AN INVESTIGATION OF EXTRAVASCULAR LUNG WATER DURING EXERCISE IN THOSE INDIVIDUALS SUSCEPTIBLE TO IMMERSION PULMONARY EDEMA OR HIGH ALTITUDE PULMONARY EDEMA

by

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B.S., The University of Vermont, 2009

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

MASTER OF SCIENCE

in

The Faculty of Graduate Studies

(Kinesiology)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

August, 2011

ABSTRACT

Introduction: High altitude pulmonary edema (HAPE) is caused by hypoxic vasoconstriction, leading to increased pulmonary artery pressure (P_{PA}). Increased P_{PA} results in extravasation of fluid from the pulmonary capillaries to the interstitial space and inhibition of gas exchange. Immersion pulmonary edema (IPE) is likely the result of increased hydrostatic pressure due to water immersion combined with cold and physical exertion, further elevating P_{PA}. During maximal exercise, some humans develop pulmonary edema independent of hypoxia or immersion; this is a possible cause of exercise-induced arterial hypoxemia (EIAH). *Purpose:* The purpose of this study was to 1) investigate the common mechanisms that are responsible for the development of HAPE, IPE, and EIAH; and 2) investigate the factors that determine an individual's susceptibility to HAPE/IPE. *Hypotheses*: We hypothesize that 1) individuals susceptible to HAPE/IPE will develop increased extravascular lung water (EVLW) following exercise; and 2) these changes will not occur in HAPE/IPE-resistant controls. *Methods:* This study included 9 healthy fit participants who previously experienced HAPE or IPE. Participants performed a 45-minute maximal exercise task on a cycle ergometer. A matched control group of 9 participants with experience at altitude or immersion and no history of HAPE/IPE also performed the task. Diffusion capacity of CO ($D_L$co) was measured before and after exercise. Computed tomography was used to confirm EVLW following exercise. *Results:* Both groups showed a significant reduction in lung density post-exercise ($p=0.013$). Participants susceptible to HAPE/IPE had a significantly lower density compared to resistant participants ($p=0.037$). $D_L$co decreased significantly after exercise ($p<0.001$), without difference in the change between groups ($p=0.77$). *Discussion:* Because of the post-exercise increase in volume, the decrease in lung density should be considered to represent no change in EVLW. The decrease in $D_L$co was

consistent with results found in other studies. Lower lung density in HAPE/IPE-susceptible participants could be the result of damage caused by HAPE/IPE, increased vascular reactivity, or decreased lymphatics. *Conclusion:* Susceptibility to HAPE/IPE does not increase risk of developing EVLW during maximal exercise. Participants susceptible to HAPE/IPE displayed a significantly lower lung density that necessitates further research.

PREFACE

Ethical review for all techniques has been carried out by the University of British Columbia Clinical Research Ethics Board for Experiments Involving Human Subjects (UBC CREB). The study CREB approval certificate is #H09-03125.

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HAPE	High Altitude Pulmonary Edema	V_A	Alveolar Volume
EVLW	Extravascular Lung Water	BAL	Bronchoalveolar Lavage
IPE	Immersion Pulmonary Edema	ARDS	Acute Respiratory Distress Syndrome
EIAH	Exercise Induced Arterial Hypoxemia	P_{PA}	Pulmonary Artery Pressure
A-a DO_2	Alveolar-Arterial Oxygen Difference	MRI	Magnetic Resonance Imaging
		ATS	American Thoracic Society
SaO_2	Arterial Oxygen Saturation	ERS	European Respiratory Society
CT	Computed Tomography	PO_2	Partial Pressure of Oxygen
SCUBA	Self Contained Underwater Breathing Apparatus	P_AO_2	Partial Pressure of Alveolar Oxygen
EPL	Environmental Physiology Laboratory	P_aO_2	Partial Pressure of Arterial Oxygen
FVC	Functional Vital Capacity	Q	Cardiac Output
$FEV_{1.0}$	Forced Expiratory Volume in One Second	P_{LA}	Left Atrial Pressure
		CVP	Central Venous Pressure
VO_{2max}	Peak Oxygen Consumption		
RER	Respiratory Exchange Ratio	PAWP	Pulmonary Artery Wedge Pressure
V_E	Minute Ventilation		
VCO_2	Volume of CO_2	MSW	Meters of Sea Water
S_PO_2	Pulse Oxygen Saturation	FRC	Functional Residual Capacity
VGH	Vancouver General Hospital	VDC	Voluntary Diaphragmatic Contractions
D_Lco	Diffusion Capacity of CO		
D_M	Membrane Diffusion Capacity	kVp	Peak Kilovoltage
V_C	Pulmonary Capillary Blood Volume	mA	Miliamperes
		HU	Hounsfield Units
Hb	Hemoglobin	R	Roentgens
PEs	Susceptible to Pulmonary Edema	N_0	Initial Number of Photons
PEr	Resistant to Pulmonary Edema	N	Number of Transmitted Photons
ANOVA	Analysis of Variance		
SPSS	Statistical Package for the Social Sciences	X	Voxel Thickness
		μ	Attenuation Coefficient

ACKNOWLEDGEMENTS

Equipment and financial, logistical, and analytical support provided by:

B.C. Sports Medicine Research Foundation
Canadian Academy of Sport and Exercise Medicine
Canadian Foundation for Innovation
UBC Hospital – Department of Radiology
UBC Thoracic Imaging Group
UBC Air Pollution Exposure Laboratory

This project could not have been completed without the generous help of my lab partners, the advice and guidance of my supervisor, and the support of my friends and family.

