source of the increased pulmonary artery PO_2 (26).

These observations indicate that O_2 penetration occurs in the precapillary vessels, leading to significant oxygen uptake by the lungs. Conhaim and Staub (6) have estimated that pulmonary arterial blood is up to 15% oxygenated by this process at rest during room air breathing, with oxygen breathing fully oxygenating the precapillary vessels (6). Staub (48) pointed out that the pulmonary arteries run parallel to the airways, suggesting that the pulmonary arteries and airways are functionally related. Furthermore, the precapillary gas exchange may be important for regional pulmonary artery vasoconstriction in response to alveolar hypoxia (23). The contribution of precapillary oxygenation is likely dependent on flow rate (time available for diffusion), as well as driving pressure. Because of the significant precapillary gas exchange which seems to occur, Conhaim and Staub (6) pointed out that anatomical shunt calculated during 100% O_2 breathing may

underestimate the true intrapulmonary shunt, especially if large artery to vein vessels exist and if they have gas exchange function similar to the small arteries.

Precapillary pulmonary gas-exchange would likely under-estimate I-P shunt calculations using MIGET. If the small arteries take part in gas exchange, then the low solubility gases from MIGET (sulfur hexafluoride) would likewise diffuse from the small vessels and would appear as though no anatomical shunt existed. Instead, the MIGET result would appear as a decreased $\dot{V}_A/\dot{Q}$ ratio or a diffusion limitation.

Tobin (51) and Cheney et al. (4) have documented intrapulmonary shunting in isolated lungs. Intrapulmonary shunting as a mechanism for increased A-aDO_2 with exercise has been previously ruled out by 100% O_2 breathing and MIGET (7, 19, 58). However, the evidence of precapillary oxygenation questions previous shunt calculations using both 100% O_2 and MIGET.

2.4 Ventilation/Perfusion Mismatch

As part of the Operation Everest II projects, Wagner et al. (58) investigated diffusion limitation, Ventilation/Perfusion ($\dot{V}_A/\dot{Q}$) mismatch and their relationship to cardiac output and pulmonary artery/wedge pressure. Eight subjects were studied, five being cyclists, three being "more sedentary" ($\dot{V}O_{2max}$ values not given). Subjects road at sea level and simulated altitude, with peak intensity 240W (mean $\dot{V}O_2$ = 3.7 L· min^{-1}, $\dot{Q}$ = 23.9 L· min^{-1}, PAP = 37.2 mmHg). It was calculated that the increase in $\dot{V}_A/\dot{Q}$ mismatch accounted for one-third of the total A-aDO_2 at peak exercise, with the remainder due to a diffusion limitation.

A limitation of the Operation Everest II research was that well-trained endurance athletes were not used. Wagner et al. (58) described half of their subjects as "cyclists" while the

others were "more sedentary" which is reflected by their relatively low peak power outputs. The highest power output that could be sustained for up to five minutes by the group was 240 Watts ($\dot{V}O_2$ = 3.7 L· min^{-1}) which is similar to anaerobic threshold in a typical competitive cyclist. In a later study, Hopkins et al. (19) examined $\dot{V}_A/\dot{Q}$ mismatch and diffusion limitation with MIGET in 10 highly trained athletes (mean VO_{2max} = 5.15 L· min^{-1}). Subjects cycled at 150W, 300W and maximal exercise (372 ± 22W). It was hypothesized that these subjects would exhibit a much greater diffusion limitation at peak exercise as compared to the less trained subjects of Wagner et al. (58) because of their larger peak cardiac output. Surprisingly, $\dot{V}_A/\dot{Q}$ mismatch accounted for the greatest amount of the A-aDO_2 (60%), with diffusion impairment comprising only the remaining 40%.

The investigations by Wagner et al. (58) and Hopkins et al. (19) illustrate that $\dot{V}_A/\dot{Q}$ mismatch is responsible for 1/3 to 60% of the A-aDO_2 during incremental exercise with $\dot{V}_A/\dot{Q}$ mismatch appearing to be greatest among well-trained endurance athletes. Both Wagner et al. (58) and Hopkins et al. (19) have speculated that the $\dot{V}_A/\dot{Q}$ mismatch is secondary to the development of pulmonary edema, which is discussed below.

2.5 Diffusion Limitation

Wagner et al. (58) and Hopkins et al. (19) have shown using MIGET that the A-aDO_2 observed is greater than that predicted from $\dot{V}_A/\dot{Q}$ mismatch and intrapulmonary shunting. The difference between predicted and observed A-aDO_2 is said to represent a diffusion limitation or alternately, a poorly predicted A-aDO_2. The two dominant theories as to the cause of the diffusion limitation are a reduction in pulmonary transit time, or an increase in diffusion distance due to pulmonary edema or lung damage.

2.6 Diffusion Limitation – Reduced Pulmonary Transit Time

One of the first theorized causes of the widened exercise A-aDO_2 was a diffusion impairment secondary to inadequate red blood cell transit time in the pulmonary capillaries (7). Pulmonary capillary blood volume expands through capillary recruitment and distension as exercise intensity increases however it is hypothesized that at a VO_2 of 3.5 L·min^{-1}, lung blood volume has reached its morphological limit (59). Any further increase in cardiac output ($\dot{Q}$) would result in a decrease in the amount of time available for gas exchange. The minimum pulmonary transit time thought to be required for complete O_2 equilibration between alveolar gas and end-capillary blood is 0.25 seconds (7). Warren et al. (59) calcuated "mean" transit time and found that it did not decrease with exercise and explained no more than 9% of the A-aDO_2. However, it should be noted that Warren et al. (59) used nitric oxide breathing to calculate pulmonary capillary blood volume which could affect vascular recruitment and distension. Furthermore, blood gases were not corrected for temperature, potentially confounding the relationship between A-aDO_2 and transit time.

Hopkins et al. (17) has calculated whole lung transit time using radionuclide angiography and MIGET in well-trained endurance athletes. Whole lung transit time decreased with increasing intensity and was related to diffusion limitation ($r=-0.58$, $p<.05$). Pulmonary capillary transit time was estimated to be as little as 0.14 seconds 15% of the time, which suggests that parts of the lung may receive high perfusion and have a correspondingly short equilibration time. Recently Zavorsky et al.(67) examined the effects of acute hypervolemia on pulmonary transit time in endurance athletes. Mean pulmonary transit time was actually increased by 0.3 seconds with hypervolemia, but A-aDO_2 was not affected. The authors acknowledged that acute hypervolemia may have affected $\dot{V}_A/\dot{Q}$ matching and diffusion limitation differently, resulting in no overall change in A-aDO_2.

However, based on the results it was concluded that rapid pulmonary transit time did not affect gas exchange.

It should be noted that calculations of "mean" transit time require extremely accurate measurements of $\dot{Q}$ and pulmonary blood volume. Any error in measurement, or a lack of sensitivity, would affect results. As the name implies, mean transit time is the average for the whole lung, it assumes equal perfusion and alveolar ventilation ($\dot{V}_A$) throughout the lung and as previously explained, $\dot{Q}$ and $\dot{V}_A$ vary greatly within the lung. Therefore, while the mean transit time may not have changed, local transit time may have dropped below the minimal amount of time for equilibration, contributing to A-aDO_2.

2.7 Diffusion Limitation – Pulmonary Edema / Damage

An alternate explanation for the diffusion limitation observed during exercise is pulmonary edema / damage secondary to high pulmonary artery pressures (58, 60). As previously mentioned, Wagner et al. (58) examined PAP and pulmonary wedge pressures (PAWP) during incremental exercise up to 240W ($\dot{V}O_2$ = 3.72 L·min^{-1}) in eight subjects. At peak exercise, $\dot{Q}$ was 23.9 L·min^{-1}, while mean PAP and PAWP were 37.2 mmHg and 21.1 mmHg respectively. Likewise, Higginbotham et al.(16) have reported a mean pulmonary artery pressures of 22.6 mmHg with wedge pressures of 10 mmHg while subjects were exercising at a lower intensity ($\dot{V}O_2$ = 2.55 L·min^{-1}).

Pulmonary capillary pressure in humans is uncertain, however based on animal studies, capillary pressure is estimated to be at least mid-way between arterial and wedge pressure (61). Studies based on fluid movement suggest that capillary pressure is closer to arterial pressure (65). Therefore, if PAP and PAWP are 37 mmHg and 21 mmHg respectively during heavy exercise, pulmonary capillary pressure should be over 29 mmHg, with capillary pressure at the base of the lung exceeding 35 mmHg (60).

The blood-gas barrier in humans has a thickness as small as 0.3 μm, which allows gas exchange to occur as efficiently as possible (60). For a capillary trans-mural pressure of 40 mmHg and a wall thickness of 0.3μm, the calculated wall stress would be 9×10^4 N/M^2 (90 kPa or 9×10^5 dyn/cm), comparable to that of the aorta, which is protected by large amounts of collagen and elastin (61). Striking ultrastructural damage has been demonstrated in the capillary walls of the lung above 40 mmHg in rabbits (54). This damage can occur to the capillary endothelial and alveolar epithelial cell layers as a direct result of high capillary trans-mural pressure. This indicates that the blood-gas barrier is thin but extremely strong relative to its wall thickness, however when pushed to extreme levels it ruptures, causing damage (61).

As pulmonary arterial pressure is raised from normal to high values, it has been shown that fluid moves from the capillary lumen into the alveolar wall interstitium, and possibly into the alveolar space (61). This induced edema would become more severe as PAP increases with hemorrhage of the blood-gas barrier the end result. Applying the empirical data collected in isolated lung models, it is hypothesized by West and Mathieu-Costello (61) that as PAP increases during exercise, pulmonary edema would first develop, with a further elevation causing pulmonary hemorrhage.

Direct evidence of edema in humans following exercise is rare and has only been documented in isolated incidences. Young et al. (66) reported neurogenic pulmonary edema in a healthy untrained subject following a marathon. McKechnie et al. (34) described two similar cases of pulmonary edema in two highly trained marathon runners who had competed in an ultra-marathon (90km) and hypothesized that edema was due to some cardiac abnormality which is susceptible to physiological changes only during

prolonged exercise. Interestingly, this conclusion by McKechnie et al. (34) was made despite an absence of cardiac abnormalities in these subjects following the race.

Because of the difficulty in measuring 'sub-clinical' pulmonary edema, many indirect methods have been used to infer pulmonary edema following exercise. Increased lung density following a triathlon has been ascribed as subclinical pulmonary edema (3). As well, a disruption in the alveolar-capillary membrane resulting in edema or hemorrhage could decrease pulmonary diffusion. A reduction in the pulmonary membrane diffusion capacity (D_M) has been suggested as a marker of edema or damage to the blood-gas barrier (14, 36), and decreased D_M has been found following short term maximal cycling (35, 44), rowing (14) and marathon running (32, 36).

Hopkins et al. (20) demonstrated the first empirical evidence of exercise-induced lung damage. Six elite male cyclists ("high caliber", no fitness data given) raced up a 4 km hill as fast as possible. Average time for completion was 7 minutes, with race intensity averaging 92% of age-predicted heart rate while three sedentary subjects acted as controls and did not race. Bronchoalveolar lavage was performed in all subjects following the race and increased red blood cells, total protein and leukotriene B_4 were found in the exercised subjects. Hopkins et al. (20) speculated that high intensity exercise greatly increases the pulmonary capillary pressure, altering the integrity of blood-gas barrier and increasing permeability to red blood cells and proteins. In a follow-up study Hopkins et al. (21) did not find evidence of damage to the blood-gas barrier following one hour of cycilng at 77% of $\dot{V}O_{2max}$. The findings of Hopkins et al. (20) are often cited as evidence for exercise-induced damage, however all the participants (n=6) had a history of hemoptysis after exercise (10). Unfortunately, gas exchange was not collected, making conclusions relating to pulmonary gas exchange unavailable.

Eldridge et al. (11) published a short report on 5 subjects who were at altitude and performed cycle ergometry at 85% of $\dot{V}O_{2max}$. Pulmonary gas exchange increased with exercise and returned to baseline 90 minutes into recovery. Bronchoalveolar lavages were performed 120 minutes and 24 hours post exercise and inflammatory markers were found within the lavage fluid, suggesting epithelial injury. Unfortunately non-exercise controls were not used, making it difficult to discern whether the damage was due to altitude, the technique, or the exercise stress.

Edwards et al. (10) examined pulmonary clearance rates and gas exchange following incremental exercise to exhaustion. Clearance rates, an indication of alveolar epithelial damage, were not increased following graded exercise and were not related to $A\text{-}aDO_2$. Recently, Hanel et al. (15) found increased clearing rates immediately following a 2000m simulated rowing race which was attributed to exercise-induced edema or damage. Clearance rates were elevated through 20 minutes post-exercise before returning towards baseline 125-132 minutes after exercise. Due to the time-dependency, Hanel et al. (15) suggested that Edwards et al. (10) failed to detect elevated clearance rates because measurements were not taken until 38 minutes after exercise.

Investigations with thoroughbred horses who all exhibit hypoxemia, pulmonary hemorrhage and severely elevated PAP during exercise, have raised questions as to the link between PAP and hemorrhage / gas-exchange impairments. Manohar et al. (33) examined pulmonary gas-exchange during repeated 120 seconds high intensity exercise bouts as they hypothesized that the first interval would cause hemorrhage, resulting in a greater impairment in gas exchange on the second interval. Despite evidence of hemorrhage following the first bout, PaO_2 was actually higher during the second interval. It was suggested that the increased PaO_2 was due to an increase in ventilation. Unfortunately respiratory gas-exchange data was not collected, making calculations of

PAO_2 and A-aDO_2 impossible. The improved PaO_2 despite significant hemorrhage questions the relationship between exercise-induced hemorrhage and pulmonary gas exchange.

Kindig et al. (28) found that when PAP is decreased with nitric oxide, horses actually had greater hemorrhage post-exercise and suggested that the high PAP during exercise may be the result of arteriole vasoconstriction which serves to protect the capillaries from the high PAP during exercise. Wilkins et al. (63) exercised horses maximally while attempting to document extravacular water, which was believed to reflect exercise-induced edema. Despite high pulmonary pressures (~75mmHg) during exercise, no increase in extravascular water was found and it was concluded that any increase in water from pulmonary hypertenstion was small and accumulated at a level that was below detection using their cold-saline/ impedence method. It should be noted that applying findings from the horse model to humans is not perfect because the two species differ in some responses to exercise. For example, unlike humans, horses maintain good ventilation / perfusion matching during high to maximal intensity exercise (57).

Human data also questions the development of exercise-induced edema. Manier et al. (31) investigated lung density using a CT scan following 2 hours of running at 75% of VO_{2max}. Following the run, subjects displayed similar lung mass compared to before exercise, indicating an absence of exercise-induced edema. As well, researchers have failed to demonstrate a relationship between arterial hypoxemia and post-exercise measurements diffusion capacity (35, 43, 44), questioning the technique as a valid marker of diffusion abnormalities during exercise. One large caveat to previous CT scan and diffusion capacity research is that resting post-exercise measures do not necessarily predict what has occurred during exercise. Quick evaluation is vital, as isolated lung models have been shown to recover / repair from pulmonary hypertension within a few

minutes (12). As a result, the relationship between post-exercise lung function and pulmonary gas exchange during exercise remains unclear.

Wetter et al. (62) investigated pulmonary gas-exchange during constant running at 90% of $\dot{V}O_{2max}$ to exhaustion (mean time = 14min) in women. An increase in A-aDO_2 was observed at the onset of exercise with no further deterioration at exhaustion. Similarly, Hopkins et al. (18) found a widened A-aDO_2 at the onset of cycling at 60% of VO_{2max}, however gas exchange was maintained over the 60 minutes of exercise. Wetter et al. (62) argued that if the gas exchange impairment was due to edema or inflammation brought on by high pulmonary artery pressure during exercise, there should have been a subsequent increase in A-aDO_2 as the blood-gas barrier is further exposed to high pressures during longer exercise. However, it is possible that edema developed rapidly at the start of exercise, but fluid balance then maintained an elevated steady state such that gas exchange was not further impaired. The consistency of A-aDO_2 during sustained exercise suggests at a minimum, that gas exchange is not further impaired with continued elevated pulmonary vascular pressures during exercise.

2.8 Pulmonary Conclusion

In all likelihood the impairment in pulmonary gas exchange during exercise is multi-factorial, with $\dot{V}_A/\dot{Q}$ mismatch and diffusion limitation being the most likely contributors. A limitation of the previous research examining gas exchange is that investigators have looked at the pulmonary system in isolation. Central to the theory of exercise-induced $\dot{V}_A/\dot{Q}$ mismatching and pulmonary edema/damage, is an increase in PAP with exercise. PAP is a function of both 'up-stream' and 'down-stream' components, but most important during exercise is left-ventricular (LV) function. A decline in either LV diastolic or systolic function during exercise would increase PAWP

and PAP, potentially affecting gas exchange. Left-ventricular function during exercise, with specific reference to diastolic function, will now be examined.

2.9 Left-Ventricular Diastolic Filling and Exercise

During exercise, cardiac output is augmented via increases in heart rate and stroke volume. Stroke volume increases via a drop in end-systolic volume, secondary to an increase in contractility and decreased afterload, while end-diastolic volume is either maintained or increased (27). Whether end-diastolic volume is increased or maintained, diastolic function must be augmented so that the trans-mitral filing pressure and filling rate are increased with exercise (30).

Several factors affect LV diastolic pressure and thus the diastolic properties of the LV. These variables include the elastic and geometric properties of the LV, the rate of relaxation, the extent of relaxation, diastolic suction, pericardial constraint, ventricular interaction, myocardial viscoelasticity, ischemia, heart rate and coronary vascular volume (13).

Chronic exercise training enhances diastolic function. Possible mechanisms for the augmented function include training induced cardiac hypertrophy, altered calcium uptake in the sarcoplasmic reticulum, and sinus bradycardia. The intermittent pressure and volume overload brought on by exercise is believed to result in myocardial hypertrophy (30), which results in increased end-diastolic volumes at both rest and during exercise (9, 56). As well, the sinus bradycardia from chronic aerobic exercise, both at rest and during exercise, increases the time available for filling (45). Libonati (29) demonstrated that endurance trained rats have a lower LV pressure over a wide range in volumes, indicating greater LV compliance. This may explain why humans with a greater exercise capacity had a shorter resting LV isovolumic relaxation time (adjusted to a standard R-R interval

of 1000 ms) despite a similar LV diastolic interval (29) and why LV early diastolic filling was the most powerful predictor of $\dot{V}O_{2max}$ (56).

The exact cellular mechanisms for improved diastolic function from training are unknown but are believed to be due to alterations within myocardial collagen metabolism, or myocyte energy metabolism. Exercise has been found to improve the rate of left ventricular pressure decline (-dP/dt) while increasing calcium uptake by the sarcoplasmic reticulum (50) and calcium stimulated myosin ATPase activity (40). Exercise training has also been found to increase myocardial LV cytochrome c concentration, as well as fatty acid oxidation rate (47).

2.10 LV Diastolic Function - Hemodynamic Data

Few investigations have directly measured LV filling pressures during exercise. Higginbotham et al. (16) investigated stroke volume during submaximal and maximal exercise in normal men and PAP and PAWP, while cardiac volumes were calculated using radionuclide angiography. Pulmonary artery pressure increased with intensity in a curvilinear fashion, with the greatest increases occurring at the lower intensities, while PW increased in a linear fashion through to 100% of $\dot{V}O_{2max}$ (2.55 L $\cdot$ min^{-1}). Mean pulmonary artery pressure reached 22.67 mmHg at peak exercise while PW reached 10 mmHg. Despite the increased PAP and PAWP pressures at peak exercise, end-diastolic volume (EDV) began to decrease past 50% of $\dot{V}O_{2max}$. The decrease in EDV with increasing PAWP pressure was believed to be the result of decreased diastolic filling secondary to a drop in LV compliance. Pericardial constraint was not considered a limiting factor because EDV was found to be larger in the supine position than at peak exercise. It should be noted that these subjects should not be considered physically active at best, with just 3 of 24 subjects exercising regularly, making the application of these findings to more physically active subjects difficult.

Reeves et al. (42) measured PAWP and right atrial pressure (RAP), as part of the Operation Everest II project that examined pulmonary gas exchange and altitude in nine aerobically fit subjects (mean $\dot{V}O_{2max}$ = 50.9 $mL \cdot min^{-1} \cdot kg^{-1}$) cycling up to 84% o $\dot{V}O_{2max}$ (43.0 $mL \cdot min^{-1} \cdot kg^{-1}$). The increase RAP was tightly coupled to increasing PAWP, with a 1 mmHg increase in RAP resulting in a 1.4 mmHg increase in PAWP. Mean peak RAP pressure was 8.25 mmHg while mean peak PAWP was 18 mmHg. Similarly to Higginbotham et al. (16), the largest increases in pressure occurred at the lower intensities. At near-maximal loads, further increases in RAP and PAWP did not result in increased stroke volume, suggesting diminished LV compliance. Reeves et al. (42) speculated that the high filling pressures may be necessary to maintain the atrial-ventricular gradient across the mitral valve which may come at a cost of high PAP pressure and fluid filtration in the lung.

2.11 LV Diastolic Function - Trans-mural Filling Pressure

The work of Higginbotham et al. (16) and Reeves et al. (42) represent the most extensive evaluations of LV filling and function during exercise in humans. However, despite being the most comprehensive to date, they do not provide a complete picture to allow for proper evaluation of LV function and filling during exercise. Belenkie et al. (1) have argued that to obtain the full picture of LV filling, volumes, pressures as well as trans-mural filling pressure needs to be reported. LV volume is not simply a function of end-diastolic pressure (which is predicted by PAWP) but also surrounding pressure which can be predicted from RAP pressure. The difference between PAWP and RAP pressure represents the diastolic trans-mural pressure, or the "true" filling pressure of the LV. Without calculation of trans-mural filling pressure, only a partial picture of LV function can be obtained, and we are left to speculate as to changes in LV compliance with exercise. Higginbotham (16) reported LV dimensions and PAWP pressure, but did not

document RAP pressure. Reeves et al. (42) did not record cardiac volumes, only stroke volume, however RAP and PAWP pressures were reported. When the data from Reeves et al.(42) is used to estimate trans-mural pressure, we see that trans-mural pressure did not increase after 66% of $\dot{V}O_{2max}$. The maintenance of "true" filling pressure may explain why stroke volume does not increase further past this intensity despite increases in absolute RAP and PAWP pressures.