In particular I would like to thank:

Dr. MS Koehle
Dr. DC McKenzie
Dr. J Mayo
Dr. H Coxson
Dr. J Rupert
Martin MacInnis
Luisa Giles
Sarah Koch
Normand Richard
Sally Lin
Janille Durity-Wingson
Xiaolin Ren

To my parents.

1. INTRODUCTION

1.1 Background and Justification

Mountaineering, diving, and competitive swimming are all common recreational and commercial activities in North America. With these activities comes the risk of developing pulmonary edema, a life-threatening condition where fluid accumulates in the lung preventing the diffusion of oxygen into the capillaries.

At elevations above 2,500 metres, it is generally established that high altitude pulmonary edema (HAPE) is the result of acute hypoxia, which causes non-uniform vasoconstriction throughout the pulmonary bed. The unprotected arterioles and capillaries receive excess blood flow and pressure. Excess pressure results in capillary stress failure and eventual fluid leak out of the capillary into the alveolus. Extravascular lung water (EVLW) interferes with gas exchange at the level of the alveolus, causing hypoxemia (and resultant dyspnea) that is characteristic of HAPE [1]. Hypoxemia is worsened by exertion. Exertion increases capillary pressures, especially in hyperperfused areas of the lung [2]. A critical factor in HAPE is the rate of ascent. HAPE is most common in cases where the patient did not properly follow acclimatization guidelines [2].

Long distance swimmers [3], triathletes [4], and competitive breath hold divers [5] are susceptible to a comparable condition known as immersion pulmonary edema (IPE) [6]. Specifically, cold and increased inspiratory load due to immersion are believed to cause an increase in pulmonary artery pressure (P_{PA}) and non-uniform vasoconstriction in the pulmonary capillaries. Immersion also increases hydrostatic pressure resulting in central pooling of blood and increased P_{PA} [7]. These factors result in capillary stress failure leading to increases in EVLW [8-10]. Physical exertion, which raises P_{PA}, is a significant risk factor for IPE [11].

Recent research has indicated that some humans develop pulmonary edema during maximal exercise [12-14]. This exercise-induced pulmonary edema was hypothesized to be a contributing factor in a condition called exercise induced arterial hypoxemia (EIAH). EIAH is characterized by a widening of the alveolar-arterial O_2 difference ($A\text{-}a\ DO_2$) and a reduction in arterial O_2 saturation (SaO_2). It is estimated that EIAH occurs in 52% of highly trained athletes, and it is known that EIAH impairs exercise performance [15]. Koskolou *et al.* found a significant decrease in maximal exercise capacity in highly trained cyclists when EIAH was induced (% S_aO_2 = 87 ± 1%) [16]. Furthermore, the detrimental effects of EIAH on performance can be reversed with hyperoxia [17]. The transient increase in EVLW demonstrated in these studies could be the cause of impaired gas exchange and hypoxemia in EIAH [18]. The proposed mechanism of this transient pulmonary edema with exercise is believed to be increased capillary leakage caused by an elevated P_{PA}, the very same mechanism proposed in both IPE and HAPE [19, 20].

As the presumed mechanism for the development of pulmonary edema in all three situations is similar, we hypothesize that there is a common underlying mechanism among these three conditions and that individuals with a susceptibility to either HAPE or IPE will be prone to increased EVLW during intense exercise in normoxia. Previous studies investigating EIAH and EVLW used only healthy subjects who had no history of pulmonary edema. It is possible that the inconsistent results from these studies suggest only a small subgroup of humans develop EVLW during sea-level exercise. The "susceptible" subgroup may also be likely to develop HAPE or IPE when exposed to their respective stressors. This study is the first to use subjects who have previously experienced HAPE or IPE as candidates for susceptibility to EVLW during exercise.

While HAPE and IPE are relatively rare, they are both potentially fatal and can occur in austere environments, away from effective medical care. In fact, although HAPE is much less common than acute mountain sickness, it kills far more visitors to altitude [6]. An analysis by Lobenhoffer *et al.* of 166 cases of HAPE revealed an 11.4% mortality rate. Of those who did not receive oxygen or undertake immediate descent, the mortality rate was 49% [21]. At present there is no clinical or laboratory test to determine susceptibility to either IPE or HAPE. If it can be shown that those individuals at risk of IPE and/or HAPE demonstrate a buildup of EVLW after exercise in normoxia, we can develop an *a priori* test for these conditions. Furthermore, by defining a common underlying pathophysiology, we can enhance our understanding of the mechanisms of these conditions leading to the development of treatments or preventative strategies.

1.2 Hypothesis

Following a 45-minute bout of intense cycling, individuals susceptible to either HAPE or IPE will develop increased EVLW. We hypothesize that these changes will not occur in HAPE/IPE resistant control participants. Changes in EVLW will be characterized by:

1. Significantly reduced pulmonary diffusion capacity following exercise.

2. A significant decrease in pulse oxygen saturation during the exercise bout as compared to control participants.

3. A significant increase in lung density following exercise.

A difference of 0.02 $g*ml^{-1}$ is considered a meaningful change in lung density. In previous studies using computed tomography (CT), a standard deviation of 0.013 $g*ml^{-1}$ was found [22, 23] corresponding to an effect size of f = 0.769. Using a power of 0.8 and an alpha set at a =

0.05, eight participants were needed for each group; however, a sample size of 18 was selected due to the likelihood of participants withdrawing from the study.

2. METHODS

2.1 Subjects

Nine healthy fit male and female participants who had previously been diagnosed with HAPE or IPE were recruited for the experimental or pulmonary edema susceptible (PEs) group. A HAPE diagnosis was made with a chest x-ray showing pulmonary edema, or hemoptysis and dyspnea preventing further gain in altitude and resolving on descent. An IPE diagnosis was made with a chest x-ray showing pulmonary edema, or hemoptysis and dyspnea that required the participant exit the water. The study physician reviewed each case to confirm the diagnosis and determine eligibility. Nine healthy fit males and females were recruited to serve as the age-, sex-, weight-, and height-matched control or pulmonary edema resistant (PEr) group. To be eligible for the PEr group, participants must have previously travelled above 3000 metres, competed in at least two Ironman distance triathlons with a swim time under 75 minutes or have a valid self-contained underwater breathing apparatus (SCUBA) certification with a minimum of 10 cold water dives (<10 deg Centigrade) without experiencing any symptoms of pulmonary edema. All participants were non-smokers with no history of lung disease, abnormal lung function, asthma, heart disease or hypertension. Participants were recruited through posted advertisements, Dr. Koehle's sport medicine practice, and existing contacts within the local mountaineering, skiing, search and rescue, swimming, and diving communities. Participants were familiarized with the test protocol, and were required to sign an informed consent form prior to their inclusion in the experiment.

2.2 Protocol

This experiment utilized a parallel design with subjects from each group performing two tests, pre- and post-exercise. Participants completed two test days. During a familiarization day,

pulmonary function was measured and participants were screened for fitness level. The intervention day included a 45-minute maximal exercise task as well as pre- and post-spirometric and radiologic measures.

2.3 Pulmonary Function and VO_{2max}

Participants reported to the Environmental Physiology Laboratory (EPL) to provide informed consent and to be familiarized with the metabolic cart, cycle ergometer, and spirometer. Participants were instructed to avoid exhaustive exercise for 24 hours, caffeine for 12 hours, and food or drink for 2 hours prior to the visit. Height and weight were measured with bare feet and wearing cycling clothing. A portable Spirobank spirometer (MIR, Roma, Italy) was used to confirm normal lung function according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [24]. Subjects were instructed to wear a nose clip, and breathe room air through a disposable mouthpiece. Once breathing comfortably, subjects were told to exhale, followed by a full inhalation and then a rapid, complete expiration. Parameters measured included forced vital capacity (FVC) and forced expired volume in 1 second ($FEV_{1.0}$). Participants then performed an incremental cycle test to exhaustion using a Velotron Dynafit Pro cycle ergometer (Racermate Inc, WA, USA) and a metabolic cart (TrueOne® 2400, ParvoMedics, UT, USA). Work rate started at 0 Watts (W), and increased by 0.5 W/sec until volitional exhaustion. To ensure that maximal oxygen consumption was attained, at least 3 of the following criteria were met:

1) A plateau in VO_2.

2) Attainment of at least 90% of age-predicted maximal heart rate (210 bpm – [0.65 x age]).

3) Respiratory exchange ratio (RER) > 1.1.

4) Inability to maintain a cadence of 60 rpm despite maximal effort and verbal encouragement.

During the test, heart rate (HR) was recorded continuously using a short-range telemetry system and periodically (every 15 s) using a Polar portable heart rate monitor (Polar Oy, Kempele, Finland). Participants inspired through a heated pneumotach (Hans Rudolph, USA) using a mouth piece equipped with a two-way non-rebreathing valve (2700 Series, Hans Rudolph, USA). Expired air passed into a mixing chamber where gas samples were analyzed for oxygen and carbon dioxide concentrations. Minute ventilation (V_E), VO_2 and carbon dioxide output (VCO_2) were averaged over 15 seconds and reported. Peak oxygen consumption was determined as an estimate of aerobic fitness by averaging the three highest consecutive 15-second values. Gas analyzers were calibrated with gases of a known concentration prior to each experiment. Peak power and time to completion of test were recorded for each participant. Pulse oxygen saturation (S_PO_2) was monitored using a Nonin 9600 pulse oximeter attached to the ear lobe (Nonin Medical Inc., MN, USA). After the test, participants performed a self-selected cool-down.