Further support for the use of "true" filling pressure is obtained when examining individual values at peak exercise. When individual values of trans-mural filling pressure are correlated to stroke volume at maximal exercise there is a significant relationship ($r=0.85$, $p=0.02$), indicating that the greater the filling pressure, the larger the stroke volume. Confidence in this relationship would be increased if pressures and stroke volume were given for individuals across all intensities, however it does suggest that trans-mural filling pressure is important to stroke volume and cardiac output regulation during exercise. However, there remains no comprehensive investigation to-date examining LV function during exercise with reference to the pericardium. As a result, we are left two speculate what is truly occurring, relying on indirect predictions of LV function with exercise.

2.12 Systolic function and Ventricular Suction

During exercise there is an increase in circulating catecholamines, which increases myocardial force of contraction. The increase in contractility, combined with the typical drop in cardiac afterload with exercise results in a lower end-systolic volume, increasing stroke volume. Yellin and Nikolic (64) have suggested that when the LV contracts below its equilibrium volume (which can arise from either a decrease in LV afterload or increased contractility), the corresponding elastic recoil produces a negative LV pressure in early diastole, and results in a decreased left atrial pressure (LAP). Increased

contractility has been shown to augment ventricular suction in dogs (22, 38, 39) and humans (55). Hori (22) has suggested that ventricular suction may be increasingly important during exercise because of the limited time for diastolic filling, and that in the absence of suction, a high LAP would be required to refill the ventricle.

Cheng et al. (5) investigated cardiac responses to exercise in dogs. Tachycardia decreased the duration of diastole from 296 to 162 msec, The maximum mitral valve pressure gradient was increased during exercise (5.5 vs. 11.8 mmHg) which was accomplished by a decrease in minimum LV pressure form 3.3 mmHg to -2.8 mmHg. A similar drop in early diastolic portion of the LV pressure-volume loop was accomplished by an infusion of dobutamine, It was therefore concluded that sympathetic stimulation and tachycardia produced the downwards shift in the early diastolic portion of the LV pressure-volume loop.

These results suggest that enhanced systolic function increases the trans-mitral filling gradient, enhancing diastolic filling. In fact, Yellin and Nikolic (64) have suggested that diastolic suction may be a requirement to keep left atrial pressure low, thus maintaining the integrity of the lungs. Unfortunately, due to the invasiveness required to measure early diastolic LV pressure, there are no reports examining trans-mitral filling pressure and early diastolic pressure healthy human during exercise. As a result, many questions remain regarding how LV function affects end-diastolic and pulmonary vascular pressures during exercise.

2.13 Dissertation Purpose

Ventilation / perfusion mismatch and a diffusion limitation brought on by pulmonary edema secondary to exercise-induced pulmonary hypertension has traditionally been one of the dominant theories proposed to explain the impairment in pulmonary gas exchange

during exercise. Pulmonary physiologists studying gas exchange have generally disregarded the cardiac mechanisms behind the increased PAP and PAWP pressures, assuming it is simply an unwanted by-product of a high exercise cardiac output. The observed exercise-induced pulmonary hypertension is principally based on a few studies as part of the Operation Everest research group, and no projects have re-visited these experiments with the goal of experimentally manipulating pulmonary hemodynamics to determine if PAP and PAWP directly affect pulmonary gas-exchange. Through three progressive research projects, this dissertation examined pulmonary and cardiovascular function during exercise in an attempt to evaluate the cardiovascular contribution to the impairment in pulmonary gas exchange.

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CHAPTER 3

The Effects of Cycle Racing on Pulmonary Diffusion Capacity and Left Ventricular Systolic Function

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3.1 Introduction

Isolated cases of clinically significant pulmonary edema have been documented following ultra-endurance running (12). These observations have led to speculation that subclinical perivascular or peribronchial edema may be a common result of exercise and could be linked to an impairment in pulmonary gas exchange. For example, Caillaud et al. (3) ascribed increased lung density following a triathlon to subclinical pulmonary edema. Reduced pulmonary membrane diffusion capacity (D_M) has also been suggested as a marker of edema (7, 14), and decreased D_M has been found following short term maximal cycling (13), rowing (7) and marathon running (11).

McKechnie et al. (12) reasoned that pulmonary edema following ultra-endurance running was secondary to left ventricular (LV) dysfunction. This argument was made despite an absence of cardiac abnormalities observed after the run. However, transient decreases in LV systolic function are well documented following prolonged exercise (21, 27). Wagner et al. (25) hypothesized that exercise-induced pulmonary hypertension caused pulmonary edema, negatively impacting gas exchange. Following this logic, impaired LV function during exercise would augment pulmonary capillary pressure contributing to edema and gas exchange impairment.

To our knowledge, the relationship between LV systolic function and pulmonary function has not been investigated. If the documented exercise-induced diffusion impairment results from pulmonary hypertension, then it follows that pulmonary diffusion may be influenced by LV function. This logic led to the hypothesis that a relationship would exist between impairment in pulmonary diffusion and LV function following high intensity exercise. During 20 km time trial racing (TT), experienced cyclists maintain a high fractional intensity which exceeds the lactate threshold for approximately thirty minutes (16, 23). As a result, this simulated race may be an ideal combination of intensity and

duration to examine heart and lung interactions. Therefore, the present study was designed to investigate the effects a 20 km simulated cycle race on pulmonary diffusion and LV systolic function.

3.2 Methods

3.3 Subjects and Design

Twelve experienced male cyclists [mean age (± SD)= 30.3 (6.9), height= 176 (6.0) cm, weight= 74.1 (5.3) kg, $\dot{V}O_{2max}$ Absolute = 4.52 (0.35) L · min^{-1}, $\dot{V}O_{2max}$ Relative = 60.9 (3.8) ml · kg^{-1} · min^{-1}] provided written informed consent to participate in this study which had received institutional ethics review board approval. All cyclists were at least Category III/Expert level racers, while some had national and international competitive experience.

Three experimental sessions were completed over a two week period in the following order: a practice TT session; the actual TT; and, a graded exercise test to determine lactate threshold (LT) and $\dot{V}O_{2max}$. The study was conducted near the end of the competitive season. Each subject agreed to modify his training regimen so that light training of consistent type, intensity and duration was performed on the days prior to each of the experimental sessions.

3.4 Practice Session

Conditions for the practice TT were identical to the actual TT except that gas exchange and blood collection were not done. All subjects were negative for exercise-induced asthma, which was assessed by spirometry before, and at 5, 10, 15, and 20 minutes after the practice race. Single-breath pulmonary diffusion capacity tests were also done at this time to familiarize the subjects with the protocol.

3.5 20km Simulated Time Trial

Each subject rode his own racing bicycle on a computerized cycle training system (Computrainer, Seattle, Washington). After a self-selected warm-up, each subject rode a simulated 20 km time trial race, from a standing start, as fast as possible. No feedback was provided on pace during the race. Subjects were not permitted to use their cycling computers and did not have access to heart rate, split-time, or total elapsed time information. An electric fan was directed at the subject for comfort and they were allowed to drink water freely.

At 2.5 km intervals, blood samples were drawn from a forearm venous catheter for subsequent determination of blood lactate concentration. All lactate samples were analyzed in duplicate using a YSI 2300 lactate analyzer (Yellow Springs, Ohio) with mean values reported. If the difference between duplicate samples was greater that 0.3 mM, the analyzer was re-calibrated and the samples re-analyzed. The lactate analyzer was calibrated every 5 samples, and in the event of analyzer drift, previous samples were re-analyzed.

Respiratory gas exchange data were recorded for 3 minutes spanning each 5 km interval using a ParvoMedics Truemax (Salt Lake City, Utah) metabolic measurement system. Gas analyzer calibration was verified at each 5 km interval. No substantial drifts (>0.0002 in FEO_2 and $FECO_2$) in the gas analyzers were noted during any test. The final gas collection period was during the last 3 minutes of the TT.

3.6 Pulmonary Function/Diffusion

Spirometry was performed and diffusion capacity (DL_{CO}) was measured before and 60 minutes after the TT using a Sensormedics 2450 Pulmonary testing system (Yorba Linda, California). Forced vital capacity (FVC), one-second forced expiratory volume (FEV_1)

and forced expiratory flow between 25 and 75% of FVC (FEF_{25-75}) were obtained according to American Thoracic Society (1) guidelines. The partitioning of D_M and pulmonary capillary blood volume (Vc) were done according to the method of Roughton and Forster (19) as described by McKenzie et al. (13). Diffusion measurements were done in duplicate first at normal and then high FIO_2 (0.208 and 0.900, respectively). Prior to performing the DL_{CO} measurement at the high FIO_2, 90% O_2 was breathed for five minutes to raise alveolar PO_2. Preceding both measurements, all subjects were seated, and rested quietly for 10 minutes. DL_{CO} values were corrected for barometric pressure as well as venous [Hb], obtained before and after the TT at the time of DL_{CO} measurement.

3.7 Echocardiography

Resting two-dimensional echocardiograms were performed using a commercially available ultrasound instrument (Sonos 5500, Hewlett Packard, Andover Massachusetts) with a 3.5 MHz transducer on all subjects. Measurements were taken before, immediately after, 5 minutes after, and 40 minutes after the TT. The echocardiographic data were obtained from the parasternal short axis view just apical to the mitral valve leaflets and were averaged over three cardiac cycles. Blood pressure was taken at the time of imaging using the same technician for each subject. Measurements were completed in accordance with the American Society of Echocardiography guidelines (20) and included: end-diastolic cavity area (EDCA), end-systolic total area enclosed by the epicardium (ESTA), end-systolic cavity area (ESCA), stroke area (end-diastolic cavity area minus end-systolic cavity area), fractional area change (stroke area / EDCA) and LV end-systolic wall-stress [1.33 x systolic blood pressure x ((ESTA – ESCA) / ESCA)]. Systolic blood pressure divided by ESCA (SBP/ESCA) was used as an index of LV contractility (8). All images were taken by the same technician and later analyzed in triplicate by a cardiologist and mean values were reported.

3.8 Graded exercise test

Subjects pedaled on an electrically-braked cycle ergometer (Sensormedics 800s, Yorba Linda, California) at a consistent self-selected cadence (range 80-110 rpm). The seat height and handle-bar position were adjusted to personal preference and each subject used his own clipless pedals and cycling shoes. After a 5 minute warm-up, the initial power output (range: 150-175 W) was selected to allow between 4 and 6 stages before the onset of the LT. Power output was increased by 25 W every 2 minutes until the ventilatory threshold (systematic increase in both the $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ ratios) was clearly surpassed. Thereafter, power output was increased by 25 W each minute until exhaustion. A 1ml blood sample was drawn after each 2 minute stage (during the first 30 seconds of the following stage) from an indwelling catheter inserted into a forearm vein to measure lactate concentration. Respiratory gas exchange data were collected continuously using the ParvoMedics Truemax system, while heart rate was recorded using the Polar telemetry system.

Blood lactate concentration (mM) was plotted against power output (W) and the change in lactate concentration with each 25W increment in power output was calculated. The LT was identified as a change in lactate concentration of ± 1.0 mM after a 25W increment (24).

3.9 Statistical analysis

Paired, two-tailed t-tests were used to compare differences in pulmonary values from before and after the TT. Repeated measures ANOVA using a Scheffé post hoc test was used to compare changes in heart function over time. Pearson product-moment correlation coefficients were calculated to estimate the strength of the relationships between pulmonary and cardiac variables. For all inferential analyses, the probability of Type I error was set at 0.05.

3.10 Results

Average (±SD) duration of the TT was 32.1 ± 1.7 minutes. Oxygen consumption during the TT averaged 3.79 ± 0.5 L $\cdot$ min^{-1} (83 ± 5.5% of $\dot{V}O_{2max}$ and 106 ± 7.9% of $\dot{V}O_2$ at LT). Heart rate was 93 ± 4.5% of maximum and 105 ± 5.5% of the HR at LT. Mean blood lactate during the TT was 8.4 ± 2.4 mM.

Both D_{LCO} and D_M were reduced ($p<0.05$) 60 minutes after the TT while Vc was not significantly decreased. Individual changes in D_M (Delta D_M: D_M before the TT minus D_M after the race) were correlated to changes in D_{LCO} ($r= 0.87$, $p<0.01$) but not Vc ($r= 0.36$, $p= 0.25$). Changes in D_{LCO} were not related to Vc ($r= 0.05$, $p= 0.88$). All of the simple spirometry measures were within normal limits or above normal for FEV_1 and FVC(5). There were no significant changes to the spirometry values following exercise.

Left ventricular contractility index and fractional area change, were significantly elevated immediately after the TT. While contractility returned to baseline 5 minutes after the TT, fractional area change was reduced. Compared to before the TT, heart rate was significantly increased both immediately and 5 minutes after the TT, while EDCA was reduced at all times during recovery.

Left ventricular contractility index and fractional area change were correlated with wall-stress immediately and 40 minutes after the TT, while fractional area change obtained 5 minutes after the TT was correlated with wall-stress over the same time period. EDCA was correlated with contractility index at all time points during recovery from exercise, while EDCA was correlated with fractional area change 40 minutes post TT. EDCA and wall-stress were correlated immediately and 40 minutes following the simulated race.

Average elapsed time between the end of the TT and the first post-exercise echocardiogram was 100 seconds (SD: 20, range 63 - 135). There was no relationship between systolic function assessed immediately after the TT and the time required to obtain these images (r=0.15).

Delta D_M was related to contractility index and fractional area change measured immediately (r= 0.75, p<0.01; r= 0.75, p<0.01 respectively) and 5 minutes (r= 0.59, p=0.05; r=0.61, p=0.04) after the TT. Subjects who had higher LV systolic function after the TT tended to have the smallest decrease in D_M, however this relationship was not significant at 40 minutes after the TT (r= 0.16, p=0.61; r= 0.29, p=0.35 respectively). The change in DL_{CO} was related to fractional area change immediately and 5 minutes after the TT (r= 0.70, p=0.01; r= 0.66, p=0.02 respectively), but no relationship was found between DL_{CO} and contractility measured immediately and 5 minutes after the TT (r= 0.53, p=0.08; r= 0.25, p=0.14). Delta D_M was not related to EDCA immediately (r=0.21, p=0.51), 5 minutes (r=0.1, p=0.9), or 40 minutes (r=0.14, p=0.66) after the TT. Delta D_M was related to wall-stress measured immediately (r=0.57, p=0.05) after the TT, but not 5 minutes (r=0.27, p=0.40), or 40 minutes (r=0.50, p=0.10) after the TT.

3.11 Discussion

When the average responses of the group of cyclists are considered, the main result of this study was that pulmonary diffusion was significantly reduced following simulated cycle racing despite enhanced LV systolic function. However, large inter-subject variability was observed in both diffusion and LV responses and when individual responses are explored, interesting relationships emerge. Individual changes in D_M were related to LV contractility index and fractional area change immediately and 5 minutes after exercise. The subjects who had the highest LV systolic function following the TT also had the least impairment in D_M. Similar relationships were found between the change in DL_{CO} and fractional area change immediately and 5 minutes post exercise.

Augmented systolic function has been shown to decrease LV pressure early in diastole, increasing the trans-mitral filling gradient, and decreasing pulmonary vascular pressures (4). It follows that the decreased pulmonary capillary pressure would reduce the likelihood of edema, which should be reflected by less diffusion impairment following exercise. In the present study, the cyclists with higher systolic function may have resisted the development of edema from exercise because of a more favorable LV filling pressure. However, if edema did develop during exercise, it was not sufficient to affect pulmonary mechanics, as post-exercise spirometry was not significantly impaired.

Some of the variability in left-ventricular systolic function following exercise may be explained by cardiac afterload. Contractility index and fractional area change were negatively related to wall-stress immediately and 40 minute after exercise, while fractional area change 5 minutes after exercise was negatively correlated with wall-stress obtained at the same time. This suggests that increased afterload adversely affected LV systolic function. Interestingly, those subjects who had greater wall-stress appeared to counteract this by increasing their preload reserve (i.e. EDCA) as wall-stress was

positively correlated with EDCA immediately and 40 minutes following exercise. This is consistent with findings of Janicki and Weber (10) who demonstrated that LV distensibility is increased with augmented afterload. The increase in preload is likely a compensatory mechanism to maintain stroke volume in the presence of increased wall-stress. The correlation between afterload and systolic function could be somewhat inflated because ESCA and systolic blood pressure are used in both calculations, however separation of these constructs in the intact exercising human is not feasible. Consistent with the relationships between LV systolic function and pulmonary diffusion, the subjects with the highest wall-stress immediately following exercise also had the largest post-exercise diffusion impairment. Our non-invasive data from exercising humans support previous research in isolated dog models (10) that diastolic compliance is increased with augmented cardiac afterload.

Grouped data from the sample indicate that EDCA was reduced at all points following the simulated race, suggesting compromised LV diastolic filling. A reduction in LV end-diastolic volume has been observed during maximal exercise despite increased pulmonary artery and pulmonary wedge pressures (9), suggesting a decrease in LV compliance with high-intensity exercise. However, a negative relationship was observed between EDCA and contractility index following exercise. Subjects who had the lowest EDCA following the TT appeared to compensate by increasing LV contractility. There was no correlation between the change in D_M and EDCA, indicating that there is no link between LV diastolic function and diffusion impairment. Further investigations are needed to examine a possible interdependence between LV systolic and diastolic function, pulmonary hemodynamics and gas exchange during exercise.

When cardiac output was estimated from exercise $\dot{V}O_2$ (mean TT $\dot{V}O_2$ = 3.79 L · min^{-1}), cyclists maintained a cardiac output of approximately 27 L · min^{-1} for over 30 minutes

during the TT, which indicates superior heart function. Even the lowest exercise cardiac output in this group was estimated at 25 L · min^{-1} and therefore it must be pointed out that systolic function observed in all our subjects was well within the range of enhanced function. This is supported by the greater fractional area change seen in our subjects during all stages of recovery, as compared to previous research following short-term exercise in healthy adults (17). The exact significance of the relationship between left ventricular systolic function and pulmonary diffusion impairment, in the presence of augmented post-exercise LV function, requires further investigation.

The decreases in DM and Vc seen 60 minutes after the simulated cycle race are consistent with previous research (7, 11, 13, 22). The development of pulmonary edema has been suggested to explain post-exercise reductions in diffusion membrane capacity (7, 15). However, previous researchers have failed to find a relationship between pulmonary gas exchange during exercise, and post-exercise changes in pulmonary diffusion (13, 18, 22). It is unknown if exercise causes the decrease in diffusion capacity, or if it is secondary to a redistribution of blood during recovery (6). Furthermore, the effects of pulmonary capillary blood volume, and therefore surface area for gas diffusion, on pulmonary membrane diffusion capacity are not completely understood (6). McKenzie et al. (13) has stated that much of the decrease in DM post-exercise is due to lower surface area for gas exchange resulting from a decrease in pulmonary capillary blood volume. However, DM has been shown to decrease despite Vc being elevated after exercise in some studies (11, 15). While capillary blood volume may affect DM, we found that Vc was not significantly decreased following the TT, and there was no correlation between DM and Vc. The relationship between LV systolic function and DM found in this study, questions the previous argument that reductions in membrane diffusion capacity are solely the result of decreases in pulmonary capillary blood volume.

Left ventricular contractility and fractional area change were enhanced immediately following the TT, which was likely due to increased circulating catacholamines or the treppe/staircase phenomenon (2). This finding is however, not consistent with previous reports of decreased systolic function following exercise of lower intensity and longer duration (21, 27). Mean values for fractional area change were reduced 5 minutes after the TT, as compared to pre-exercise values, however no other LV systolic impairment was observed during recovery. Therefore, thirty minutes of cycling at 83% of $\dot{V}O_{2max}$ (or 106% of $\dot{V}O_2$ at LT) did cause consistent LV systolic dysfunction in our subjects.

A fundamental limitation of the present study, and others (13, 21, 22, 27), is that post-exercise measures of heart and lung function were used to infer what was occurring during exercise. Echocardiography performed immediately after exercise should be interpreted with caution, as it may not represent what is occurring during exercise (17). Investigating a relationship between LV function and pulmonary gas exchange is therefore hampered by the time constraints in making the measurements. Measuring diffusion capacity and partitioning D_M and Vc takes several minutes and requires the subjects to be in a somewhat recovered state. Also, obtaining echocardiography images of acceptable quality during exercise is difficult. The non-invasive assessment of heart function using gas-dilution techniques requires normal gas exchange in the lung (26), which cannot be assumed when subjects exhibit impairments in gas exchange.

Resting values for pulmonary capillary blood volume in the present study were found to be higher than previous reports (13, 22). Previous studies had the subjects rest quietly for 30 to 60 minutes, while in the present study subjects rested for only 10 minutes because of the requirement of echo imaging to be done as close to DLCO measurements as possible. The shorter rest period, while standardized, would have resulted in elevated cardiac output and filling pressures, explaining our higher Vc values.

The present study examined LV systolic and pulmonary function following sustained high-intensity exercise. D_{LCO} and D_M were reduced following the 20 km simulated time trial. In contrast to other reports of decreased LV systolic function following ultra-endurance exercise, we found that shorter but more intense exercise does not have the same result. The reduction in D_M was correlated with LV systolic function following the TT, suggesting that the post-exercise diffusion impairment can be explained by cardiovascular function. This relationship provides grounds for further research to investigate the interaction between cardiovascular function, hemodynamics and pulmonary gas exchange during exercise in athletes.