2.4 Maximal Exercise Task

The intervention visit took place in the Radiology Department at Vancouver General Hospital (VGH). Participants were instructed to avoid exhaustive exercise for 24 hours, caffeine for 12 hours, and food or drink for 2 hours prior to the visit. The maximal exercise task consisted of a stationary-cycle test on a Velotron Dynafit Pro cycle ergometer (Racermate Inc, Seattle WA) with a protocol similar to one used in other studies to induce EIAH [25]. The task began with a 10-minute warm-up at 30% of peak power output achieved in the VO_{2max} test, followed by three 5-minute "high-intensity" bouts of exercise separated by 10 minutes of recovery at 30% peak

power. The exercise bouts were performed at an intensity between 80 and 90% (self selected) of the recorded peak power output achieved during the VO_{2max}. During the last two minutes of each interval, resistance was increased toward the peak power output attained at VO_{2max} to ensure a maximal effort. Heart rate and S_PO_2 were monitored continuously during the exercise task. Following the exercise task, subjects were immediately transferred to a wheelchair where they rested until their HR reached a recovery plateau within a range of 5 bpm and remained at that rate for at least five minutes.

2.5 Computed Tomography

Prior to, and following HR stabilization after the maximal exercise task, participants completed a chest CT scan to evaluate lung density ($g_{*}ml^{-1}$). Three slices of the lung were scanned at the level of the aortic arch, the tracheal carina, and the superior end plate of T10 with the subject breathing at functional residual capacity and pausing at the end of an inspiration. Scans were completed using a single turn 360 degree helical acquisition on a Sensation 16, 16 detector row "rotate-rotate" CT scanner (Siemens AG, Germany). The detector array uses 16 0.75 mm detector tracks which can give ten images 1 mm thick, five images 2 mm thick or two images 5mm thick. Due to technical difficulties, three subjects were scanned using a Sensation 64, 64 detector row "rotate-rotate" CT scanner (Siemens AG, Germany). The detector can give thirteen images 1 mm thick, seven images 2 mm thick, or three images 5 mm thick. The scanner generates a potential difference of 120 kVp, a current of 80 mA, and a 0.5 second rotation time, with a field of view of 380 mm. Tube current modulation is automatically applied in the x and y planes with an average dose length product per acquisition of 34 ± 1.4 mGy/cm. The scan yielded an effective dose of .95 mSev. The radiation dose from this scan is minimized as only 3

slices of the lung are imaged; equivalent to approximately one half of the yearly background radiation exposure in Vancouver, B.C. [22, 23].

Images were reconstructed using either a low (B35), intermediate (B45), or high (B60 with edge-enhancement) spatial frequency reconstruction algorithm. Once the images were reconstructed, the radiologist screened them for relevant abnormalities that would prevent inclusion in the analysis. Upon approval, images were transferred to a computer for density analysis.

Custom software (EmphylxJ) was used to analyze the x-ray attenuation values of the lung following segmentation of the lung parenchyma. Lung tissue was segmented from the chest wall and mediastinum, and the voxel dimensions were summed in order to calculate CT lung volume. Once the mean CT attenuation of the lung (in Hounsfield units (HU)) is known, it can be converted to a density measure in $g_{*}ml^{-1}$ using equation one presented below.

1) $$\text{Density} = (HU + 1000)/1000$$

2.6 Diffusion Capacity of Carbon Monoxide

Pulmonary diffusion capacity was measured according to the ATS/ERS guidelines [26] using standard diffusion measuring equipment (W.E. Collins Inc, MA, USA). The protocol was consistent with previous studies performed within our group [13, 27, 28]. The pre-exercise diffusion capacity measurement was performed immediately before the exercise task. Participants remained seated for approximately 30 minutes prior to this measurement to mitigate any potential prior exercise effect on diffusion capacity. Measurements were again performed post-exercise after HR stabilized and after the CT scan was completed. Pulmonary diffusion capacity was measured using the single breath carbon monoxide diffusion capacity method

($D_L$co). The rate of disappearance of carbon monoxide (CO) ($ml*min^{-1}*mmHg^{-1}$) was assessed after the participant inhaled a test gas of 21% O_2, 10% helium (He), and 0.3% CO with a balance of nitrogen (N_2). After a full inhalation, the participants held their breath for approximately 10 seconds after which they were instructed to exhale rapidly. This procedure was repeated until two trials were performed with values within 3 $ml*min^{-1}*mmHg^{-1}$. Participants then underwent a five-minute washout period breathing a gas mixture containing 90% O_2 and 10% N_2. Diffusion capacity of CO measurements were then repeated using a second, high O_2, gas mixture (10% He, 0.3% CO, Balance O_2). The expired gas was compared by the spirometer to determine the proportion of the carbon monoxide that has diffused into the blood. The measurement of $D_L$co with high O_2 gas mixture allowed for the partitioning of $D_L$co into its two components, membrane diffusion (D_M) and capillary blood volume (V_C), according to the method developed by Roughton *et al*. [29, 30] and previously used by our research group [6, 13, 27, 28]. This partition will provide differentiation between a change in diffusion capacity due to variation in the permeability of the membrane (which would be expected with an increase in EVLW) and variation in capillary blood volume (usually caused by a confounding exercise effect). The gases were pre-mixed from a commercial supplier to minimize the chance of error. Hemoglobin (Hb), the concentration of which would affect measurements of D_M and V_C due to its affinity for oxygen, was measured with a HemoCue analyzer, using a single drop of capillary blood from the fingertip (HemoCue AB, Ängelholm, Sweden).

2.7 Statistical Analysis

In this study, n = 18 with nine subjects in the experimental (PE*s*) group and nine subjects in the control (PE*r*) group. The primary outcome variable analyzed was lung density as measured by CT. Two-by-two Analysis of Variances (ANOVA) tests were used to compare lung density,

mass, and volume between groups (PEr and PEs) pre- and post-exercise. Changes in $D_L$co, D_M, and V_C were analyzed using two-by-two ANOVA tests between groups (PEr and PEs) pre- and post-exercise. All continuous variables were expressed as a mean of the group (± standard deviation). All data analyses were performed using the software program, Statistical Package for the Social Sciences (SPSS 17.0). Alpha was set at $\alpha = 0.05$. A difference with $p < 0.05$ was considered statistically significant.

3. RESULTS

3.1 Descriptive Data

Anthropometric data for all participants are presented in Table 3.1. Individual data are presented in Table B1 (Appendix). Independent samples t-tests were used to compare anthropometric and spirometric characteristics between groups to confirm a homogeneous sample. No differences were found between groups in any of the descriptive variables.

Table 3.1. Anthropometric and spirometric characteristics of 18 subjects.

Group	Statistic	Age (years)	Height (cm)	Weight (kg)	FVC (L)	$FEV_{1.0}$ (L)
PE*s*	Mean	38	172	70.8	5.52	4.09
	SD	13	9	13.3	1.64	1.32
PE*r*	Mean	37	175	77.4	5.12	3.92
	SD	15	9	11.3	0.99	0.69

SD, Standard deviation; PEs, Pulmonary edema susceptible; PEr, Pulmonary edema resistant.

3.2 VO2max

Table 3.2 shows the results for the VO_{2max} test. All subjects had a resting pre-test S_PO_2 of 99-100%. Individual data are found in Table B2. An independent samples t-test was used to compare fitness levels between groups, and no significant difference was found.

Table 3.2. Maximal oxygen consumption (VO_{2max}), maximal oxygen consumption per kilogram (VO_{2max}), peak power, maximum heart rate (MHR) and minimum arterial oxygen saturation (S_PO_2).

Group	Statistic	VO_{2max} (L_*min)	VO_{2max} (mL_*min_*kg)	Peak Power (watts)	MHR (bpm)	Min S_PO_2 (%)
PE*s*	Mean	3.46	48.36	314.67	184.22	92.78
	SD	1.00	10.27	64.74	6.55	8.38
PE*r*	Mean	4.05	51.89	334.00	177	90.67
	SD	1.20	12.57	76.785	11.16	11.69

SD, Standard deviation; PEs, Pulmonary edema susceptible; PEr, Pulmonary edema resistant.

3.3 Maximal Exercise Task

Table 3.3 shows the result of the 45-minute stationary cycle ergometry task. Heart rate values during the maximal exercise task were comparable to the maximal HR attained during the VO_{2max} test. All subjects had a resting pre-test S_PO_2 of 99-100%. Individual data can be found in Table B3. Maximal exercise task variables were compared between groups with independent samples t-tests to confirm that both groups performed equal workloads. Oxygen saturation did significantly decrease in all subjects during exercise ($t(1, 16) = 4.176$, $p < 0.001$). The difference in S_PO_2 between groups was not significant ($p = 0.261$), but there appeared to be a trend towards lower S_PO_2 values in PEs participants compared to PEr participants.

Table 3.3. Maximum heart rate (MHR), minimum arterial oxygen saturation (S_PO_2) during the third interval, mean interval power (INT Power), mean percent maximal power (INT Intensity).

Group	Statistic	MHR (bpm)	Min S_PO_2 (%)	INT Power (watts)	INT Intensity (%)
PE*s*	Mean	188	91	233	73
	SD	8	6	59	6
PE*r**	Mean	181	95	230*	71*
	SD	11	4	58	6

*Power data for participant 002 was not measured, n = 8. *SD*, Standard deviation; PEs, Pulmonary edema susceptible; PEr, Pulmonary edema resistant.