Table 3-1
Measurements of pulmonary function (±SD) before and after the time trial

	Before TT	After TT	P-Value
$D_{L_{CO}}$ ($ml \cdot min^{-1} \cdot mmHg^{-1}$)	38.0 (3.5)	34.5 (4.0)	<0.01*
D_M ($ml \cdot min^{-1} \cdot mmHg^{-1}$)	49.2 (6.3)	45.1 (6.7)	0.03*
Vc (ml)	128 (30)	114 (30)	0.09
FVC (L)	5.75 (0.737)	5.84 (0.74)	0.24
FEV1 (L)	4.43 (0.64)	4.51 (0.70)	0.11
FEV1/FVC	0.77 (0.07)	0.77 (0.07)	0.95
FEF_{25-75} ($L \cdot s^{-1}$)	3.88 (1.16)	3.97 (1.30)	0. 42

Table 3-2
Echocardiography measurements (±SD) before, immediately, 5 minutes, and 40 minutes after the time trial

	Before	Immediate Post	5 Minutes Post	40 Minutes Post
EDCA (cm^2)	23.7 (4.5)	21.6 [1] (3.4)	21.7 [1] (3.2)	22.1 [1] (2.6)
ESCA (cm^2)	11.5 (3.0)	8.5 [1] (2.3)	11.6 [2] (2.4)	11.1 [2] (2.0)
Systolic Blood Pressure (mmHg)	112 (13)	134 (19)	110 (10)	102 (7)
Wall-Stress ($dynes \cdot cm^{2\,-1}$)	64.5 (14.9)	56.1 (15.6)	68.3 [2] (13.4)	59.0 (13.7)
Stroke Area (cm^2)	12.2 (2.4)	13.1 (2.3)	10.2 [1 2] (1.7)	11.0 [2] (0.8)
Fractional Area Change (%)	0.518 (0.06)	0.610 [1] (0.07)	0.458 [1 2] (0.06)	0.501 [2] (0.04)
SBP/ESCA ($mmHg \cdot cm^{2\,-1}$)	10.6 (4.0)	17.0 [1] (5.8)	9.9 [2] (2.3)	9.5 [2] (1.8)
Heart Rate ($beats \cdot min^{-1}$)	57 (6.1)	106 [1 2] (15.4)	89 [1 2] (10.7)	66 [2] (11.0)

[1] $p < 0.05$ vs. Baseline
[2] $p < 0.05$ vs. Immediate Post

Table 3-3

Correlation matrices for echocardiographic data: Panel A - immediately following the 20 km simulated time trial; Panel B - 5 minutes following the 20 km simulated time trial; and Panel C - 40 minutes following the 20 km simulated time trial.

A

	EDCA	Wall-Stress	SBP/ESCA	Fractional Area Change
EDCA	1	0.62*	- 0.62*	- 0.28
Wall-Stress	0.62*	1	- 0.75*	- 0.84*
SBP/ESCA	- 0.62*	- 0.75*	1	0.82*
Fractional Area Change	- 0.28	- 0.84*	0.82*	1

B

	EDCA	Wall-Stress	SBP/ESCA	Fractional Area Change
EDCA	1	0.44	- 0.72*	- 0.07
Wall-Stress	0.44	1	- 0.45	- 0.81*
SBP/ESCA	- 0.72*	- 0.45	1	0.40
Fractional Area Change	- 0.07	- 0.81*	0.40	1

C

	EDCA	Wall-Stress	SBP/ESCA	Fractional Area Change
EDCA	1	0.69*	- 0.94*	- 0.84*
Wall-Stress	0.69*	1	- 0.65*	- 0.93*
SBP/ESCA	- 0.94*	- 0.65*	1	0.80*
Fractional Area Change	- 0.84*	- 0.93*	0.80*	1

* $p < 0.05$

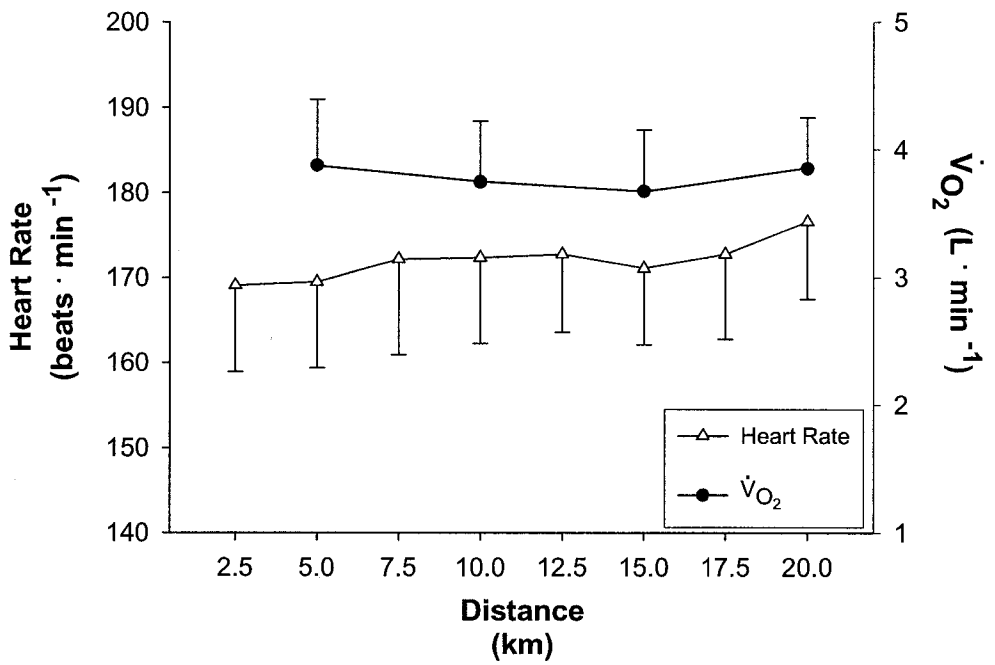

Figure 3-1. Mean (±SD) heart rate and oxygen consumption ($\dot{V}O_2$) during the 20 km simulated race.

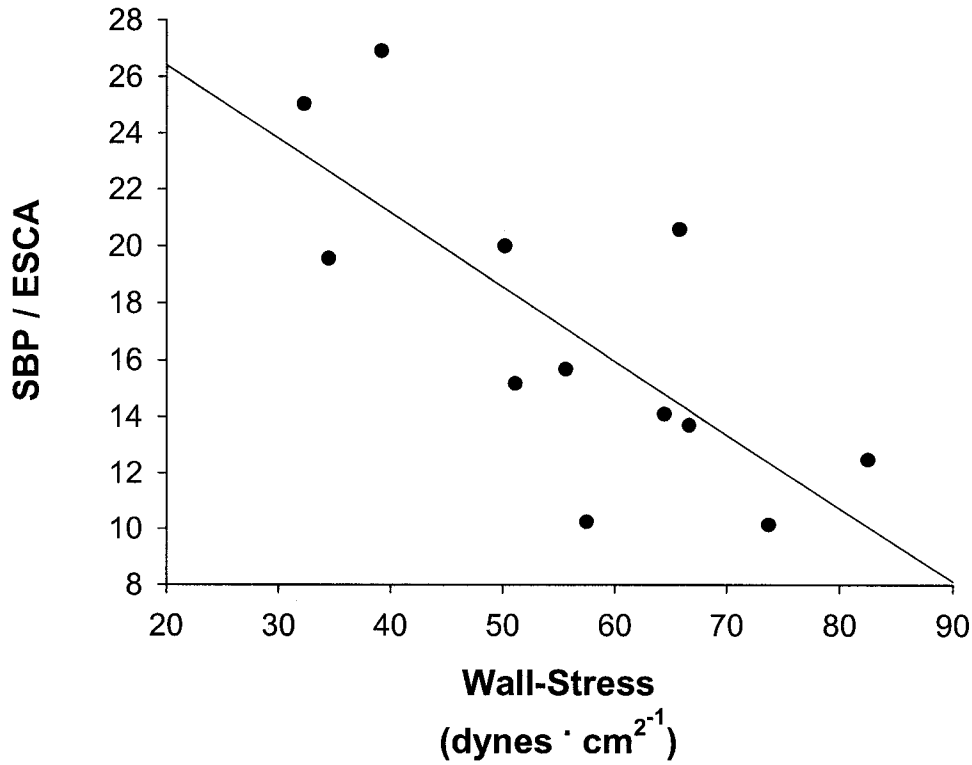

Figure 3-2. Relationship between cardiac afterload (wall-stress) and LV contractility index (SBP/ESCA) assessed immediately following the 20 km time trial ($r= -0.75$, $p<0.01$).

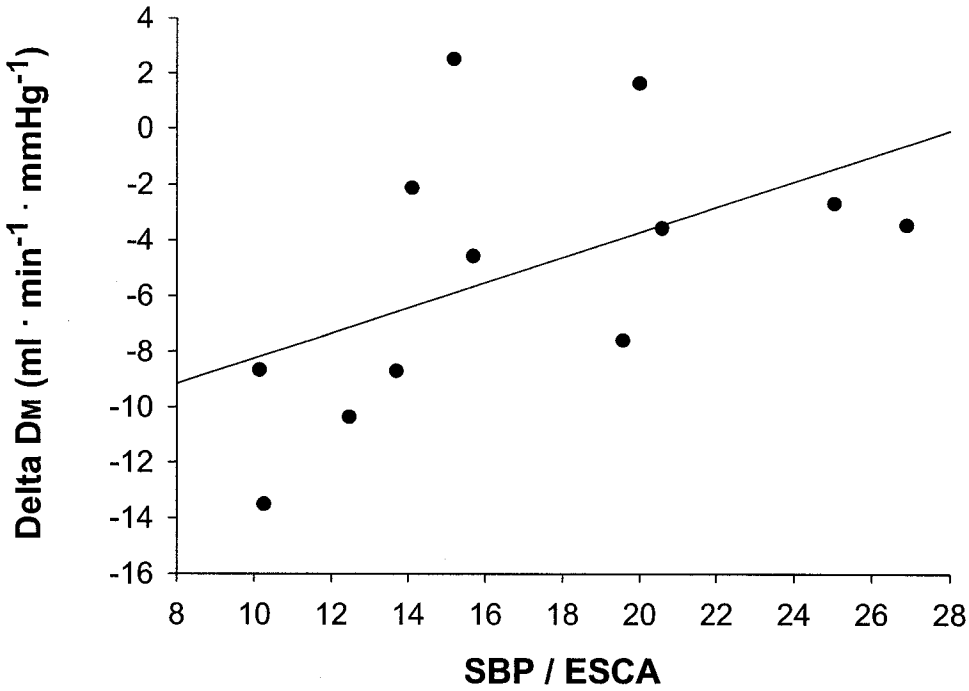

Figure 3-3. Relationship between the change in pulmonary membrane diffusion capacity (Delta D_M) and LV contractility index (SBP/ESCA) assessed immediately following the 20 km time trial ($r= 0.75$, $p<0.01$).

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CHAPTER 4

Effects of Prolonged Exercise to Exhaustion on Left-Ventricular Function and Pulmonary Gas Exchange

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4.1 Introduction

Decreased pulmonary diffusion capacity has been reported following both short and long duration aerobic exercise (20, 22, 23). The reason for this is not well understood, but it may be related to transient pulmonary edema or damage to the lung gas exchange barrier secondary to exercise-induced pulmonary hypertension (33). Exercise-induced impairment in diffusion capacity could be a cause for the widened alveolar-arterial PO_2 difference (A-aDO_2) and arterial hypoxemia observed during exercise (5). Reports of impaired pulmonary gas exchange during exercise, and decreased pulmonary diffusion capacity following exercise, suggest some form of exercise-induced pulmonary impairment that persists even after exercise.

The majority of research examining exercise-induced impairments in pulmonary gas exchange has focused on short duration, near-maximal intensity exercise. Examination of pulmonary gas exchange during longer, submaximal exercise may provide a different perspective on its etiology (5). Several researchers have studied non-exhaustive submaximal prolonged exercise (4, 15, 18, 32, 35), while Wetter et al. (38) investigated pulmonary gas exchange during relatively short-term (14 minutes) exercise to fatigue. Hopkins et al. (18) found an increase in ventilation/perfusion ($\dot{V}_A/\dot{Q}$) mismatch during 60 minutes of prolonged exercise and suggested that this was due to the development of pulmonary edema. In this study, we examine the effects of more prolonged (>60 min) constant-work exercise to exhaustion on gas exchange as we reasoned that this exercise model would exaggerate any gas exchange abnormality, if pulmonary edema were the cause.

Transient left-ventricular (LV) systolic dysfunction or "cardiac fatigue" has been reported following prolonged exercise and is characterized by reduced LV ejection fraction independent of changes in preload and afterload (29, 39). A significant decline in LV

function could increase pulmonary wedge and pulmonary artery pressures during constant work exercise. According to West (36), increased pulmonary capillary pressure results in stress failure and edema during exercise and a subsequent impairment in pulmonary gas-exchange. Previously, we have documented that pulmonary gas exchange can be influenced by the cardiovascular system (30). Endurance cyclists with the greatest diffusion impairment following simulated cycle racing also had blunted left-ventricular (LV) systolic function and higher LV afterload (30) and these results led us to suggest that the subjects with higher systolic function resisted exercise-induced edema because of a more favorable LV filling pressure.

Diffusion capacity and echocardiographic measurements of LV function have been done predominantly at rest before and after exercise. It is unclear if the changes seen at rest, before and after exercise, actually have physiological relevance during exercise or may be partially influenced by recovery. Also, other studies of cardiopulmonary function following endurance exercise (including our own) have typically used field or race conditions where subjects exercised at a self-paced intensity, making quantification and maintenance of workload difficult. It is therefore unclear if the reported changes in cardiopulmonary function result in fatigue or task failure.

The purpose of the present study was to investigate a potential cardiovascular contribution to the gas exchange impairment during exercise, by examining cardiopulmonary function throughout prolonged submaximal cycling to exhaustion. We hypothesized that the exercise-induced impairment in pulmonary gas exchange is related to LV function.

4.2 Methods

4.3 Subjects

Eleven male competitive cyclists [Mean (± SD) absolute $\dot{V}O_{2max}$ = 4.6 ± 0.3 L · min^{-1}, relative $\dot{V}O_{2max}$: 60.1 ± 4.5 ml · min^{-1} · kg^{-1}, age: 31.8 (7.1) years] provided informed consent to participate in this study which had previously received institutional ethics review board approval. All subjects were healthy, non-smoking and exhibited no exercise-induced bronchospasm upon screening. All cyclists were provincial, national or international level racers.

4.4 Research Design

Three experimental sessions were completed over a two-week period in the following order: (1) a graded exercise test to determine lactate threshold (LT) and $\dot{V}O_{2max}$ (2) a practice endurance ride and (3) an endurance ride (ER) to exhaustion. The study was conducted near the end of the competitive season and the subjects modified their training so that light training was performed on the days prior to the experimental trials.

4.5 Graded-Exercise Test

Each subject rode his own racing bicycle on a computerized cycle training system (Computrainer, Seattle, Washington) at a consistent self-selected cadence (range 80-110 rpm). After a 5 minute warm-up, the cycle trainer was calibrated and verified. The initial power output (range: 150-175 W) was selected to allow between 4 and 6 stages before the onset of the LT. Power output was increased by 25 W every 2 minutes until the ventilatory threshold, identified by a systematic increase in both the $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ ratios (34), was clearly surpassed. Thereafter, power output increased by 25 W each minute until exhaustion. A 1 ml sample of blood was drawn after each 2 minute stage (during the first 30 seconds of the following stage) from an indwelling catheter previously inserted into a forearm vein to measure lactate concentration. Respiratory gas

exchange data were collected continuously using a non-rebreathing valve (Hans-Rudolph, 2700, Kansan City MO) and a metabolic measurement system (ParvoMedics, Truemax, Salt Lake City, Utah) while heart rate was recorded using a telemetry system (Polar, Kempele, Finland).

An aliquot of venous blood was stored in preservative tubes (Yellow Springs Instruments, 2315, Yellow Springs, Ohio) and frozen until analysis could be performed in duplicate (Yellow Springs Instruments, 2300 Analyzer, Yellow Springs, Ohio). Blood lactate concentration (mM) was plotted against power output (W) and the change in lactate concentration with each 25W increment in power output was calculated. The LT was identified as the workload before a change of 1.0 mM in lactate concentration was observed following a 25W increment (31). This criterion was robust for all subjects.

4.6 Practice Ride

The power output selected for the endurance ride [mean (± SD) = 218 ± 16W] was 25W below the power output that elicited LT. The purpose of the practice ride was to familiarize the subject with the procedures as well as ensure the power output selected was appropriate. Following a five minute warm-up and calibration of the trainer, subjects cycled at their ER power output for 20 minutes. Heart rate and respiratory gas exchange data were collected to ensure the physiological responses were similar to the same power output during the graded exercise test. Each subject confirmed that he could maintain the target intensity for one hour or longer.

4.7 Endurance Ride

The ER was conducted following 2 days of light training. Subjects were told to prepare for the ride as they would for a typical race, which included usual dietary and hydration practices on the days leading up to the ride. Each cyclist was weighed prior to warm-up

and 10 minutes after the ride in the same dry clothing. Ambient temperature was kept constant at 21 °C, while fans were used to aid heat convection. During the ride subjects were free to consume water, sports drinks (eg. Gatorade®) and food (eg. Powerbars®). Once the ride began, shifting of gears was not permitted to minimize any slight change in intensity.

All physiological measurements were taken concurrently before, during and after exercise while the subject was seated on his racing bike, with hands resting on the handlebars. The baseline readings were done fifteen minutes after arterial catheter insertion, but before warm-up. Exercise measurements were taken at minute 15, 30 and every 30 minutes thereafter until exhaustion. Typically the participant informed the investigators when he had less than ten minutes remaining until exhaustion, at which point a final set of data were collected, labeled 'End'. After exercise, the participant pedaled at 100W for four minutes followed by one minute of rest while remaining on the bike. At this time, a final set of data were collected and labeled 'Post' exercise.

4.8 Blood-gas Measurement

Samples (2-3 ml) of arterial blood were drawn anaerobically from an indwelling catheter in the radial artery. Samples were immediately analyzed for arterial PO_2 (PaO_2), arterial PCO_2 ($PaCO_2$), pH, Hct and [Hb] (ABL 700 blood-gas analyzer, Copenhagen, Denmark). Blood gases were corrected for increases in tympanic temperature during exercise. We have found that tympanic temperature compares very well to core temperature during cycle exercise (mean bias = -0.4 °C, mean absolute difference = 0.5 °C, standard error of measurement = 0.1 °C). Arterial oxygen content (CaO_2) was calculated from hemoglobin saturation (SaO_2), [Hb] and PaO_2.Between samples a saline-drip (3 cc · hr^{-1}) was used to keep the catheter patent.

4.9 Respiratory gas-exchange

Respiratory gas exchange (RGE) data were collected over a two minute period using the same set-up as described for the graded exercise test. The same hose and breathing valve was used throughout the experiment in order to keep external deadspace constant. Mean values from the last minute of sampling were used for subsequent calculations. Alveolar PO_2 was calculated using the alveolar gas equation with water vapour pressure corrected for temperature. Alveolar ventilation was calculated from $\dot{V}CO_2$ and $PaCO_2$, while deadpace ventilation ($\dot{V}D$) was determined from the difference between $\dot{V}E$ and $\dot{V}A$ (37).

4.10 Echocardiography

Two-dimensional trans-thoracic echocardiograms were performed using ultrasound (Hewlett Packard, Sonos 5500, Andover, Massachusetts) with a 3.5 MHz transducer. During data acquisition, subjects were instructed to maintain a consistent position with their hands resting on the tops of their bicycle handlebars. As the intensity was below the LT, there was minimal interference from high ventilatory rates. As well, the typical slight body-build of the endurance cyclists allowed for the acquisition of good quality images. Measurements were completed in accordance with the American Society of Echocardiography guidelines (28). The 2D echocardiographic images were obtained from the parasternal short axis view just apical to the mitral valve leaflets. LV images recorded included end-diastolic cavity area (EDCA, largest cavity area) and end-systolic cavity area (ESCA, smallest cavity area). Stroke volume (SV) was calculated from the product of the velocity time integral and aortic cross-sectional area measured at rest (27), cardiac output ($\dot{Q}$) was determined from the product of heart rate and SV. It should be noted that aortic cross-sectional area was obtained at all points during exercise, and was not found to be different from rest. Fractional area change was quantified as (EDCA-ESCA)/EDCA, systolic blood pressure divided by ESCA (SBP/ESCA) was used as a

measure of contractility index while LV end-systolic wall stress was taken as 1.33 x systolic blood pressure x (end-systolic cavity / end-systolic myocardial area) (16). All images were acquired and subsequently analyzed in triplicate by the same experienced sonographer who was naïve as to the hypothesis of the study. Within subject coefficient of variation for aortic velocity time integral, ESCA and EDCA obtained at each time point averaged 3.1, 4.5 and 4.9% respectively. Within subject coefficient of variation for aortic diameter obtained at rest was 2.0%. Blood pressure (BP) was taken at the time of imaging using either intra-arterial blood pressure recorded by an arterial pressure transducer (N=9, Hewlett Packard, Viridian CMS, Andover, Massachusetts) or non-invasively by a blood-pressure cuff (N=2) with the same technician obtaining the readings for each subject.

4.11 Hematology

A second arterial blood sample was drawn for determination of arterial blood lactate and glucose. Blood was analyzed in duplicate with the same YSI 2300 analyzer used for lactate determination in the graded exercise test. Venous blood samples were taken immediately before exercise, and 20-24 hours after the endurance ride. Troponin-I was used as a biochemical marker of cardiac myocyte damage (ADVIA Centaur cTnI assay). This post-exercise time was selected because cardiac troponin-I levels are most sensitive and specific within this time period (9). Changes in [Hb] and hematocrit observed between baseline and end-exercise were used to estimate relative changes in blood volume and plasma volume (6).

4.12 Statistical Analysis

An arterial catheter could not be placed in one subject, therefore only his cardiovascular data are reported. ANOVA for repeated measures was used to test for changes over the endurance ride. Upon detection of an effect, t-tests for correlated samples were performed

between: pre-exercise and 15 minutes, 15 minutes and end-exercise, and pre-exercise and post exercise. A Bonferroni correction factor was applied to maintain familywise error rate at 0.05 (for each comparison p= 0.017). Pearson product-moment correlation coefficients were calculated to estimate the strength of relationships. For all inferential analyses, the probability of Type I error was set at .05.