3.4 Computed Tomography

3.4.1 Mean Lung Values

Table 3.4 shows results for lung density, mass, and volume measured with CT pre- and post-exercise using the B35 spatial frequency reconstruction algorithm with 1-mm slice thickness, a standard densitometry research setting. Participants were scanned immediately before and approximately 11 minutes (± 1) after cessation of exercise. A review of previous studies evaluating EVLW after exercise (Table A1) suggests that a time to scan between 0 and 120 min does not affect the presence of EVLW on imaging. Individual results are located in Tables B4, B5, and B6. Pre- and post-exercise density, mass, and volume data are displayed in Figures 3.1, 3.2, and 3.3. Individual changes pre- and post-exercise are displayed in Figures B1, B2, and B3.

Table 3.4. CT Lung data pre- and post- exercise.

Group	Statistic	Density ($g_{*}mL^{-1}$)		Mass (g)		Volume (mL)	
		Pre	Post	Pre	Post	Pre	Post
PE*s*	Mean	.192‡	.179*‡	127.9‡	125.9‡	666.6	701.6*
	SD	.035	.023	88.5	100.0	24.2	21.3
PE*r*	Mean	.220‡	.212*‡	149.0‡	147.9‡	681.9	700.2*
	SD	.003	.030	19.2	21.3	95.7	88.4

*Significantly different from pre-exercise mean ($p < 0.05$). ‡Significant difference between groups. SD, Standard deviation; PEs, Pulmonary edema susceptible; PEr, Pulmonary edema resistant.

A two-by-two repeated measures ANOVA was used to assess the impact of pulmonary edema susceptibility (PEr, PEs) on the participant's CT lung density, mass and volume before and after the maximal exercise task. There was no significant interaction effect between pulmonary edema susceptibility and time for any of the CT variables. There was a significant main effect for time with both groups showing a reduction in density post-exercise ($F (1, 16) = 7.869$, $p = 0.01$). This corresponds to the significant increase in volume and the lack of change in mass following exercise ($F (1, 16) = 9.649$, $p = 0.006$; $F (1, 16) = 0.5725$, $p = 0.460$, respectively). The main effect of pulmonary edema susceptibility on density was significant ($F (1, 16) = 5.20$, $p = 0.04$), suggesting lower lung density in PEs subjects. There was no significant interaction effect for density, mass, or volume ($F (1, 16) = 0.5038$, $p = 0.488$; $F (1, 16) = 0.0549$, $p = 0.818$; $F (1, 16) = 0.9574$, $p = 0.342$; respectively). The main effect of pulmonary edema susceptibility on mass approached significance ($F (1, 16) = 3.788$, $p = 0.069$), suggesting a difference between groups at both time points that was unrelated to the exercise task.

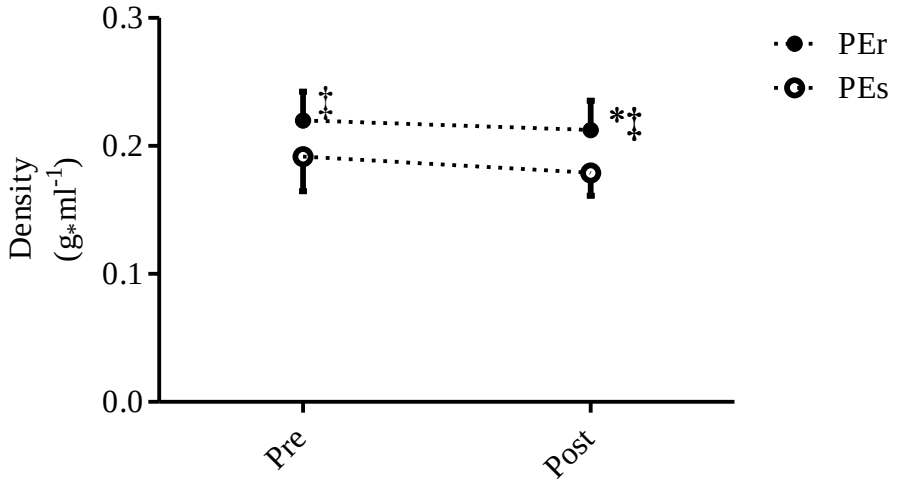


Figure 3.1. CT lung density pre- and post-exercise in subjects susceptible (PEs) and resistant (PEr) to pulmonary edema. *Significantly different from pre-exercise mean ($p < 0.05$). ‡Significant difference between groups.