4.13 Results

Mean time to exhaustion was 2.51 (±SD) 0.86 hours (Range: 1.11 - 3.50 hrs), mean oxygen consumption during the ride was 3.22 (0.10) L ± min^{-1} or 70 (0.05) % of $\dot{V}O_{2max}$. Average weight loss was 1.0 (0.9) kg (Range: 0.6 kg gain to 2.6 kg loss), average blood volume loss was 4.5 (4.3) % while plasma volume declined 8.3 (7.7) %. Tympanic temperature increased 1.1 (0.6) ° C during exercise.

Cardiovascular Function

At 15 minutes of exercise, compared to baseline, there were significant increases in stroke volume, heart rate, cardiac output, systolic and mean arterial pressures, SBP/ESCA and fractional area change

Systolic and mean arterial pressures were reduced at end exercise compared to 15 minutes. Left-ventricular end-systolic wall stress, a measure of cardiac afterload, was significantly lower at end-exercise compared with the 15 minute value, while fractional area change and SBP/ESCA were maintained through to exhaustion.

There was no significant change in cardiac output from the 15 minute value to the end of exercise. End-diastolic cavity area did not change significantly (p=0.10) at the end of exercise compared to the 15 minute value. The individual increases in heart rate during the ER were related to increases in body temperature (r=0.63, p = 0.05).

Pulmonary Gas Exchange

Within the first 15 minutes of exercise there was a significant decrease in PaO_2, an increase in A-aDO_2 and a decrease in SaO_2. The magnitude of the A-aDO_2 did not change over the ride, and it quickly returned to baseline 5 minutes after exercise. Arterial PCO_2 was decreased before exercise, indicating a mild anticipatory hyperventilation. There was no significant change in $PaCO_2$ or pH during the ER.

The alveolar-arterial PO_2 difference at 15 minutes of exercise was not related to PAO_2 ($r=0.13$, $p=0.71$), $PaCO_2$ ($r=0.20$, $p=0.59$) or $\dot{V}A$ ($r=0.41$, $p=0.24$) measured at the same time point.

The A-aDO_2 at 15 minutes of exercise was not significantly related to EDCA ($r=0.58$, $p=0.08$), ESCA, ($r=-0.01$, $p=0.99$), wall stress ($r=-0.03$, $p=0.93$), SBP/ESCA ($r=0.22$, $p=0.53$), fractional area change ($r=0.22$, $p=0.54$), stroke volume ($r=0.14$, $p=0.69$), or cardiac output ($r=0.02$, $p=0.96$) recorded at the same time point. Similarly, A-aDO_2 was not related to EDCA ($r=-0.02$, $p=0.95$), ESCA ($r=0.09$, $p=0.81$), wall stress ($r=0.12$, $p=0.74$), SBP/ESCA ($r=-0.11$, $p=0.76$), fractional shortening ($r=-0.14$, $p=0.71$), stroke volume ($r=-0.47$, $p=0.18$), or cardiac output ($r=-0.49$, $p=0.15$) at end exercise.

There was a significant increase in total ventilation during the ER despite the maintenance of alveolar ventilation, indicating an increase in physiological deadspace. The increase in deadspace ventilation was the result of significant increases in breathing frequency (50%), and absolute deadspace (93%) from 15 minutes to end exercise.

Hematology

There were no significant changes in arterial blood lactate or glucose throughout the ER. One subject had detectable levels of cardiac troponin-I before exercise (0.2 μg · L-1), however troponin-I was unchanged in this subject 24 hrs after the ER. No other subjects had detectable levels of troponin-I either before or after exercise.

4.14 Discussion

One of the main results of this experiment was the lack of interaction between pulmonary gas exchange and cardiovascular function. In the present study, left-ventricular systolic function (as measured by fractional area change or SBP/ESCA) and cardiac output increased during the first 15 minutes of exercise and were maintained through to exhaustion. Systolic function did not deteriorate during exercise, which suggests that any change in pulmonary vascular pressures should not be attributed to impaired LV function. A significant impairment in pulmonary gas exchange was observed in all subjects at the onset of exercise, but this did not deteriorate as exercise continued. The repeated measures ANOVA with selected cardiopulmonary variables during the time course of the experiment, and correlation analyses on data from both the beginning and end of exercise collectively indicate that there was no cardiovascular contribution to impaired pulmonary gas exchange.

Previously, we have reported that pulmonary gas exchange is influenced by the cardiovascular system (30). Specifically, cyclists with the greatest diffusion impairment following simulated cycle racing also had blunted left-ventricular (LV) systolic function and higher LV afterload (30). Interestingly, Agostoni et al. (1) found a decrease in post-exercise diffusion capacity in heart failure patients but not in normal controls. Heart failure patients have blunted LV systolic and diastolic function, and Agostoni et al. (1) suggested that edema developed in the heart failure patients due to their greater increase

in pulmonary capillary pressure. However, the significance of post-exercise decreases in diffusion has been questioned (14) and it is possible that the previously reported cardiopulmonary interactions are secondary to a post-exercise re-distribution of blood volume. In the present study, LV function and pulmonary gas exchange data were acquired throughout exercise rather than during recovery. The differences in methodology (1, 30) and sample (1) make comparisons to previous work difficult without further experiments.

Cardiovascular function

Our observation that prolonged exercise was associated with an increase in fractional area change and SBP/ESCA is divergent from other reports that found prolonged strenuous exercise results in a transient impairment in LV systolic function (7, 8, 29, 39). As well, there was no evidence of cardiac damage as indicated by cardiac Troponin-I. Much of the research describing cardiac fatigue or damage was conducted following exercise in excess of five hours (7, 8, 16, 25, 39) while research examining shorter endurance events and myocardial function are more equivocal (21, 24, 29) suggesting that the exercise model selected likely dictates the cardiovascular response. Our findings are congruent with Goodman et al. (13) who found no LV systolic dysfunction during 150 minutes of riding at a fixed workrate (60% of VO_{2max} power output). Goodman et al. (13) concluded that the discrepancies between their data and previous research examining cardiac fatigue were likely due to the method of LV evaluation (supine at rest vs. upright during exercise). Our results indicate that LV systolic dysfunction does not occur during constant-load, high-intensity, sub-maximal exercise to exhaustion of up to 3.5 hours duration, which is consistent with the results of Goodman et al. (13).

Cardiovascular drift

Cardiovascular drift is characterized by the downward drift in central venous pressure, stroke volume, pulmonary and systemic arterial pressures and central blood volume (26).

The decline in stroke volume is offset by an increase in heart rate that maintains cardiac output. It is believed that cardiovascular drift is due partly to a decrease in blood volume and venous return to the heart, resulting in a decline in stroke volume (2). Between 15 minutes and the end of exercise, we observed a decrease in systemic arterial pressure, and an increase in heart rate, while stroke volume was not reduced during exercise. Recently, Fritzsche et al.(11) found that when heart rate was controlled, stroke volume was maintained during prolonged exercise, suggesting that cardiovascular drift results from a decrease in filling time brought on by an increase in heart rate. We found that preload (EDCA) was relatively well maintained in the present investigation despite a significant increase in heart rate and corresponding decrease in filling time, which argues against impaired LV filling as a mechanism for the increase in heart rate. A rise in core temperature has been shown to increase the intrinsic heart rate (19) while catecholamine levels rise with prolonged exercise (12). Coyle and Gonzalez-Alonso (3) suggested an interaction effect with body temperature and sympathetic activity on heart rate and stroke volume. We found that individual increases in body temperature during the ER were related to increases in exercise heart rate ($r=0.63$, $p = 0.05$) supporting a relationship between body temperature and exercise heart rate.

Pulmonary Gas Exchange

The majority of research examining the exercise-induced impairment in pulmonary gas exchange has focused on short duration, near-maximal intensity exercise. The use of submaximal exercise models has been done infrequently (4, 15, 17, 18, 32, 35, 38) but may provide additional information (5). The constant and persistent gas-exchange impairment seen in the present study is consistent with the findings of Hopkins et al. (18) who examined one hour of cycling at a lower intensity than in the present study. Wetter et al. (38) reported similar increases in A-aDO_2 at the onset of exercise, which persisted over 14 minutes of exercise to exhaustion. Despite the excessive increase in A-aDO_2

during exercise in the present study, there was a relatively mild (3.8%) decrease in SaO_2 due to the maintenance of a neutral pH and a relatively small increase in temperature. The slight drop in SaO_2 was offset by an increase in hemoglobin concentration and the net effect maintained arterial oxygen content near resting levels. These results indicate that, at least with respect to the current exercise model, the overall impact of a widened A-aDO_2 on oxygen content during submaximal exercise is minimal.

Wetter et al. (38) hypothesized that if the widening A-aDO_2 during exercise was due to edema or inflammation brought on by high pulmonary artery pressure during exercise, there should have been a continuous increase in A-aDO_2 as the blood-gas barrier is exposed to high pressures for long periods of time. Unfortunately, our currents methods did not allow for sub-division of the A-aDO_2 into the possible components (diffusion limitation, $\dot{V}_A/\dot{Q}$ mismatch or shunt), which may have given addition information regarding the etiology of impairment. However, the rapid widening of A-aDO_2, the consistency during exercise, and rapid return to normal following exercise all argue against the development of pulmonary edema during prolonged exercise.

Previously, Hanson et al. (15) documented an increase in the deadspace to tidal volume ratio with prolonged running and reasoned that this was the result of a decrease in tidal volume and an increase in breathing frequency. However, the increase in absolute VD (deadspace per breath) during the present study indicates an increase in alveolar deadspace ventilation, suggesting greater $\dot{V}_A/\dot{Q}$ mismatch. Using the multiple inert gas elimination technique, Hopkins et al. (18) found progressive $\dot{V}_A/\dot{Q}$ mismatch during one hour of cycling and suggested that this was due to the development of interstitial edema. However, both Hopkins et al. (18) and Ekelund (10) found decreased pulmonary artery pressure with prolonged exercise. A decline in pulmonary vascular pressure during exercise would have the effect of decreasing capillary recruitment, increasing

physiological deadspace and may explain our increase in absolute VD. While we did not measure pulmonary artery pressures, mean systemic arterial pressure, which parallels pulmonary pressure during prolonged exercise (10) decreased at the same time that deadspace increased (see Fig. 3.). It is unlikely that the increased deadspace negatively affected gas exchange, as total ventilation increased to maintain alveolar ventilation. Further investigations are needed to examine pulmonary hemodynamics, central blood volume and gas exchange during prolonged strenuous exercise to better understand the potential pulmonary consequences of cardiovascular drift.

Individual Responses to Exercise

There was considerable variability in the time to fatigue despite the consistent relative intensity (25W below lactate threshold). Anecdotally, it appears that the time to fatigue was related to racing experience and racing ability, with the better, more experienced cyclists able to exercise longer. The variability in end-exercise times makes some physiological comparisons across individuals and time difficult. Five subjects exercised for three hours or more. The patterns in cardiopulmonary function in this sub-group were very similar to the entire group, regardless of exercise duration (Fig. 4 and 5).

Conclusion

The present investigation examined cardiopulmonary function during exhaustive constant-work cycling in endurance athletes. No evidence of cardiac fatigue was seen since the augmented LV systolic function observed at the onset of exercise was maintained through to exhaustion. The maintenance of systolic function during exercise indicated that an increase in pulmonary vascular pressures secondary to LV dysfunction was unlikely. Pulmonary gas exchange deteriorated at the beginning of exercise but thereafter did not change. Pulmonary gas exchange was unrelated to cardiovascular function during exercise. The maintenance of increased A-aDO_2 through to exhaustion

suggests a functionally based mechanism, which quickly recovers following exercise. LV systolic function and pulmonary gas exchange do not appear to limit endurance performance through 2.5 (range 1.1 - 3.5) hours of exhaustive sub-maximal exercise. Considerable variability existed in endurance capacity, necessitating further research to understand the limits to endurance performance.

Table 4-1. Selected cardiovascular variables (±SD) before, during and after the endurance ride.

	Baseline	15 min	30 min	60 min	90 min	120 min	150 min	180 min	End	Post
EDCA (mm^2)	17.8 (1.6)	19.5 (2.0)	19.8 (1.9)	19.2 (1.9)	20.1 (1.7)	19.5 (2.1)	19.2 (2.1)	18.5 (1.6)	18.4 (2.7)	17.9 (2.1)
ESCA (mm^2)	9.1 (2.2)	6.7 [1] (1.6)	5.6 (1.1)	5.5 (0.7)	5.3 (0.9)	5.1 (0.4)	4.8 (0.5)	4.4 (0.5)	5.0 [2] (1.5)	7.7 (1.4)
Wall Stress (dynes · $cm^{2\,-1}$)	81.5 (23.4)	72.3 (14.1)	60.8 (11.8)	56.3 (10.2)	52.0 (8.5)	53.5 (7.1)	45.0 (3.9)	40.7 (5.1)	47.2 [2] (11.9)	60.3 [3] (16.3)
SV (ml)	131 (41)	153 [1] (29)	154 (28)	153 (23)	160 (15)	156 (21)	156 (14)	153 (24)	142 (27)	100 [3] (18)
Heart Rate (beats · min^{-1})	62 (10)	158 [1] (12)	162 (13)	165 (16)	163 (14)	171 (5)	172 (6)	172 (7)	174 [2] (13)	116 [3] (18)
$\dot{Q}$ (L · min^{-1})	8.0 (2.1)	24.2 [1] (4.3)	24.9 (3.8)	25.7 (2.8)	26.0 (2.8)	26.8 (3.7)	26.7 (2.3)	26.0 (3.6)	24.4 (4.2)	11.5 [3] (25)
Systolic BP (mmHg)	146 (13)	180 [1] (24)	179 (27)	174 (20)	168 (25)	168 (22)	149 (11)	148 (9)	158 [2] (24)	121 [3] (11)
Diastolic BP (mmHg)	80 (6)	75 (9)	75 (10)	73 (10)	72 (10)	70 (11)	70 (9)	68 (8)	67 [2] (10)	82 (10)
Sample Size (n)	11	11	11	11	10	7	6	5	11	11

[1] $p < 0.05$ Baseline vs. 15 minutes, [2] $p < 0.05$ 15 minutes vs. End, [3] $p < 0.05$ Baseline vs. 5min Post

Table 4-3. Respiratory gas exchange data (±SD) before, during and after the endurance ride.

	Baseline	**15 min**	**30 min**	**60 min**	**90 min**	**120 min**	**150 min**	**180 min**	**End**	**Post**
$\dot{V}_E$ ($L \cdot min^{-1}$)	15.6 (8.1)	86.3 [1] (14.3)	85.9 (12.0)	89.2 (12.2)	89.3 (8.4)	92.0 (11.3)	95.7 (12.0)	93.9 (12.0)	106.5[2] (18.0)	24.8 [3] (10.6)
$\dot{V}_{O_2}$ ($L \cdot min^{-1}$)	0.41 (0.09)	3.21 [1] (0.21)	3.10 (0.25)	3.17 (0.19)	3.17 (0.24)	3.29 (0.12)	3.40 (0.16)	3.25 (0.20)	3.27 (0.23)	0.52 [3] (0.13)
$\dot{V}_{CO_2}$ ($L \cdot min^{-1}$)	0.43 (0.17)	3.08 [1] (0.22)	2.92 (0.25)	2.97 (0.19)	2.94 (0.25)	2.98 (0.10)	2.99 (0.12)	2.88 (0.20)	2.91 (0.39)	0.53 (0.16)
RER	1.07 (0.30)	0.96 (0.02)	0.94 (0.02)	0.93 (0.02)	0.93 (0.02)	0.91 (0.02)	0.89 (0.02)	0.88 (0.02)	0.89 (0.10)	1.03 (0.17)
$\dot{V}_A$ ($L \cdot min^{-1}$)	11.3 (7.1)	77.4 [1] (12.3)	73.3 (14.7)	75.1 (14.6)	74.7 (11.6)	75.5 (6.4)	79.9 (4.5)	75.3 (6.2)	82.3 (14.3)	14.8 (6.2)
$\dot{V}_D$ ($L \cdot min^{-1}$)	4.3 (1.8)	8.8 (7.0)	12.6 (9.1)	14.1 (8.6)	14.6 (8.6)	16.6 (7.4)	15.8 (5.5)	18.9 (7.1)	24.2 [2] (11.9)	10.0 [3] (5.6)
Tidal Volume (L)	1.18 (0.8)	2.92 (0.6)	2.77 (0.6)	2.58 (0.6)	2.62 (0.7)	2.55 (0.5)	2.67 (0.9)	2.61 (1.0)	2.47 (0.8)	1.4 (0.9)
Breathing Frequency	14.6 (3.1)	31.4 (10.0)	32.9 (9.1)	36.6 (10.9)	37.3 (14.2)	37.8 (10.0)	40.1 (16.0)	41.3 (16.8)	47.1 (17.0)	19.5 (7.2)
Sample Size (n)	10	10	10	10	9	7	6	5	10	10

[1] $p < 0.05$ Baseline vs. 15 minutes, [2] $p < 0.05$ 15 minutes vs. End, [3] $p < 0.05$ Baseline vs. 5min Post

Table 4-2. Pulmonary gas exchange data (±SD) before, during and after the endurance ride.

	Baseline	**15 min**	**30 min**	**60 min**	**90 min**	**120 min**	**150 min**	**180 min**	**End**	**Post**
PA_{O_2} (mmHg)	102.4 (10.4)	102.1 (3.7)	102.1 (4.7)	101.9 (4.1)	101.6 (3.9)	101.1 (2.0)	101.0 (3.5)	101.9 (3.3)	103.1 (4.3)	105.4 (6.8)
Pa_{O_2} (mmHg)	96.3 (12.0)	71.2 [1] (5.4)	74.3 (6.4)	73.5 (6.0)	74.0 (7.1)	72.6 (2.8)	71.0 (3.0)	74.1 (2.3)	76.0 (4.9)	92.6 (10.4)
Pa_{CO_2} (%)	34.3 (5.5)	34.8 (3.8)	34.3 (4.7)	33.6 (4.6)	34.2 (3.8)	34.2 (2.4)	33.9 (2.8)	33.3 (2.6)	32.1 (3.1)	32.7 (4.4)
pH	7.44 (0.06)	7.40 (0.02)	7.41 (0.03)	7.42 (0.03)	7.44 (0.02)	7.44 (0.02)	7.44 (0.04)	7.43 (0.06)	7.44 [2] (0.05)	7.43 (0.05)
Sa_{O_2} (%)	97.9 (1.0)	94.1 [1] (1.2)	94.6 (1.3)	94.5 (1.4)	94.9 (1.6)	94.9 (1.0)	93.9 (0.8)	95.2 (0.6)	94.8[2] (1.1)	97.0 (0.9)
Hb ($g \cdot L$ of $blood^{-1}$)	151 (5)	157 (9)	158 (9)	158 (8)	159 (5)	161 (7)	157 (6)	153 (4)	159 (7)	156 (7)
Ca_{O_2} (L of $O_2 \cdot L$ of $blood^{-1}$)	0.200 (0.01)	0.200 (0.01)	0.202 (0.01)	0.202 (0.01)	0.204 (0.01)	0.206 (0.01)	0.200 (0.01)	0.198 (0.01)	0.204 (0.01)	0.206 0.01)
Sample Size (n)	10	10	10	10	9	7	6	5	10	10

[1] $p < 0.05$ Baseline vs. 15 minutes, [2] $p < 0.05$ 15 minutes vs. End, [3] $p < 0.05$ Baseline vs. 5min Post

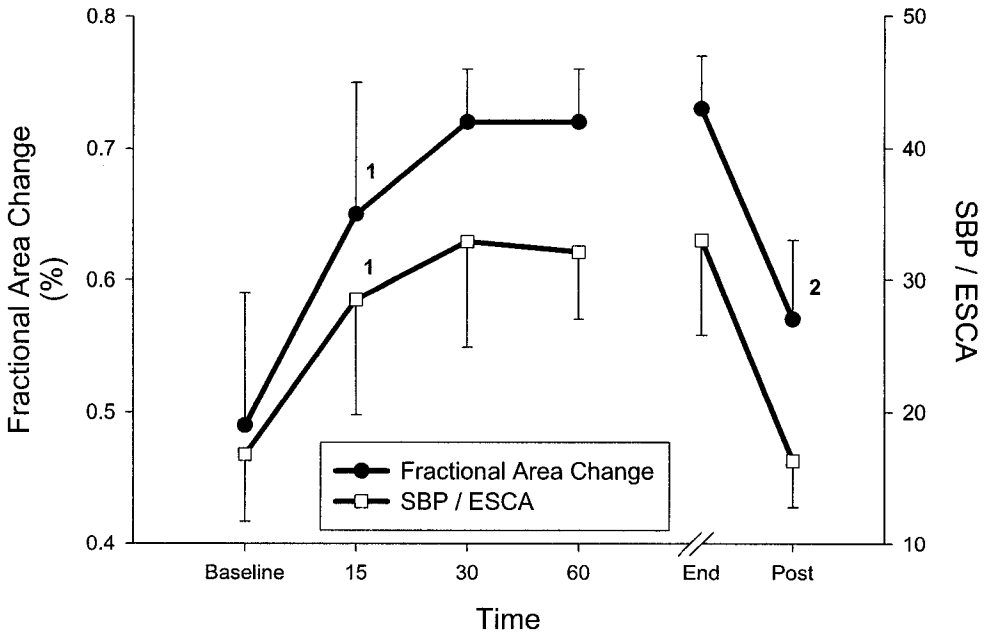

Figure 4-1. Mean (±SD) fractional area change and SBP / ESCA before, during and after the endurance ride (n=11). [1] $p < 0.05$ Baseline vs. 15 min, [2] $p < 0.05$ Baseline vs. Post.

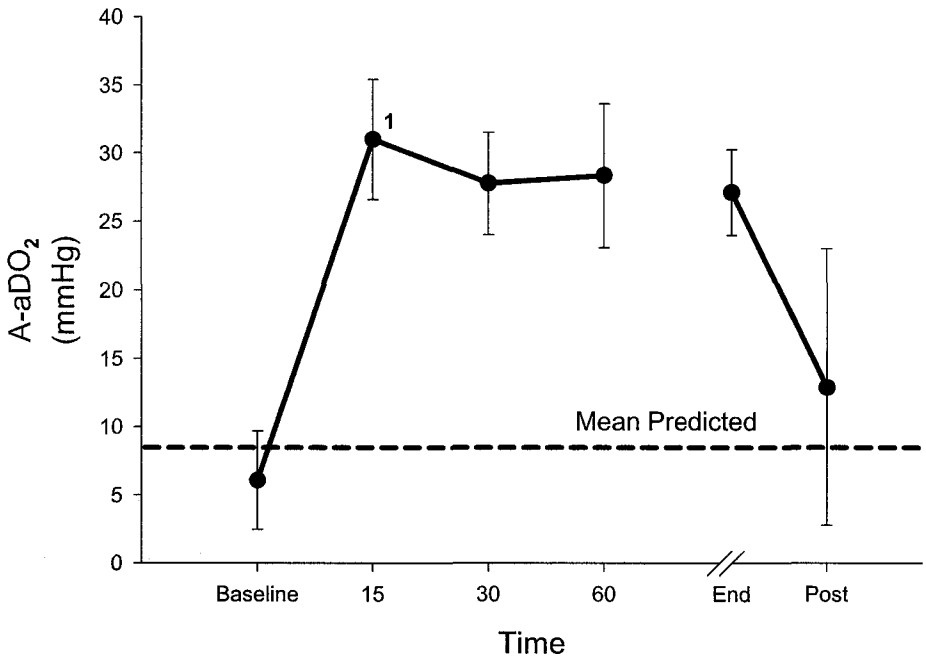

Figure 4-2. Mean (±SD) alveolar - arterial pressure difference ($A\text{-}aDO_2$) before during and after the endurance ride (n=10). [1] $p < 0.05$ Baseline vs. 15 min.

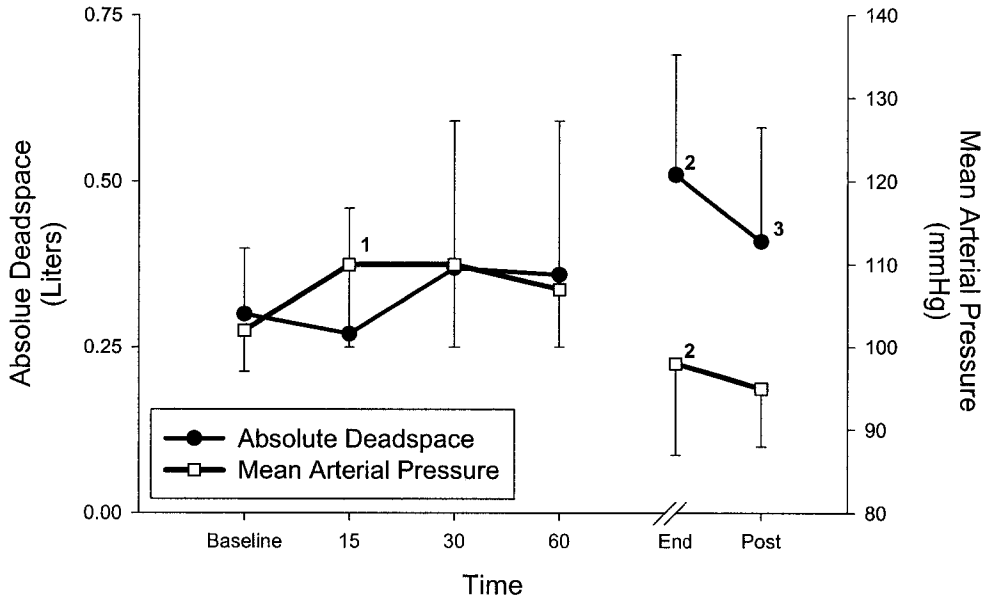

Figure 4-3. Mean (±SD) absolute deadspace and mean arterial pressure before during and after the endurance ride (n=10). [1] $p < 0.05$ Baseline vs. 15 min, [2] $p < 0.05$ 15 min vs. end, [3] $p < 0.05$ Baseline vs. Post.

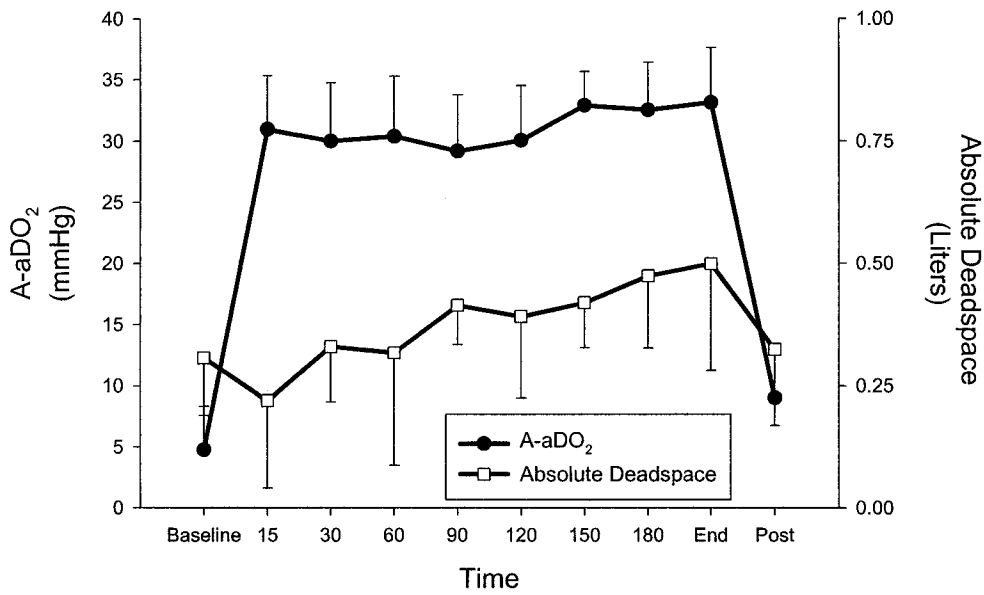

Figure 4-4. Mean (±SD) alveolar arterial pressure difference ($A\text{-}aDO_2$) and absolute deadspace before during and after the endurance ride in subjects who completed over three hours of cycling (n=5).

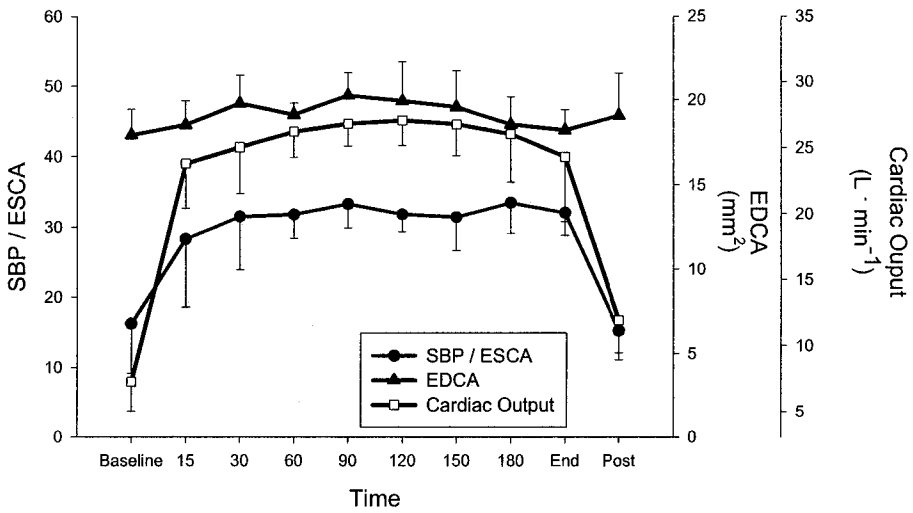

Figure 4-5. Mean (±SD) SBP / ESCA, end-diastolic cavity area (EDCA) and cardiac output before during and after the endurance ride in subjects who completed over three hours of cycling (n=5).

4.15 References

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CHAPTER 5

The Effect of Lower-Body Positive Pressure on Pulmonary Gas Exchange and Intrapulmonary Shunt

A portion of this chapter is under review

5.1 Introduction

During aerobic exercise, there is typically an impairment in pulmonary gas exchange as demonstrated by an increase in the alveolar-arterial pressure difference for oxygen (A-aDO_2). Depending on the ventilatory response and magnitude of A-aDO_2, exercise-induced arterial hypoxemia can develop (10). Abnormalities in pulmonary gas exchange could result from ventilation/perfusion ($\dot{V}A/\dot{Q}$) mismatch, diffusion impairment, extra pulmonary shunt or intra-pulmonary (I-P) arterial to venous shunt. Current theories to explain the widened A-aDO_2 during exercise include inadequate blood transit time in the lung (9), and a mismatch of $\dot{V}A/\dot{Q}$ secondary to pulmonary hypertension (40).

Intra-pulmonary shunt has been previously dismissed as an explanation for the increased A-aDO_2 during exercise because oxygen breathing (9, 16, 38, 40) and the multiple inert gas elimination technique (MIGET) (10, 20, 30) consistently failed to detect significant physiological shunt. However, precapillary gas exchange has been documented in both humans (22, 23, 32) and cats (6). Conhaim and Staub (1980) reasoned that because of precapillary gas exchange, 100% O_2 breathing would underestimate shunt and similarly, MIGET may underestimate I-P shunt during exercise. Tobin et al. (36, 37) demonstrated the presence of large arteriovenous vessels in normal post-mortem human lungs, and for those reasons, we previously questioned whether these arterial-venous anastamoses could act as shunt vessels during exercise (33). Whyte et al.(49) has previously documented an increase in shunt during exercise using technicium labeled macroaggregated albumin microsperes in normal control subjects, and Eldridge et al. (in-press) demonstrated I-P shunts during exercise with agitated saline contrast echocardiography. Accordingly, the purpose of this investigation was to confirm that I-P shunts occur during exercise and if so, determine the relationship to A-aDO_2 and hemodynamic responses. We hypothesized that the recruitment of anatomical I-P shunts contribute to the widened A-aDO_2 during exercise. As well, to determine if shunt recruitment or the increased A-aDO_2 are caused

by increases in cardiac output or alternately, pulmonary artery pressure, lower-body positive pressure (LBPP) was selectively applied to augment central blood volume, increasing pulmonary vascular pressures to values higher than those typically seen under normal exercise conditions.

5.2 Methods

5.3 Research Design

Institutional ethics review board approval was obtained and all participants provided written informed consent to participate. Three experimental sessions were completed during a three week period in the following order: a graded exercise test for $\dot{V}O_{2max}$, a practice session, and the experimental day.

5.4 Subjects

Nine healthy males (mean ± SD, age: 29 ± 3.9 yr, mass: 78.5 ± 6.0 kg) were initially recruited for participation in the study. Participants were free of exercise-induced bronchospasm, hematological abnormalities, and ECG abnormalities. All subjects were physically active [mean $\dot{V}O_{2max}$: 4.20 (0.6) L · min^{-1}, 53.7 (9.0) ml · kg^{-1} · min^{-1}], and the sample included several recreational and competitive endurance athletes. During the study, one subject was found to develop a right to left intra-cardiac shunt with exercise. His data were removed, and therefore we report the results of eight subjects [mean age: 30 (3.9) yr, $\dot{V}O_{2max}$: 4.28 (0.6) L · min^{-1}, 54.7 (9.0) ml · kg^{-1} · min^{-1}].

5.5 Day 1 - Graded-Exercise Test

Subjects performed a graded-exercise test to determine ventilatory threshold (VT) and $\dot{V}O_{2max}$. Exercise was performed on an electrically braked Seimens 740E ergometer (Malvern, PA) with a custom-built seat and back rest to limit torso movement. Respiratory gas exchange data were collected continuously using a non-rebreathing valve (Hans-Rudolph, 2700, Kansas City MO) and a metabolic measurement system (ParvoMedics, Truemax, Salt Lake City, UT) while heart rate was recorded using a telemetry system (Polar, Kempele, Finland). The criteria for VT was a non-linear increase in the $\dot{V}_E/\dot{V}CO_2$ (41) ratio. During the graded exercise test subjects were requested to self-select a consistent cadence between 70 – 90 RPM, while power output was increased 25W every 2 minutes until exhaustion.

5.6 Day 2 – Practice Session

A practice session was conducted to familiarize each subject with the protocol. The set-up and exercise workloads were similar to those during the full experiment, however, blood, echocardiography and invasive pressure measurements were not performed.

5.7 Day 3 – Experimental Trial

5.8 Subject Preparation

A radial artery catheter (20-gauge Angiocath; Becton-Dickson, Sandy, UT) was inserted into the left radial artery using sterile technique and local anesthetic (Lidocaine HCl, 1%, Astra, Mississauga, ON). Thereafter, a Swan-Ganz catheter (Edwards Lifesciences; Irvine, CA) was inserted through a standard Cordis sheath via an antecubital vein and advanced under fluoroscopy to ensure proper placement. Patency of the catheters was maintained with a pressurized flush system of normal saline at a rate of 15 $ml \cdot h^{-1}$. Following placement of the catheters, each subject rested quietly for 10 minutes before data collection.

5.9 Protocol

Data were collected in a total of 15 conditions, seven under the control condition, and 8 with the LBPP. At rest, supine data was first collected [control, then LBPP to 52 mmHg (1psi)]. The subject then moved onto the cycle ergometer, where a series of resting, upright data were collected (control, LBPP to 52 mmHg). In six of the subjects, LBPP was then increased to 104 mmHg (2psi), with another set of data collected. Subsequently, the exercise protocol was conducted at each of the following intensities: I) 75W, II) 150W, III) power output at VT, IV) 25W above VT, V) 90% of $\dot{V}O_{2max}$. At each exercise workload the order of condition (control vs. LBPP to 52 mmHg) was randomized and between conditions a 5 minute rest period was given to allow for redistribution of blood volume. Workloads III and IV were purposely selected to span VT as opposed to a percentage $\dot{V}O_{2max}$ because arterial pH is believed to affect pulmonary artery pressure, and inter-subject variability in VT may have confounded the pulmonary pressure/cardiac output relationship (31). For workloads below 90% of $\dot{V}O_{2max}$, data collection began after the first 2 minutes of exercise. At 90% $\dot{V}O_{2max}$, data collection began once the target $\dot{V}O_2$ was reached (typically 90 seconds), and the workload usually lasted about three minutes before the subject became fatigued. During the experimental session, subjects were encouraged to consume water, sports drinks (eg. Gatorade®) and food (eg. Powerbars®) and a fan was provided to avoid hyperthermia.

5.10 Lower-body positive pressure

Lower body positive pressure (LBPP) was applied via a 'Canadian Sting II' antigravity suit which has an air bladder that is inflated pneumatically, and when inflated, provides pressure around the calves, thighs and abdomen (14). This device is similar to military anti-shock trousers that have been used previously during exercise (12). Prior to the experimental session each subject was fitted with the suit such that under the control

condition no positive pressure was exerted on the leg or abdomen, however upon inflation a relatively equal pressure was distributed across the lower-body.

5.11 Respiratory Gas-exchange Measurement

Respiratory gas exchange (RGE) data were collected continuously during all conditions using the same system as for the graded-exercise test. Mean values from the final minute of sampling were used for subsequent analysis.

5.12 Blood-gas Measurement

Arterial blood samples (2-3 ml) drawn from the radial artery catheter and mixed venous samples drawn from the distal port of the Swan Ganz catheter were immediately placed in ice water. Samples were later (<1 hour) analyzed for PaO_2, $PaCO_2$, pH, hematocrit and hemoglobin (ABL 700 blood-gas analyzer, Copenhagen, Denmark). Blood gases were corrected for pulmonary arterial temperature as measured by the Swan-Ganz catheter, with SaO_2 and SvO_2 corrected for temperature and pH.

5.13 Systemic and Pulmonary Pressures

Systemic arterial blood pressure was measured from a pressure transducer attached to the radial arterial catheter, mean pulmonary artery (PAP) and pulmonary artery wedge (PAWP) and right atrial pressures were obtained from the Swan-Ganz catheter. The pressure transducer was set at the level of the right atrium with the positioning monitored continuously. Pressure tracings were monitored constantly and recorded during the third and forth minute of each workload. Mean pressures over at least three respiratory cycles are reported (15, 17, 40).

5.14 Contrast Echocardiography

Echocardiograms were performed by the same experienced sonographer using cardiac ultrasound (Sonos 5500, Hewlett Packard, Andover MA). The agitated saline contrast echocardiography technique was used to detect intra-cardiac and I-P shunt. Standard procedures were employed for injection of the solution (46). Briefly, 10 ml of saline was combined with 0.5ml of air and the solution forcefully agitated through a three-way stop-cock between two syringes to form fine suspended bubbles. The solution was then injected through the proximal port of the Swan-Ganz catheter during the third minute of each 5 minute workload. Concurrently, all four chambers of the heart were imaged by the sonographer and recorded onto a VHS tape. This procedure has been performed repeatedly during exercise without any reported complication (18).

Agitated saline contrast echocardiocraphy is a standard technique (46) with excellent inter-observer reproducibility [$\kappa = 0.926$, (28)]. Saline echocardiography has been shown to be more sensitive at detecting I-P shunt vessels than 100% oxygen breathing (7) and pulmonary angiography (3, 25) with a low incidence of false positives (3). The technique produces stable air bubbles which are generally much larger than the pulmonary capillaries (46). Some bubbles less than 10 μm in diameter are produced which could theoretically transverse the pulmonary capillaries. However, Meltzer et al.(26) estimated that the survival time for bubbles below 10 μm is less than 200 msec, and mean whole-lung transit time in well-trained endurance athletes has been shown to exceed two seconds at intensities above 90% of $\dot{V}O_{2max}$ (19, 51). Furthermore, bubble dissolution is greater with increasing fluid pressure (39) and increasing flow velocity (50), both of which occur during incremental exercise. Therefore it is highly unlikely that contrasts observed in the left ventricle during exercise could be the result of small (<10 μm) diameter bubbles passing through the pulmonary capillaries. The presence of intra-cardiac shunt is determined by contrast appearance in the left ventricle in less than five

heart beats, while with I-P shunt, contrast appearance in the left ventricle is after at least five heart beats (46).

At a later date, the images were reviewed by a cardiologist with substantial experience in echocardiography. The cardiologist was naïve as to the exact condition, however he did have an indication of exercise intensity due to heart rate data. Each injection was categorized into one of (46): 1) No shunt: visible contrast injection into the right ventricle, no contrast in the left ventricle. 2) I-P Shunt: visible contrast injection into the right ventricle, and visible contrast in the left ventricle following atleast 5 heart beats. 3) Intra-Cardiac Shunt: visible contrast injection into the right ventricle, and visible contrast in the left ventricle in less than 5 heart beats. 4) Inconclusive: no visible contrast injection into the right ventricle or no consistently visible left ventricle on echocardiogram. To evaluate intra-observer reliability, a total of 25 contrasts were re-analyzed from five randomly selected subjects by the same cardiologist after a time delay of at least two months. All of the injections were classified into the same category as when first analyzed (100% repeatability).

5.15 Calculations

Cardiac output ($\dot{Q}$) was calculated from the Fick equation. Systemic vascular resistance was determined as the difference between mean arterial pressure and mean right atrial pressure divided by $\dot{Q}$. Similarly, pulmonary vascular resistance was calculated as the difference between mean PAP and mean PAWP divided by Q (43).

5.16 Statistical Analysis

Group data for each dependent variable were analyzed with a two-way ANOVA with repeated measures. Not all subjects completed the LBPP condition at workload V, therefore workload V was not included in the ANOVA To protect against violation of

the sphericity assumption, the Geisser-Greenhouse conservative F-test procedure was used [for details see (24)]. When the main effect was statistically significant, the Tukey honestly significant difference (HSD) procedure was utilized to compare means. The Tukey HSD procedure compared the means of each workload against the mean in the rest upright condition resulting in a total of 5 comparisons for each variable, while comparisons between condition (control vs. LBPP were done for resting data up to workload IV. For all inferential analyses, the probability of Type I error was set at .05. Pearson product-moment correlation coefficients were calculated to describe the strength of the relationships. Of the 118 saline contrast echocardiography injections, 4 were non-diagnostic. These time-points were excluded from correlational analyses (Figures 5-5 – 5-10).

5.17 Results

Exercise Hemodynamics

Group values for hemodynamic measures at rest and during graded exercise are shown in Table 5-1. Stroke volume, PAP and PAWP decreased when the subjects went from the supine to the upright position (Table 5-1, Figure 5-1). Exercise resulted in significant increases in $\dot{V}O_2$, $\dot{Q}$, heart rate, stroke volume, PAP and PAWP while pulmonary and systemic vascular resistance decreased. Lower-body positive pressure significantly increased RAP, PAP and PAWP in the upright position and at all points during exercise (Table 5-1a and 5-1b, Figure 5-1 and 5-2). Lower-body positive pressure increased $\dot{Q}$ upright at rest, however cardiac output and $\dot{V}O_2$ were not affected by LBPP during exercise.

Pulmonary Gas Exchange and I-P Shunt

As expected, A-aDO_2 increased and SaO_2 decreased with progressive exercise (Figure 5-3 and 5-4). Two subjects had evidence of I-P shunt when supine at rest, however none

had shunt in the upright position. With incremental exercise, seven of eight subjects developed I-P shunt (Table 5-2). In the seven subjects who developed shunt, mean within-subject correlations show that shunt development was related to A-aDO_2 (r = 0.68), $\dot{Q}$ (r = 0.76), and PAP (r = 0.73) (Table 5-4). Mean within-subject correlations of all eight participants in the control condition demonstrated that A-aDO_2 was related to $\dot{Q}$ (r = 0.86) and PAP (r = 0.75) (Table 5-5). Similar values were found when the LBPP data were added to the correlational analyses (Table 5-6 and 5-7).