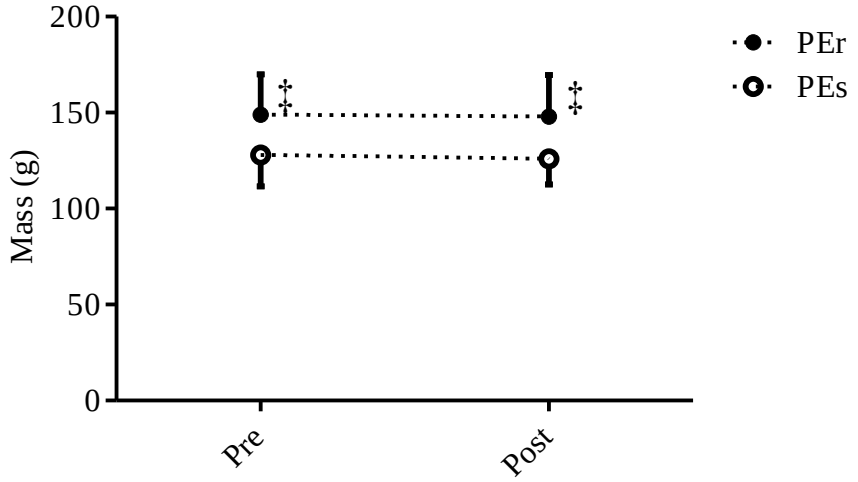


Figure 3.2. CT lung mass pre- and post-exercise in subjects susceptible (PEs) and resistant (PEr) to pulmonary edema. ‡Significant difference between groups.

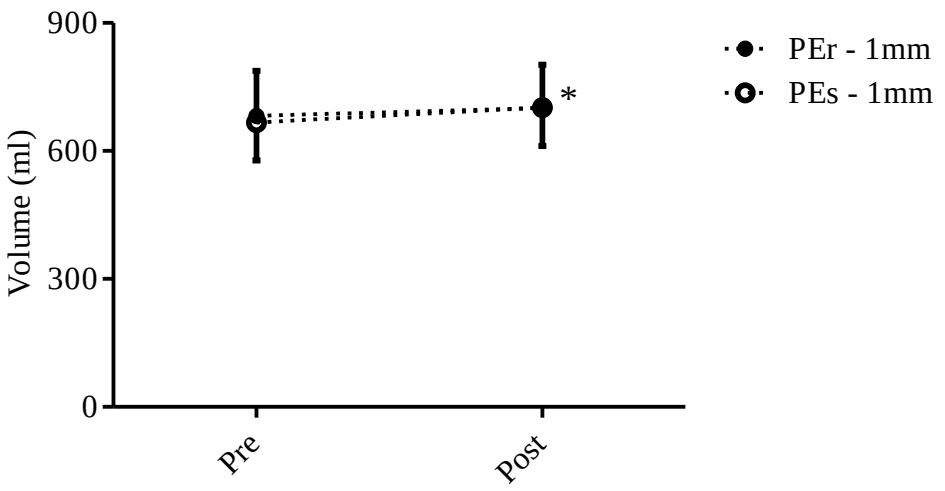


Figure 3.3. CT lung volume pre- and post-exercise in subjects susceptible (PEs) and resistant (PEr) to pulmonary edema. *Significantly different from pre-exercise mean ($p < 0.05$).

3.4.2 Receiver Operating Characteristic

A receiver operating characteristic graph, using lung density as a continuous rating scale to predict susceptibility to pulmonary edema, is plotted in Fig. 3.4. At a density of 0.2367 $g_{*}ml^{-1}$, the sensitivity for pulmonary edema susceptibility was 88%, and the specificity was 39%. A density greater than 0.2367 $g_{*}mL^{-1}$ has a negative predictive value of 76% for HAPE and IPE susceptibility. The area under this curve was 0.757.