Lower-body positive pressure did not significantly affect A-aDO_2 or shunt frequency during exercise (Figure 5-3, 5-4, 5-9 and Table 5-2). While LBPP shifted PAP up relative to $\dot{Q}$, (Figure 5-10) it did not affect the relationship between A-aDO_2 and $\dot{Q}$ (Figure 5-10). The application of 104 mmHg (2 p.s.i.) of LBPP at rest resulted in a modest increase in A-aDO_2, shunt frequency and $\dot{Q}$ (Table 5-3). At 90% of VO_{2max}, A-aDO_2 was positively correlated with $\dot{Q}$ (r = 0.71) and negatively correlated with PAP (r = - 0.71) (Figure 5-11).

5.18 Discussion

With incremental exercise in healthy males, development of I-P shunt and increased A-aDO_2 were both strongly related to $\dot{Q}$ and to a lesser extent PAP (Figures 3 and 4). Likewise, the occurrence of I-P shunt was related to A-aDO_2 and we hypothesize that these anatomical shunts partially explain the impairment in pulmonary gas exchange observed during exercise. According to classic theory on capillary recruitment (44), increasing pulmonary blood flow increases pulmonary microvascular pressure. At some critical flow the resulting microvascular pressure leads to recruitment of additional pulmonary capillaries. We propose a similar explanation for the recruitment of I-P shunts during exercise; specifically that at some critical flow, artery-venous vessels open and I-P shunt occurs. West (44) also suggested that during exercise the additional kinetic energy

of the blood, which is not reflected in the pressure measured lateral to flow, would likewise increase capillary recruitment and, as we suggest, I-P shunts. Whether shunts are recruited through flow-induced increases in microvascular pressure, or kinetic energy, the dominant factor for recruitment would be flow, thus explaining the stronger relationship of $\dot{Q}$ with I-P shunt and A-aDO_2. This hypothesis is supported by data from the subject who had the lowest $\dot{V}O_{2max}$, $\dot{Q}$ and A-aDO_2 during exercise, as he did not develop I-P shunts despite very high pulmonary artery pressures.

Anatomical Shunt

The detection of shunt with agitated saline contrast echocardiography implies recruitment of large diameter vessels within the pulmonary circulation. This is consistent with the documentation of I-P shunts in cadavers (36, 37) and isolated lung models (21, 29). These anatomical shunt vessels can be in excess of 500μm in diameter and they seem to predominate in the lung apecies (37), which is congruent with the findings that shunt increases with an elevation in pulmonary artery pressure in dogs (4) and with increases in $\dot{Q}$ in humans (27) and dogs (1, 2). In addition, Sykes et al. (35) demonstrated a widening A-aDO_2 with hypervolemia-induced increases in pulmonary artery pressure in resting dogs and ascribed this to right to left shunts in the lung. Our results are consistent with several previous investigations that showed I-P shunt during exercise (11, 49) and conditions of increased $\dot{Q}$ and/or increased PAP (1, 2, 4, 27, 35). In addition to the contribution to impaired gas exchange, the evidence supporting I-P shunt raises questions about the effectiveness of the lungs as a biological filter during exercise.

Right Ventricular Afterload

According to Poiseuille's law, an increase in vessel diameter would decrease the driving pressure needed to maintain flow. Berk et al. (1) suggested that I-P shunts act as "pop-off valves" in response to increases in flow and pulmonary vascular resistance. Exercise-

induced pulmonary shunts may be an adaptive mechanism to reduce the potential damaging effects of high perfusion pressures during exercise (42). Alternately, the development of I-P shunt may be a beneficial response to reduce right-ventricular afterload. Whyte (47) postulated that the higher $\dot{Q}$ during exercise in patients with pulmonary arteriovenous malformations (direct right to left shunt vessels 23-45μm in diameter) was the direct result of the lower pulmonary vascular resistance caused by these shunt vessels. We do not know the diameter nor the length of the anatomical shunts, and are unsure if flow is laminar through these vessels, therefore it is impossible to calculate the impact of their recruitment on right ventricular afterload. However, Figure 5 illustrates that the single subject who did not develop shunt during exercise had, at a cardiac output of 20 $L \cdot min^{-1}$, a PAP that was approximately 10 mmHg higher than the average PAP for the other seven subjects. This represents a substantial unloading of the right ventricle with I-P shunt recruitment. However, when we remove the contribution of the Bohr effect on oxyhemoglobin saturation in those subjects who shunted, the SaO_2 decreased less than 3% at peak exercise. If we assume all anatomical shunt is also physiological shunt (which may not be correct – see below), this indicates a minor arterial to venous shunt which would have a correspondingly small affect on mean PAP. The impact of I-P shunt on right ventricular afterload is unclear, and it remains to be determined if the development of I-P shunt is a consequence of, or a requirement for, a high cardiac output.

Previous Studies and Gas Exchange Methods to Measure Shunt

Previous research has failed to detect significant pulmonary shunt during exercise with oxygen breathing (9, 16, 38, 40). However, Conhaim and Staub (6) demonstrated that precapillary pulmonary arterial oxygenation occurs in the small arteries of isolated cat lungs. The small pulmonary arteries (100μm) were found to take up oxygen from the alveoli during ventilation with room air, while blood in larger diameter arteries (400-

500μm) was completely oxygenated during 100% O_2 ventilation. Similarly, rapid increases in oxygen and hydrogen in the pulmonary artery have been detected with increasing F_IO_2 and F_IH_2 in humans via the ports of a pulmonary arterial catheter (22, 23, 32). These changes occur rapidly (0.4-0.7 sec) following a change in inhaled gas and precede the arrival of these gases in the descending aorta, arguing against the possibility of a bronchial arterial source for the increased pulmonary artery gas concentration (23, 32). As pointed out by Conhaim and Staub (1980), in the presence of a large PO_2 gradient such as what would occur when breathing 100% O_2, precapillary vessels up to 500μm are fully oxygenated. However with the removal of this large pressure gradient during normoxic breathing, these vessels may not take part in gas exchange. As a result, the 'unphysiological' state of 100% O_2 breathing may underestimate arterial-venous shunts during normoxia. Additional support for the impact of precapillary gas exchange can be found in published reports demonstrating that physiolocial shunt calculated by oxygen breathing is lower than anatomical shunt calculated using technicium labeled albumin macroaggregates (8, 13, 48).

Intra-pulmonary shunt during exercise has not been detected with MIGET (10, 20, 30). However we hypothesize that precapillary gas exchange in the presence of a large diffusive pressure gradient (6) may also impact MIGET. The low solubility gas sulfur hexafluoride has an extremely large relative diffusion gradient and could be excreted from precapillary vessels without reaching the alveolar capillaries. As a result, true *physiological* intra-pulmonary shunt may not be recorded with MIGET, although *anatomical* arterial-venous shunts which *prevent* full O_2 diffusion during normoxic exercise may exist.

Genovesi (13) reported that large channels exist within the lungs of patients with hemorrhagic telangiectasia and suggested that these vessels are large enough for 20-60

μm radiolabelled albumin macroaggregates to pass through, but small enough to permit partial oxygen equilibration, thus explaining the underestimation of shunt with oxygen breathing. The concept of large vessel gas exchange fits nicely into our findings. It is possible that a relatively large volume of blood transits the lungs through the I-P shunt vessels resulting in a significant reduction in right ventricular afterload, but at the same time, this shunted blood is partially oxygenated, modestly impacting A-aDO_2. Interestingly, diffusion limitation as measured by MIGET typically develops above an oxygen consumption of 2.5 $L \cdot min^{-1}$ (16, 20, 30, 40), and our results indicated that I-P shunt are also most common above this intensity. Therefore, a diffusion limitation within these large shunt vessels secondary to inadequate transit time may develop during exercise, contributing to the impairment in gas exchange. Clearly, our results documenting anatomical I-P shunts go against the current understanding of pulmonary gas exchange during exercise and require further research.

Lower-body Positive Pressure and A-aDO_2 During Exercise

The application of lower-body positive pressure (LBPP) resulted in significant increases in PAP and PAWP during exercise (Figures 5-1 and 5-2), however A-aDO_2 was not adversely affected (Figures 5-3 and 5-4). Using our current data, wall stress of the pulmonary capillaries can be estimated based on assumptions by West and Mathieu-Costello (45). If we assume fixed values for blood-gas barrier thickness (0.34μm), capillary radius (3.6 μm), and that capillary pressure is mid-way between PAP and PAWP, capillary wall-stress at workload IV is calculated to be $1.97 \times 10^5 N \cdot m^{-1}$ while wall-stress at 90% of VO_{2max} would be $2.36 \times 10^5 N \cdot m^{-1}$. With the application of LBPP wall-stress at workload IV and V would be $2.38 \times 10^5 N \cdot m^{-1}$ and $2.78 \times 10^5 N \cdot m^{-1}$ respectively. Despite the approximate 20% increase in capillary wall-stress with LBPP, A-aDO_2 was not significantly increased, indicating that the impairment in pulmonary gas

exchange typically observed during normoxic exercise is primarily flow-dependent and not directly affect by pulmonary hypertension.

Lower-body Positive Pressure and I-P Shunt

Similarly, I-P shunt frequency was not consistently affected by the increased pulmonary vascular pressure with LBPP. We did observe greater shunt frequency and a small increase in resting A-aDO_2 with the application of 104 mmHg LBPP at rest. This is similar to Cohen et al. (5) who found an increase in A-aDO_2 with water immersion in resting subjects and speculated that the increased A-aDO_2 was due to either greater $\dot{V}_A/\dot{Q}$ heterogeneity or increased shunt. However, it must be noted that LBPP also resulted in a significant increase in $\dot{Q}$ at rest, making discussion of pressure vs. flow difficult. When the difference between control and LBPP conditions are examined at workload I (75W, Figure 5-2), we do see that shunts are more common with LBPP and correspondingly, the A-aDO_2 is slightly (but not significantly) greater. At higher workloads however, LBPP increased pulmonary vascular pressures but not I-P shunt frequency, indicating that pulmonary blood flow is also the dominant factor contributing to I-P shunt recruitment with exercise.

Supine Data

Strauss et al. (34) and Whyte et al. (49) have both documented a small amount of shunt with albumin microaggregates in the supine position in normal resting humans. Two of the subjects from the present study had I-P shunt while supine at rest, which disappeared once the subjects sat upright. Our hemodynamic data does not specifically explain why these two subjects shunted when supine, however this would be consistent with shunt vessels located predominately in the apex of the lung, which would be more likely recruited in the supine position.

Conclusion

Normal healthy male subjects developed anatomical I-P shunts and a widened A-aDO_2 with incremental exercise, both of which were related to $\dot{Q}$ and to a lesser extent, PAP. The recruitment of I-P shunts was related to A-aDO_2 and we hypothesize that these anatomical shunts contribute to the impairment in pulmonary gas exchange observed during exercise. Shunt frequency and A-aDO_2 were not affected by enhanced pulmonary vascular pressures during exercise, suggesting that $\dot{Q}$ is the dominant factor in both I-P shunt recruitment and the widened A-aDO_2. Further research is needed as these observations contradict a large body of research examining pulmonary gas exchange and exercise. It remains undetermined if these shunts are a consequence of, or a requirement for, a high cardiac output.

Table 5-1a. Mean (±SE) hemodynamic responses at rest (supine and upright) and during graded exercise (n=8) in the control condition.

	SUP	UP	I	II	III	IV	V
VO_2 ($L \cdot min^{-1}$)	0.36* (0.01)	0.41 (0.02)	1.59* (0.05)	2.49* (0.07)	3.22* (0.21)	3.69* (0.23)	4.08 (0.21)
Cardiac Output ($L \cdot min^{-1}$)	7.83* (0.45)	6.06 (0.39)	16.64* (0.64)	22.23* (0.69)	25.07* (0.99)	26.89* (1.63)	29.69 (1.61)
Stroke Volume ($mL \cdot beat^{-1}$)	124* (9)	94 (5)	147* (4)	152* (5)	151* (4)	149* (7)	159 (8)
Heart Rate ($beats \cdot min^{-1}$)	64 (3)	65 (3)	113* (3)	147* (4)	166* (5)	180* (3)	187 (2)
Mean Arterial Pressure (mmHg)	98* (2)	109 (3)	120* (6)	126* (7)	130* (7)	132* (7)	136 (6)
Systemic Vascular Resistance ($mmHg \cdot L^{-1} \cdot min^{-1}$)	12.1* (0.8)	18.1 (1.4)	7.1* (0.4)	5.7* (0.4)	5.1* (0.3)	4.9* (0.5)	4.4 (0.4)
Pulmonary Vascular Resistance ($mmHg \cdot L^{-1} \cdot min^{-1}$)	0.62 (0.08)	0.84 (0.17)	0.62 (0.08)	0.50* (0.06)	0.44* (0.05)	0.38* (0.05)	0.39 (0.05)

Note: SUP: supine, UP: upright, Level I – V: exercise load, $\dot{V}O_2$: oxygen consumption.

* $p<0.05$ vs. upright at rest (UP)

Table 5-1b. Mean (±SE) hemodynamic responses at rest (supine and upright) and during graded exercise (n=8) in the LBPP condition.

	SUP	UP	I	II	III	IV	V
VO_2 ($L \cdot min^{-1}$)	0.34* (0.01)	0.40 (0.02)	1.69* (0.07)	2.50* (0.07)	3.34* (0.24)	3.72* (0.21)	3.94 (0.21)
Cardiac Output ($L \cdot min^{-1}$)	7.66 (0.43)	8.53# (0.58)	16.79* (0.64)	22.30* (0.53)	26.02* (1.04)	27.61* (1.57)	28.74 (2.05)
Stroke Volume ($mL \cdot beat^{-1}$)	125* (8)	133# (8)	141* (4)	152* (5)	152* (4)	153* (8)	156 (10)
Heart Rate ($beats \cdot min^{-1}$)	62 (3)	64 (3)	119* (3)	148* (3)	172* (4)	180* (3)	183 (3)
Mean Arterial Pressure (mmHg)	102* (2)	115# (3)	129*# (6)	134*# (6)	135*# (7)	139*# (7)	142 (7)
Systemic Vascular Resistance ($mmHg \cdot L^{-1} \cdot min^{-1}$)	12.9 (0.9)	13.0# (1.2)	7.4* (0.5)	5.7* (0.3)	5.0* (0.4)	4.9* (0.5)	4.8 (0.6)
Pulmonary Vascular Resistance ($mmHg \cdot L^{-1} \cdot min^{-1}$)	0.65 (0.07)	0.53# (0.07)	0.58 (0.09)	0.51 (0.02)	0.44 (0.03)	0.36 (0.08)	0.29 (0.04)

Note: SUP: supine, UP: upright, Level I – V: exercise load, $\dot{V}O_2$: oxygen consumption.

* $p<0.05$ vs. upright at rest (UP), # $p<0.05$ vs. control condition

Table 5-2. Frequency of shunt as assessed by agitated saline contrast echocardiography across condition (Control vs. LBPP) and workload.

	SUP	UP	I	II	III	IV	V
Control							
No shunt	6	8	4	3	1	1	1
Intra-pulmonary shunt	2	0	3	5	7	6	7
Non-diagnostic	0	0	1	0	0	1	0
Inflated							
No shunt	6	7	2	3	1	1	1
Intra-pulmonary shunt	2	1	5	5	7	6	7
Non-diagnostic	0	0	1	0	0	1	0

Table 5-3. Sub-sample of five subjects who received 52 mmHg (1psi) and 104 mmHg (2 psi) of LBPP at rest in the upright condition.

	Control	**52 mmHg (1psi) LBPP**	**104 mmHg (2 psi) LBPP**
Cardiac Output ($L \cdot min^{-1}$)	5.9 (0.6)	8.3* (0.9)	8.3* (0.9)
Heart Rate (beats $\cdot min^{-1}$)	62 (4)	60 (4)	64 (6)
Right Atrial Pressure (mmHg)	3.1 (0.9)	8.3* (0.9)	9.2* (0.9)
Mean Pulmonary Artery Pressure (mmHg)	13.5 (0.9)	17.0* (1.1)	17.6* (1.5)
Pulmonary Wedge Pressure (mmHg)	8.2 (1.3)	12.7* (1.1)	12.1* (1.5)
A-aDO_2 (mmHg)	1.6 (0.6)	1.8 (0.9)	4.2*# (0.9)
Shunt Frequency	0	0	1

Note: * $p<0.05$ vs. control

Table 5-4. Mean, standard deviation and range of within subject correlation coefficients between intra-pulmonary shunt as evaluated by agitated saline contrast echocardiography and alveolar-arterial PO_2 difference ($A\text{-}aDO_2$), cardiac output, mean pulmonary artery pressure – control condition only (n = 7).

$A\text{-}aDO_2$		
Mean	**SD**	**Range**
0.68	0.19	0.53 (0.41 – 0.94)

Cardiac Output		
Mean	**SD**	**Range**
0.76	0.12	0.31 (0.59 – 0.90)

Mean Pulmonary Artery Pressure		
Mean	**SD**	**Range**
0.73	0.19	0.50 (0.41 – 0.91)

Note: Highest and lowest values reported in parenthesis. The subject who did not develop intra-pulmonary shunt was excluded from analysis as no variance in shunt was present and therefore correlations coefficients between shunt and cardiopulmonary variables could not be determined.

Table 5-5. Mean, standard deviation and range of within subject correlation coefficients between alveolar-arterial PO_2 difference and cardiac output and mean pulmonary artery pressure – control condition only (n=8).

Cardiac Output		
Mean	**SD**	**Range**
0.86	0.10	0.25 (0.71 – 0.96)
Mean Pulmonary Artery Pressure		
Mean	**SD**	**Range**
0.75	0.18	0.48 (0.46 – 0.95)

Note: Highest and lowest values reported in parenthesis.

Table 5-6. Mean, standard deviation and range of within subject correlation coefficients between intra-pulmonary shunt as evaluated by agitated saline contrast echocardiography and alveolar-arterial PO_2 difference ($A\text{-}aDO_2$), cardiac output, mean pulmonary artery pressure – Control and lower body positive pressure conditions combined (n = 7).

$A\text{-}aDO_2$		
Mean	**SD**	**Range**
0.65	0.17	0.56 (0.37 – 0.93)

Cardiac Output		
Mean	**SD**	**Range**
0.73	0.14	0.38 (0.52 – 0.90)

Mean Pulmonary Artery Pressure		
Mean	**SD**	**Range**
0.65	0.17	0.47 (0.43 – 0.90)

Note: Highest and lowest values reported in parenthesis. The subject who did not develop intra-pulmonary shunt was excluded from analysis as no variance in shunt was present and therefore correlations coefficients between shunt and cardiopulmonary variables could not be determined.

Table 5-7. Mean, standard deviation and range of within subject correlation coefficients between alveolar-arterial PO_2 difference and cardiac output and mean pulmonary artery pressure – Control and lower body positive pressure condition combined (n = 7).

Cardiac Output		
Mean	**SD**	**Range**
0.79	0.18	0.52 (0.45 – 0.97)
Mean Pulmonary Artery Pressure		
Mean	**SD**	**Range**
0.70	0.19	0.52 (0.36 – 0.88)

Note: Highest and lowest values reported in parenthesis.

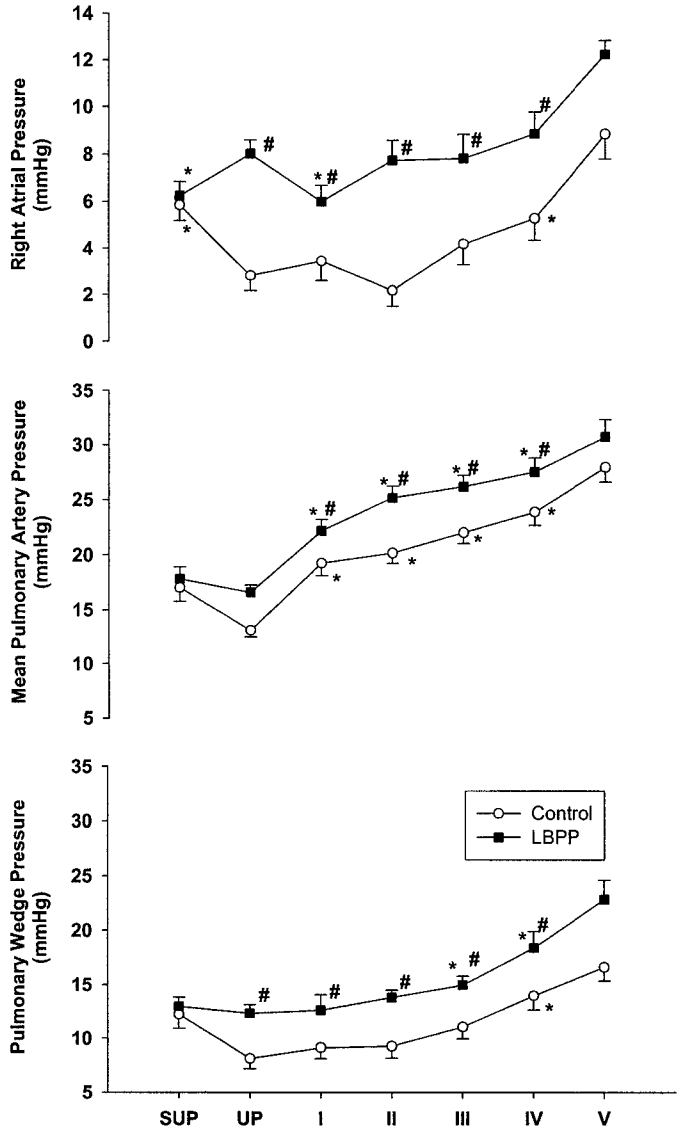


Figure 5-1. Mean (±SE) right atrial, pulmonary artery pressure and pulmonary artery wedge pressure at rest (supine and upright) and during graded exercise (n=8).

Note: SUP: supine, UP: upright, Level I – V: exercise load, * $p<0.05$ vs. upright at rest, # $p<0.05$ vs. control condition.

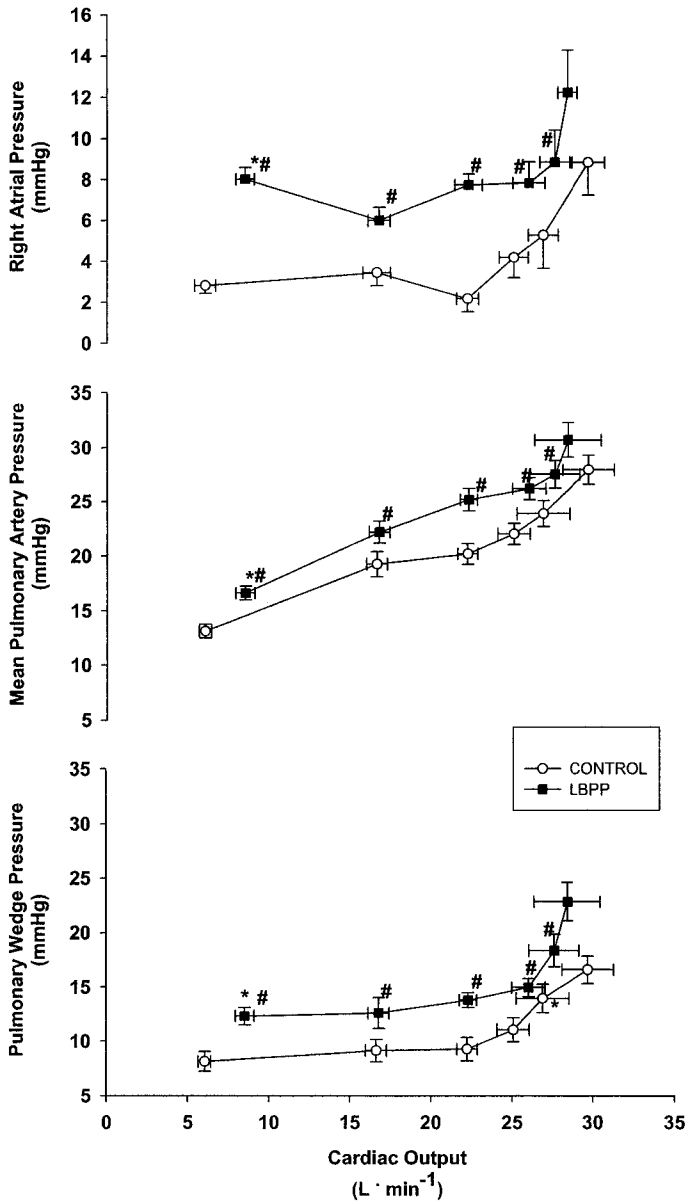


Figure 5-2. Mean (±SE) right atrial, pulmonary artery pressure and pulmonary artery wedge pressure upright at rest and during graded exercise relative to cardiac output (n=8). Note: * Cardiac output different ($p<0.05$) than control upright, # $p<0.05$ vs. control condition.

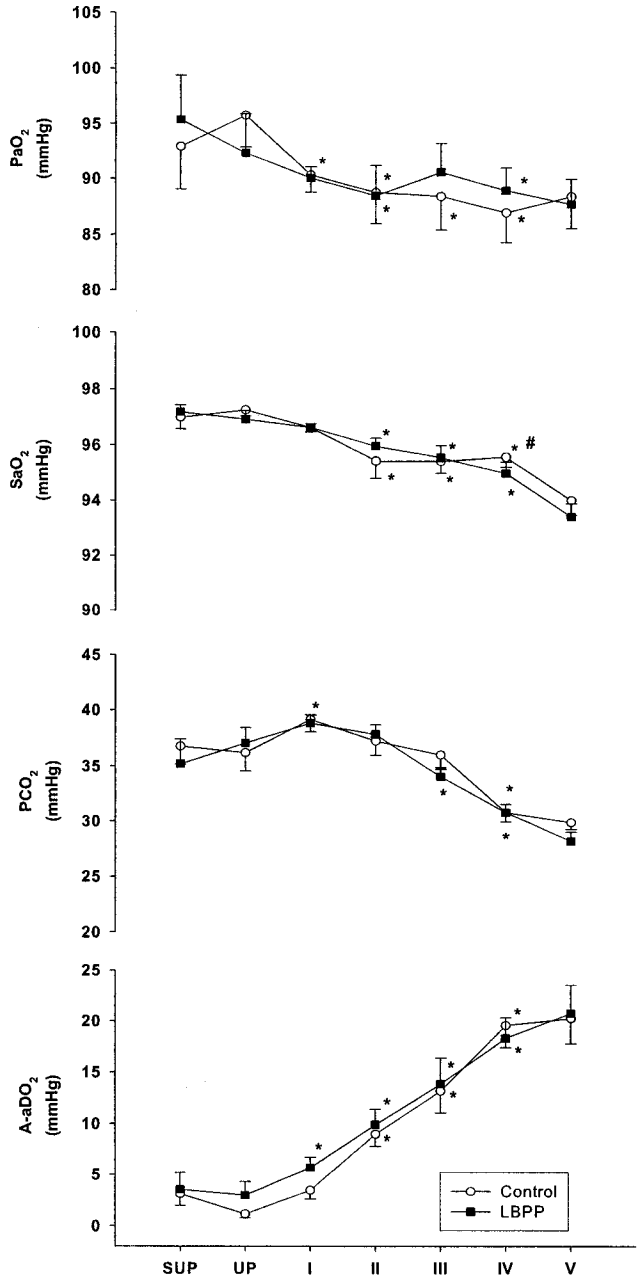


Figure 5-3. Mean (±SE) pulmonary gas exchange at rest (supine and upright) and during graded exercise (n=8).

Note: SaO_2: arterial saturation, $PaCO_2$: arterial PCO_2, A-aDO_2: alveolar-arterial PO_2 difference, SUP: supine, UP: upright, Level I – V: exercise load, * $p<0.05$ vs. upright at rest, # $p<0.05$ vs. control condition.

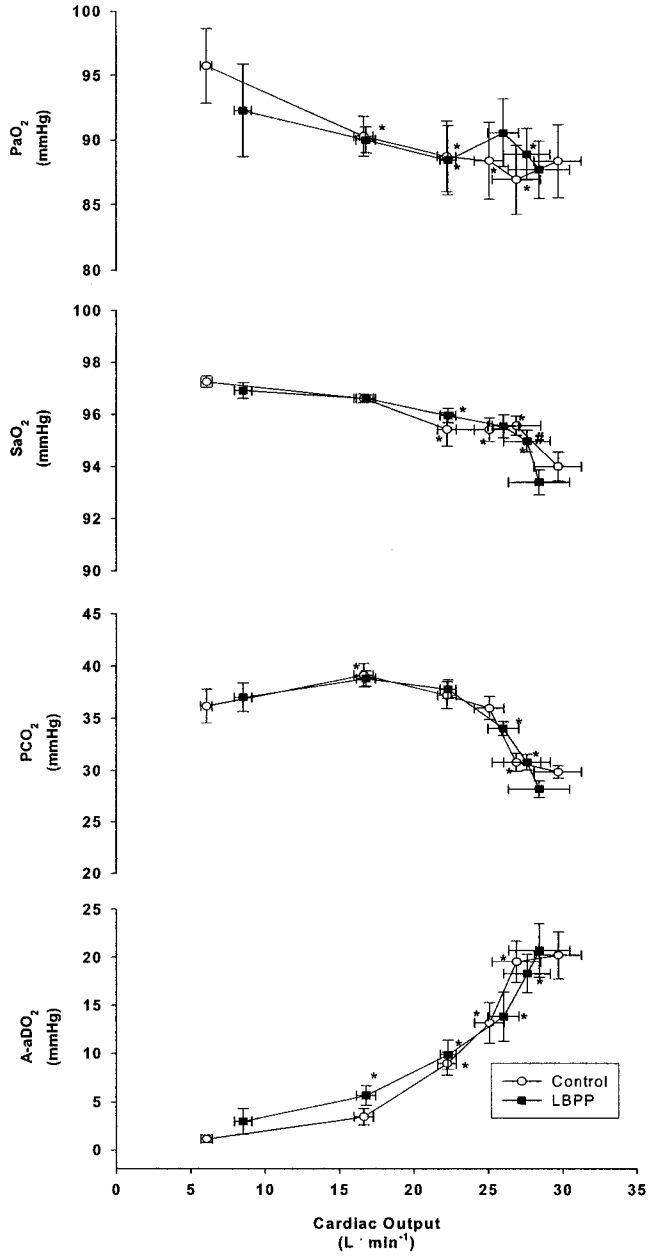


Figure 5-4. Mean (±SE) pulmonary gas exchange upright at rest and during graded exercise relative to cardiac output (n=8). Note: SaO_2: arterial saturation, $PaCO_2$: arterial PCO_2, A-aDO_2: alveolar-arterial PO_2 difference, * Cardiac output different ($p<0.05$) than control upright, # SaO_2 $p<0.05$ vs. control condition.

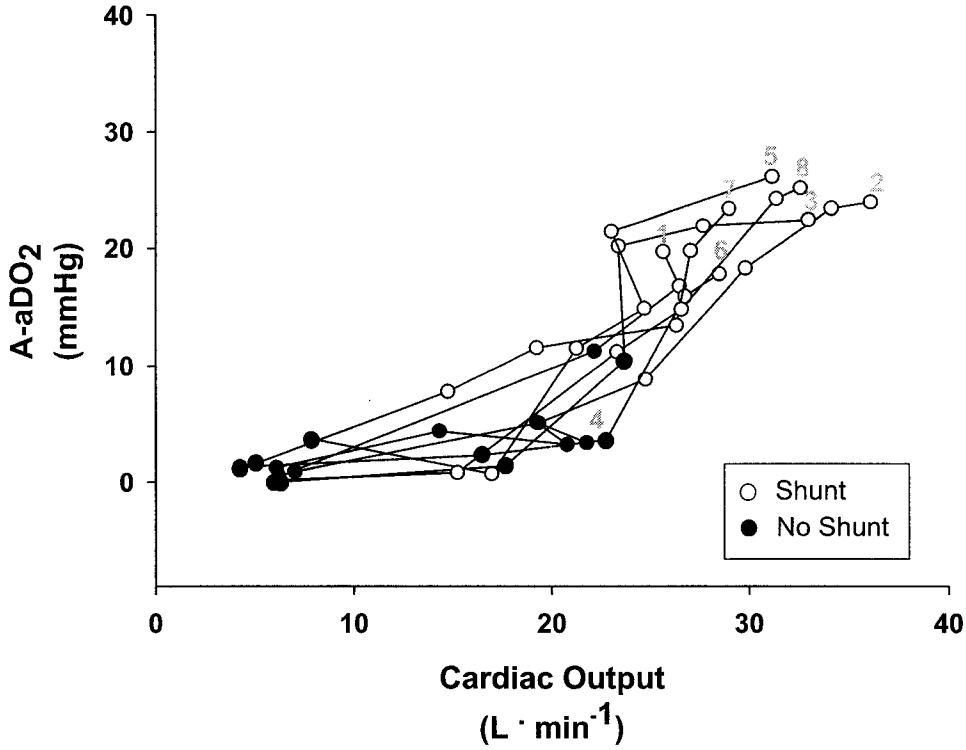


Figure 5-5. Individual relationships for subjects 1-8 during upright rest and graded exercise between cardiac output and alveolar-arterial PO_2 difference upright at rest and during graded exercise.

Note: A-aDO_2: alveolar-arterial PO_2 difference. All subjects were upright at rest and during graded exercise.

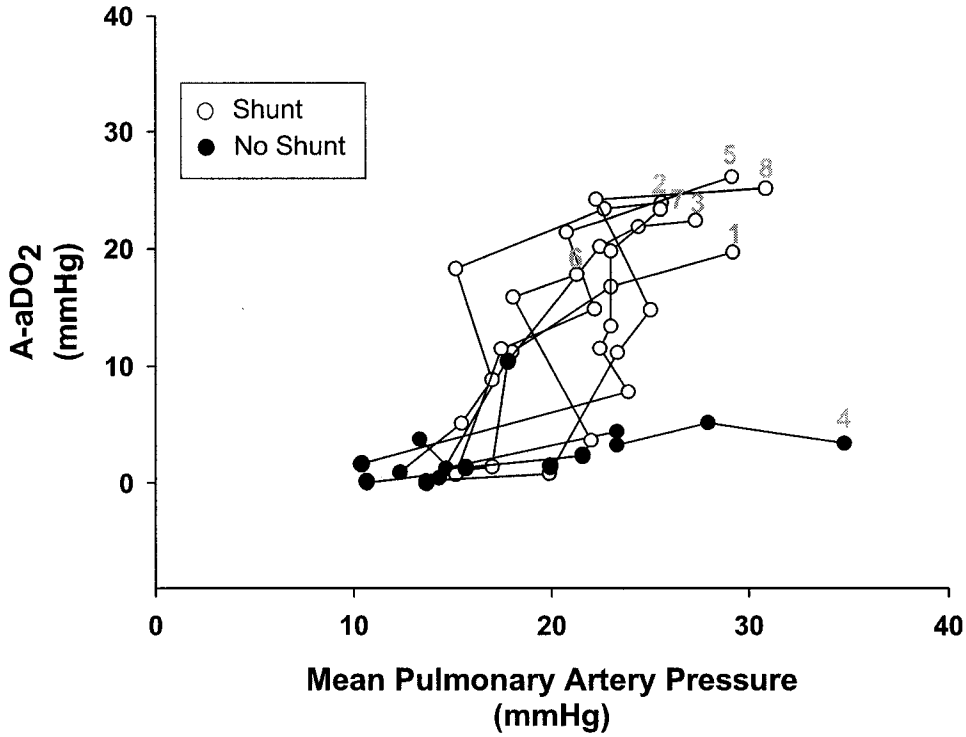


Figure 5-6. Individual relationships for subjects 1-8 during upright rest and graded exercise between mean pulmonary artery pressure and alveolar-arterial PO_2 difference. Note: A-aDO_2: alveolar-arterial PO_2 difference. All subjects were upright at rest and during graded exercise.

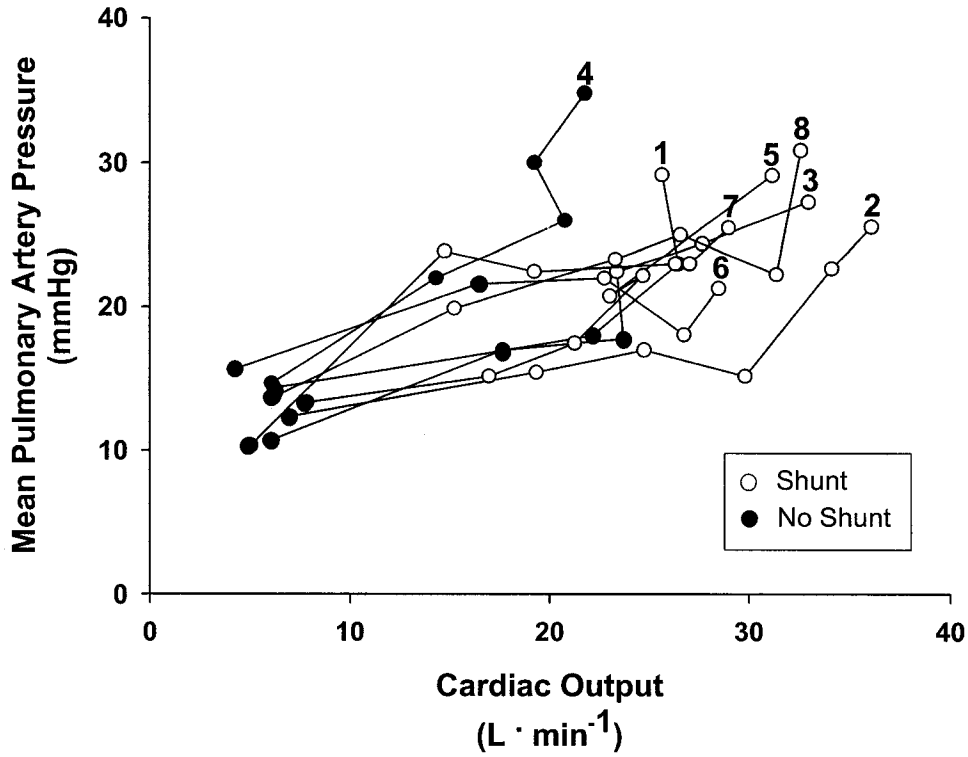


Figure 5-7. Individual relationships for subjects 1-8 during upright rest and graded exercise between cardiac output and mean pulmonary artery pressure.

Note: All subjects were upright at rest and during graded exercise.

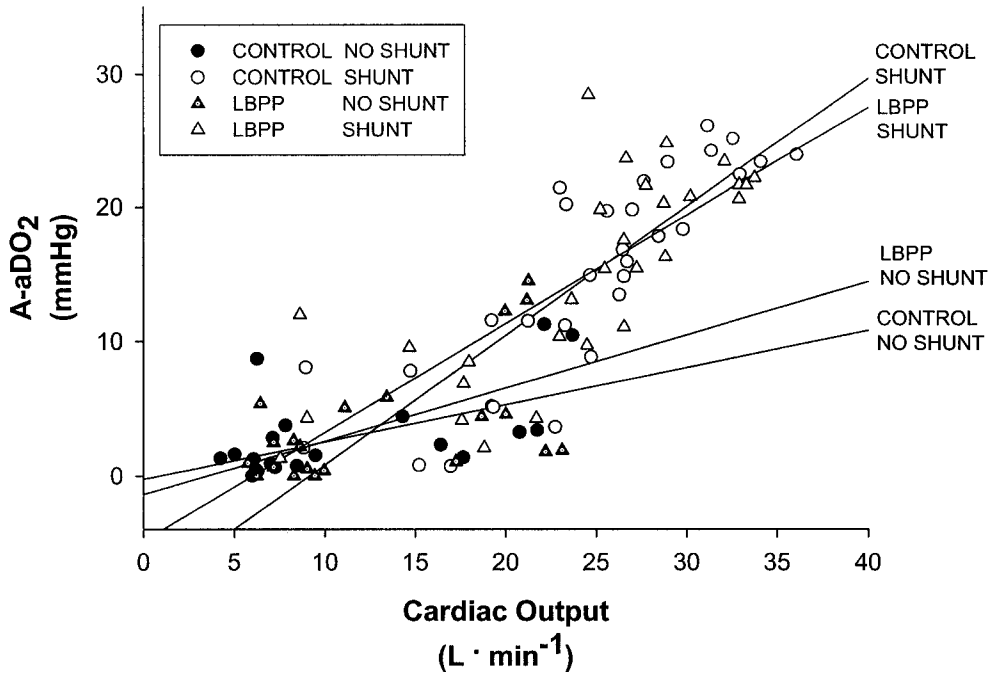


Figure 5-8. Scatterplots of cardiac output and alveolar-arterial PO_2 difference at rest and during exercise under control and LBPP conditions.

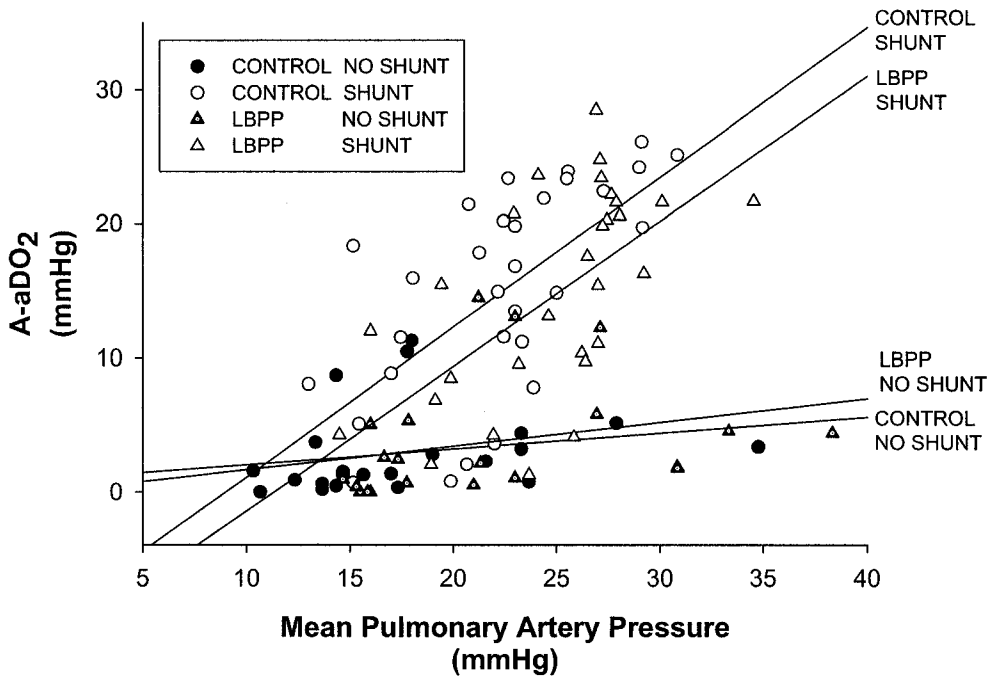


Figure 5-9. Scatterplots of mean pulmonary artery pressure and alveolar-arterial PO_2 difference at rest and during exercise under control and LBPP conditions.

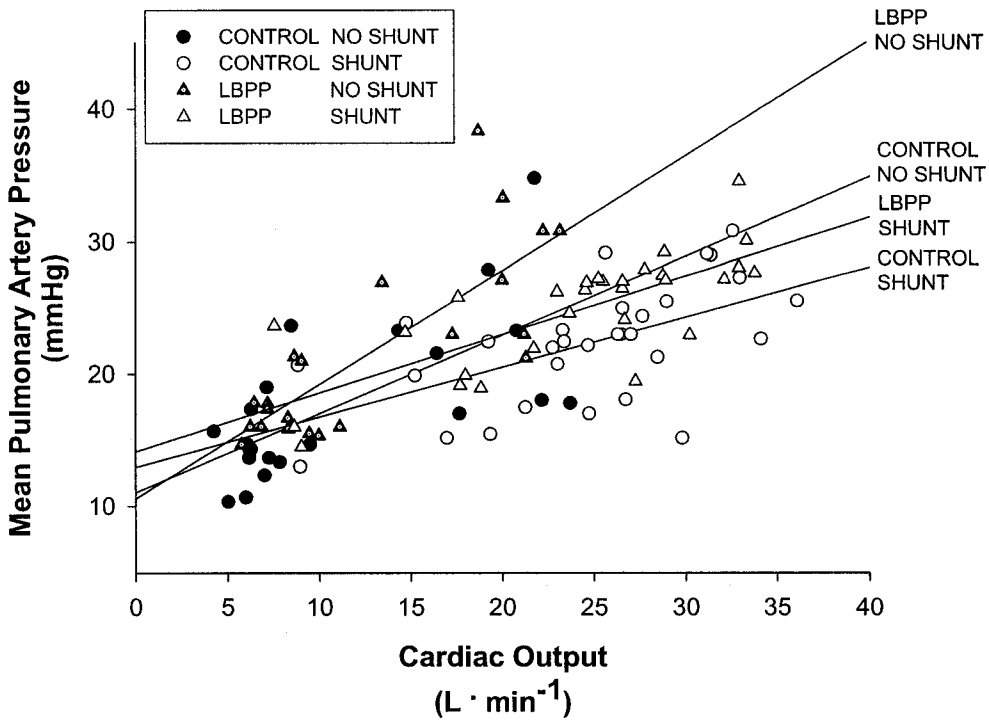
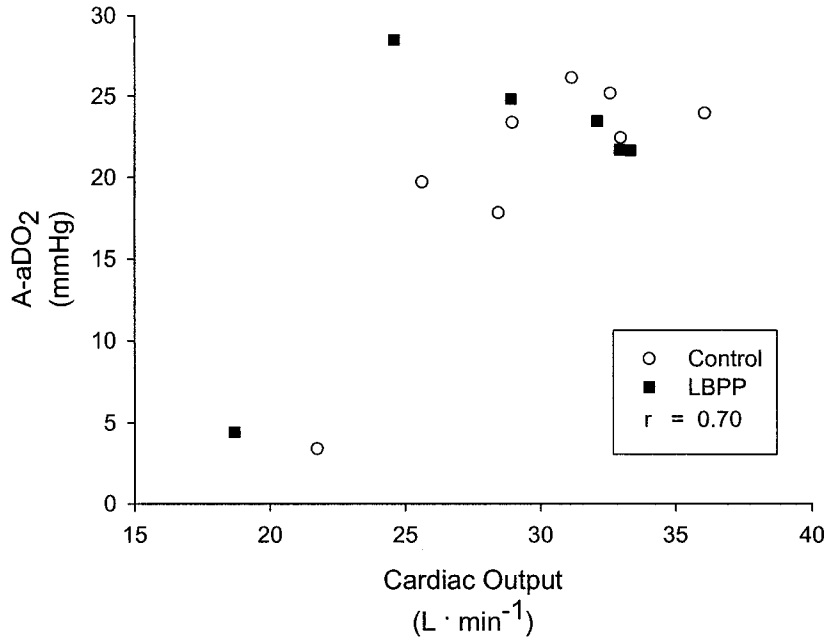


Figure 5-10. Scatterplots of mean pulmonary artery pressure and cardiac output at rest and during exercise under control and LBPP conditions.

A



B

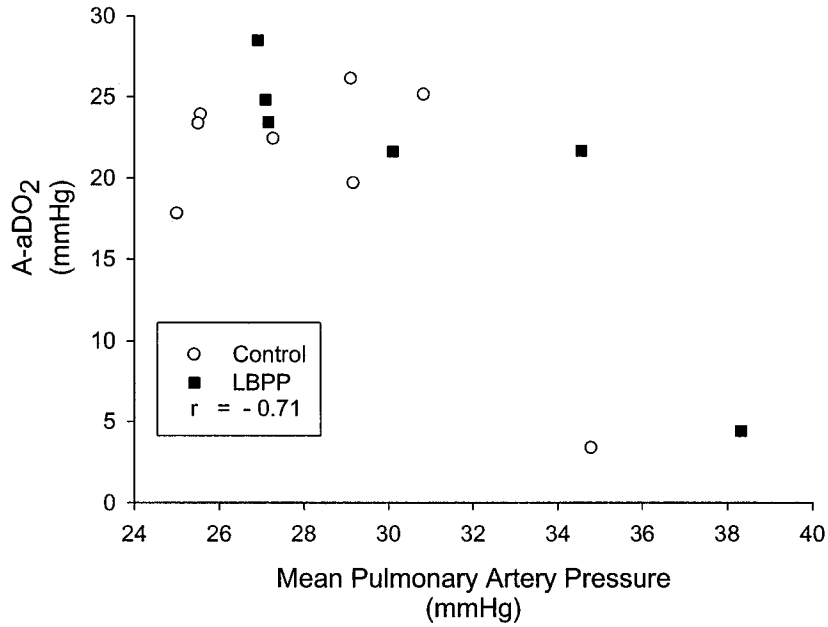


Figure 5-11. Correlations of A-aDO_2 and cardiac output (A) and pulmonary artery pressure (B) at 90% VO_{2max}.

Note: A-aDO_2: alveolar-arterial PO_2 difference. Control N = 8, LBPP N = 6.

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CHAPTER 6

GENERAL DISCUSSION

6.1 Research Program Overview

The purpose of this research program was to examine pulmonary and cardiovascular function together in an attempt to evaluate a cardiovascular contribution to the impairment in pulmonary gas exchange typically observed during exercise. In the first project, diffusion capacity was used as a non-invasive evaluation of gas exchange. High-intensity simulated cycle racing resulted in a diffusion impairment that was related to cardiac function. Subjects with the greatest diffusion impairment post exercise had blunted left ventricular (LV) systolic function and higher LV afterload. The diffusion impairment may be reflective of a mild exercise-induced pulmonary edema or damage, which may not affect the alveolar arterial PO_2 difference ($A\text{-}aDO_2$).

In subsequent projects, gas exchange was evaluated by calculation of $A\text{-}aDO_2$ from arterial blood samples and respiratory gas exchange data. In the second study, prolonged exhaustive exercise resulted in an immediate and persistent impairment in $A\text{-}aDO_2$, while cardiovascular function was maintained during exercise to exhaustion. In this experiment, cardiac function was not related to the impairment in pulmonary gas exchange. The consistency of $A\text{-}aDO_2$ during this exercise model suggested a functionally based mechanism primarily related to cardiac output ($\dot{Q}$).

In the final project, pulmonary gas exchange was examined during graded exercise. The impairment in pulmonary gas exchange observed with exercise was related to the recruitment of anatomical intra-pulmonary shunts, suggesting that I-P shunts may contribute to the widened $A\text{-}aDO_2$. These shunts and the associated $A\text{-}aDO_2$ appear flow-mediated and were not directly affected by increases in pulmonary vascular pressures from lower-body positive pressure. There appears a cardiovascular contribution to the impairment in gas exchange and I-P shunt in that higher cardiac function and cardiac output are associated with higher $A\text{-}aDO_2$ but in-fact *lower* pulmonary vascular

pressures. These results question the contribution of pulmonary vascular pressures to the impairment in pulmonary gas exchange and indicate that both the I-P shunt recruitment and the associated widened A-aDO_2 are likely flow dependent.

6.2 Evidence of Edema or Damage?

The methods selected in this dissertation did not quantify pulmonary edema or damage. Instead, a "black-box" approach was taken, examining the potential impact of edema or damage on pulmonary gas exchange during exercise. In the first project, pulmonary gas exchange was evaluated by diffusion capacity post-exercise while in subsequent studies, A-aDO_2 was calculated. Arterial blood samples are considered a more accurate technique for evaluating arterial oxygenation, since unlike pulse oximetry, these measurements are not confounded by shifts in the oxyhemoglobin dissociation curve. However, more advanced procedures such as the multiple inert gas elimination technique allow for the calculation of $\dot{V}_A/\dot{Q}$ mismatch and diffusion limitation, which can provide additional information as to the determinants of A-aDO_2.

A fundamental limitation of the first project, and others (1, 10, 15, 16, 18, 20, 28, 29, 36), is that post-exercise measures were used to infer what was occurring during exercise. The decrease in pulmonary diffusion was consistent with previous research (1, 10, 15, 18, 20, 29) and has been suggestive of the development of pulmonary edema (1, 10, 20). However, previous researchers have not found a relationship between pulmonary gas exchange during exercise and post-exercise changes in pulmonary diffusion. The absence of such a relationship raises questions regarding the significance of the post-exercise diffusion measurement (18, 25, 29).

The work of Hopkins et al. (14) is the most-cited empirical evidence of exercise-induced pulmonary damage. While there are other case studies documenting pulmonary edema

(17, 38), some researchers have used indirect methods to suggest that edema or damage has occurred with exercise (4, 9, 10, 20). It is entirely possible that these indirect methods, including diffusion capacity, are sensitive to a mild form of exercise-induced edema or damage, which is not sufficient to impact whole lung gas exchange as measured by A-aDO_2. There is still no well-defined documentation of exercise edema or damage *and* the associated impairment in pulmonary gas exchange as evaluated by A-aDO_2 in exercising humans. Therefore, until an apparent link is established, the influence of pulmonary edema or damage on A-aDO_2 in healthy humans during exercise remains unclear.

6.3 Gas Exchange Impairment - Pressure vs. Flow?

A limitation of much of the previous research examining gas exchange during exercise, including our own, is that these projects are essentially correlational in nature. That is, with incremental exercise there are increases in: oxygen consumption, cardiac output, pulmonary vascular pressures, ventilation, $\dot{V}_A/\dot{Q}$ mismatch, calculated diffusion limitation and A-aDO_2 (6, 13, 25, 32). As all these variables are increasing with exercise intensity, it is difficult to discern the factors which cause the widened A-aDO_2 in normoxia and as a result, the debate as to whether the widened A-aDO_2 is due to pressure or flow has remained.

The second project examined pulmonary gas exchange during prolonged exercise to exhaustion. The impairment in pulmonary gas exchange paralleled $\dot{Q}$, in that A-aDO_2 was elevated during exercise and quickly returned to baseline when exercise intensity and $\dot{Q}$ decreased following exercise. In the final project, during graded exercise, A-aDO_2 was more strongly related to $\dot{Q}$ than mean pulmonary artery pressure (PAP). The application of LBPP resulted in a significant increase in pulmonary artery and wedge pressures, while $\dot{Q}$ was unchanged. Pulmonary capillary wall-stress was estimated to increase by

20% with LBPP. However A-aDO_2 was not affected, questioning exercise-induced pulmonary edema secondary to elevated pulmonary vascular pressures as the explanation for the increased A-aDO_2 (32).

Previous studies provide further evidence that $\dot{Q}$ is the dominant factor for the increase in A-aDO_2 in normoxia. Zavorsky et al. (39) and Robertson et al. (26) demonstrated that acute hypervolemia did not adversely affect pulmonary gas exchange during exercise. Zavorsky et al. (39) and Robertson et al. (26) did not measure pulmonary hemodynamics, however it is likely that pulmonary vascular pressure were increased with hypervolemia (26). That hypervolemia did not affect A-aDO_2 provides additional evidence that pulmonary gas exchange is not further impaired with pulmonary hypertension.

Left-ventricular systolic and diastolic function determine pulmonary artery wedge pressure (PAWP) during exercise. Whether through enhanced diastolic compliance (7) or early diastolic suction (31, 37), an efficient, healthy ventricle is able to fill at a low end-diastolic pressure, which is equivalent to PAWP (24). Reeves and Taylor (24) have shown that PAWP accounts for 80% of the variance in PAP, indicating that LV function not only affects PAWP but also PAP. As a result, heart failure patients who have impaired LV function also have very high PAP and PAWP during exercise despite low peak work-rates and $\dot{Q}$. While diffusion capacity is lower in these patients at rest (23), as well as during (30), and following exercise (1), they do not become hypoxemic (5, 19) and show a minimal increase in A-aDO_2 with exercise (27) despite the considerable exercise-induced pulmonary hypertension. Herrlin and Sylven (11) examined pulmonary gas exchange and hemodynamics during exercise in two groups of stable heart failure patients. The more compromised group had higher PAWP but lower $\dot{Q}$ at peak exercise. Despite a mean PAWP that was 76% higher than the fitter group, PaO_2 was higher and A-aDO_2 lower, indicating better gas exchange with higher pulmonary vascular pressures.

Guazzi (8) has postulated that the pulmonary vasculature in heart failure is functionally changed due to the chronic pulmonary hypertension, thus explaining the decreased diffusion membrane capacity. However, if the widened A-aDO_2 observed during exercise was the direct result of elevated pulmonary vascular pressures as previously proposed (32), we would expect a large increase in A-aDO_2 during exercise in heart failure patients who show heightened vascular pressures during exercise.

The greatest increase in A-aDO_2 during exercise is typically observed in well-trained endurance athletes who have a high maximal $\dot{Q}$ (6). The subjects in the third project had a range of fitness levels and included endurance trained and recreational athletes. As a result of the heterogeneous sample, considerable variability was observed in peak $\dot{Q}$, PAP and A-aDO_2. Individual correlational analysis of the data at 90% of $\dot{V}O_{2max}$ demonstrated that the subjects with the highest exercise $\dot{Q}$ also had the largest A-aDO_2 ($r = 0.71$). As expected, the subjects with the highest $\dot{Q}$ were the endurance trained cyclists who also had relatively low PAWP. Indeed, when the relationship between PAP and A-aDO_2 is examined at peak exercise, a low PAP was negatively correlated with a high A-aDO_2 ($r = -0.71$). These results demonstrate that superior cardiac function allows for a high peak cardiac output that is actually associated with *higher* A-aDO_2 but *lower* pulmonary vascular pressures.

While it is acknowledged that flow and pressure in the pulmonary vascular system of a human are highly inter-related, a compelling argument is presented that pulmonary vascular pressures are not the dominant contributor to the increased A-aDO_2 during exercise. Firstly, A-aDO_2 paralleled $\dot{Q}$ in both projects two and three. More importantly, elevating pulmonary vascular pressures during exercise with lower-body positive pressure did not affect A-aDO_2. As well, heart failure patients do not show an elevated exercised A-aDO_2 despite significant elevations in PAP and PAWP at low peak work

rates. Finally, subjects with the greatest impairment in gas exchange in the third project actually had *lower* pulmonary vascular pressures. Together this provides substantial evidence that cardiac output primarily determines the impairment in pulmonary gas exchange during exercise.

6.4 I-P Shunt - Pressure vs. Flow?

The recruitment of I-P shunts during exercise also appears primarily flow mediated and not affected by elevations in pulmonary vascular pressures from LBPP. While some subjects developed shunt at low intensities, shunt was present at all work-rates above an exercise $\dot{Q}$ of 25 $L \cdot min^{-1}$. As previously noted, the one subject who did not develop I-P shunt had the lowest $\dot{V}O_{2max}$, $\dot{Q}$ and A-aDO_2 during exercise *and* very high pulmonary vascular pressures. Himelman et al. (12) previously employed the agitated saline contrast echocardiography technique to examine pulmonary patients and healthy controls during exercise. Neither group developed I-P shunt during exercise despite significant pulmonary hypertension in the clinical patients. The results of Himelman et al. (12) are consistent with current data suggesting that pulmonary vascular pressures are likely not the dominant factor for I-P shunt recruitment.

6.5 I-P Shunt - Accuracy

The validity of our conclusions regarding shunt are dependent on the accuracy of the agitated saline contrast echocardiography technique. Each contrast injection was read by an experienced cardiologist and categorized into one of the following (35): 1) No shunt. 2) I-P Shunt. 3) Intra-Cardiac Shunt. 4) Inconclusive. Each injection was typically viewed by the cardiologist several times in series, however there was the possibility of a false negative or positive. At a later date, 25 images from five randomly selected subjects were re-analyzed by the same cardiologist to assess intra-observer reliability. All of the injections were classified into the same category as when first analyzed (100%

repeatability). The injections were not read by a second cardiologist, and therefore inter-observer variability has not been be determined. However, data from two subjects provide some additional support for the accuracy of this technique. One subject developed an intra-cardiac shunt with exercise, diagnosed as visible contrast in the left ventricle within five heart beats of contrast in the right ventricle (the data from this subject were not reported within this dissertation). This subject was referred for follow-up where an intra-cardiac shunt was later diagnosed by another cardiologist using the same techniques. A second subject did not increase his A-aDO_2 with exercise and shunt was not detected at any point during exercise. If there was a high probability for false-positive I-P shunts with the agitated saline technique, we might expect at least one of the 10 exercise injections given to this subject to be categorized as shunt. The high intra-observer reliability, the diagnosis of intra-cardiac shunt by a second cardiologist, and the lack of shunt in a subject with no impairment in gas exchange provide additional evidence as to the accuracy of this technique.

6.6 I-P Shunt and Inflammation

Perfusion through larger diameter vessels would decrease the driving pressure to maintain flow. In addition to unloading the right ventricle, this could potentially reduce pulmonary capillary pressure, preventing capillary damage or edema. Previous research has examined a relationship between A-aDO_2 and lung inflammation (2, 22, 33, 34), as it has been hypothesized that the widened A-aDO_2 was due to elevated inflammation / damage. Surprisingly, Wetter et al. (33) found that subjects with the greatest amount of hypoxemia tended to have lower, not higher, plasma histamine. While I-P shunt was not examined by Wetter et al. (33), a higher PaO_2 would be consistent with little to no I-P shunt and based on current data, these subjects would likely have high pulmonary vascular pressures. It is possible that I-P shunt development decreases pulmonary vascular pressures, PaO_2, and inflammation. Contrary to previous theories, an elevated A-aDO_2 during exercise may be

reflective of healthy lungs with low levels of inflammation or damage. Future research should examine grouped responses of shunt vs. non-shunt subjects to determine how I-P shunts affect exercise-induced lung inflammation.

6.7 I-P Shunt and Pulmonary Vascular Resistance

Classic theory states that the decrease in pulmonary vascular resistance (PVR) with exercise is due to capillary recruitment and vessel distention (24). However, current results indicate that recruitment of large diameter shunt vessels may contribute to the drop in PVR. Reeves and Taylor (24) have noted that while the arteriovenous pressure gradient (driving pressure) clearly increases with increasing flow, the driving pressure for a given flow is variable between subjects. Intra-pulmonary shunt may explain some of the intra-individual variability in driving pressure. Reeves and Taylor (24) have also shown that individuals who demonstrate large increases in pulmonary wedge pressure with exercise dilate their pulmonary vessels and show a lower increase in driving pressure with increasing flow. Therefore, individual variability in cardiac responses to exercise (reflected by changes in wedge pressure) may confound comparisons of driving pressure, making determination of I-P shunt contribution to PVR complex.

6.8 The Lung as a Biological Filter

While their primary function is gas exchange, the lungs have an important secondary role as a biological filter. The lungs are the only organ to receive all the blood pumped from the heart. The pulmonary capillaries and the pulmonary lymphatic system are able to filter particles greater than 8-10 μm in diameter from the blood, trapping thrombi, platelet aggregates, and various emboli returning from the peripheral tissue before these potential infarcting agents enter the systemic arterial system (3). Based on current results, the role of the lungs as an effective physiological filter would be reduced during exercise. The recruitment of I-P shunts may unload the right ventricle and reduce PAP during exercise,

yet may also predispose subjects to exercise-induced embolization. For example, patients with hereditary hemorrhagic telangiectasia who have significant arteriovenous shunt vessels are at an increased risk of stroke and brain abscess (21). The exercise-induced pulmonary shunt data presented in this dissertation are contrary to the common perception of pulmonary circulation and the role of the lungs as a biological filter.

6.9 Exercise Model

It is important to note that the exercise model selected likely dictated the cardiopulmonary responses observed. Three dissimilar cycling models would used in this dissertation and as a result, various observations and conclusions were made. In the first project, cardiopulmonary physiology was examined *following* sustained intense exercise. The recovery from exercise may have confounded the interactions observed between heart and lung function. In the second project, a lower-intensity, longer duration protocol to fatigue was used. Data was collected at set points during exercise, however due to the prolonged exercise model, other variables such as dehydration and hyperthermia likely began to play an important role in task failure. The final project examined cardiopulmonary function during graded exercise. Unlike the previous two projects where exercise intensity was relatively stable, this study examined heart and lung function from rest up to 90% of $\dot{V}O_{2max}$. This large variance in exercise intensity, combined with the central pressure intervention from LBPP, allowed for a greater examination of cardiopulmonary function across physiological states.

6.10 Future Research

Chapter Five presents speculation as to whether I-P shunt is a consequence of, or a requirement for, a high cardiac output. If I-P shunt does play an important role in reducing right-ventricular afterload, then subjects who fail to recruit shunts would be at a mechanical disadvantage. It would be of great interest to take subjects who do not shunt

and exercise train them to determine if I-P shunt recruitment is an adaptive mechanism. This may provide additional information to explain the heterogenous response to chronic exercise training. Alternately, pharmacological interventions could be given during exercise to elevate exercise $\dot{Q}$ and determine if shunt vessels can be recruited with increased pulmonary blood flow.

The agitated saline technique allows for the categorization of data points, but does not quantify shunt. As well, the exact diameter of shunt vessels cannot be determined with the present technique. Microsphere studies are required to determine shunt fraction and vessel diameter. Comparisons are also needed between non gas-dependent methods of shunt detection, such as microspheres or agitated saline contrast echocardiography, and gas exchange methods such as MIGET and oxygen breathing, however precision is vital as all of the exercise A-aDO_2 in normoxia could be explained by less than 5% I-P shunt.

The development of I-P shunt during exercise in normal humans is contrary to the traditional view of pulmonary circulation and gas exchange. The recruitment of shunt vessels raises important questions regarding previous gas-dependent methods of shunt quantification. These anatomical shunts appear to affect pulmonary gas exchange and open up an exciting avenue for future research in cardiopulmonary physiology.

6.11 References

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