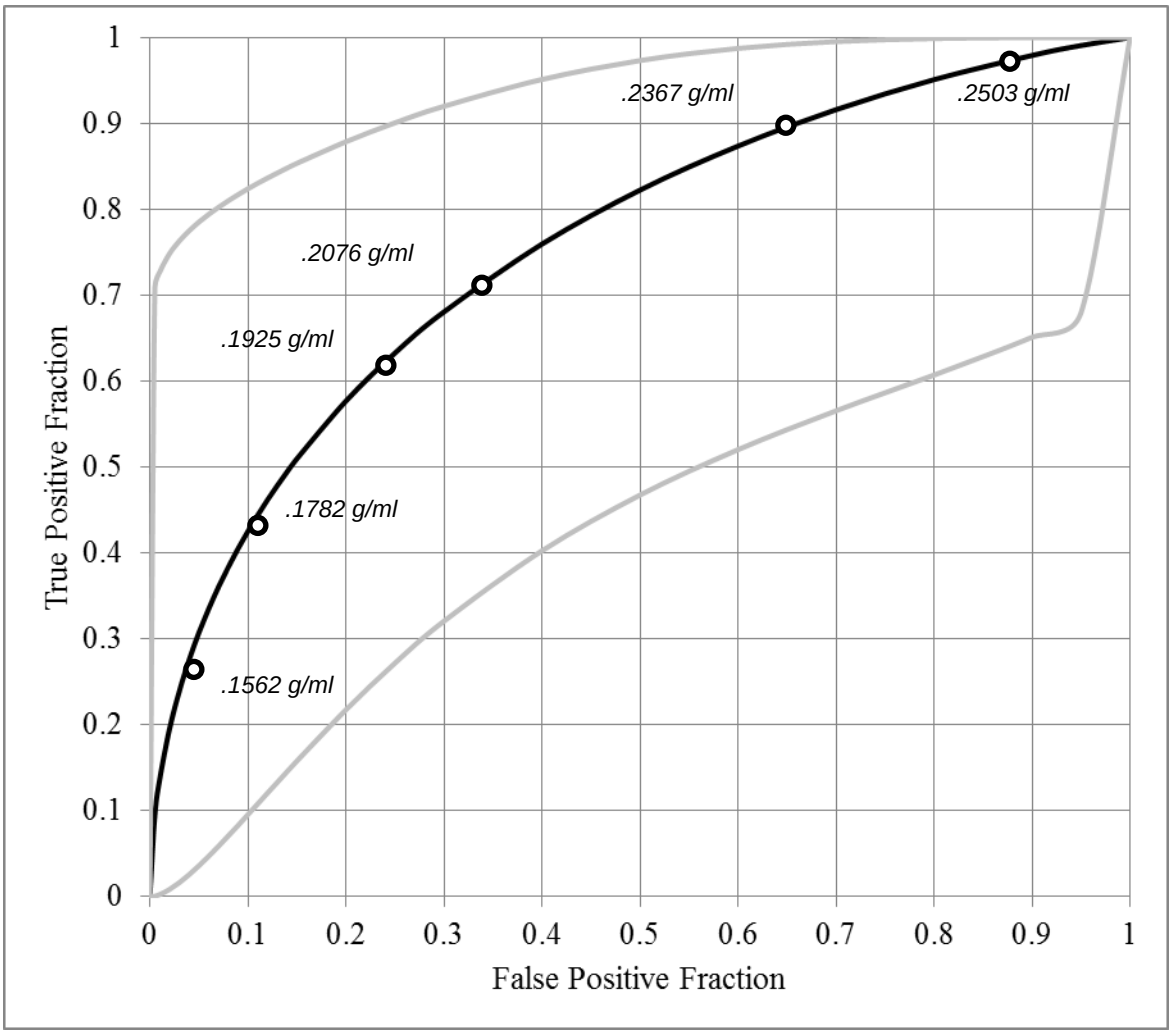


Figure 3.4. Receiver operating characteristic graph for the ability to predict pulmonary edema susceptibility with CT lung density. Corresponding density is labeled at points on the curve. Upper and lower limits of the 95% confidence interval are indicated in light grey lines.

3.4.3 Regional Density Distribution

Density was determined in each subject at three positions along the lung. Each of the three slices was 10-mm thick. Slices were taken at the level of the aortic arch, the tracheal carina, and the top of the T10 vertebrae. In each group (PEs and PEr), CT density at each slice location (arch, carina, T10) did not differ pre- and post- exercise (PEr: $F(2, 24) = 1.072$, $p = 0.358$; PEs: $F(2, 24) = 1.438$ $p = 0.257$; Figure 3.5)

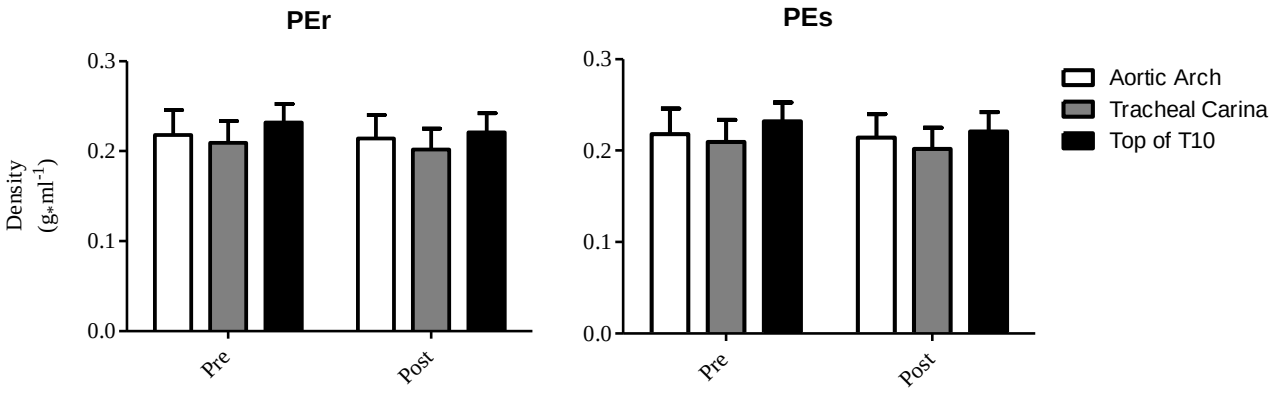


Figure 3.5. Mean lung density for each slice (aortic arch, trachea carina, top of T10) at each time point for resistant (PEr) and susceptible (PEs) subjects.

3.5 $D_L$co

Diffusion capacity of CO was measured prior to the exercise task and again after the second CT scan, approximately 23 minutes (± 4) following cessation of exercise. Table 3.5 gives alveolar volume (V_A) and $D_L$co using 21% O_2 for each group. $D_L$co was then partitioned into the D_M and V_C components, which are listed in Table 3.6. A two-by-two repeated-measures ANOVA was used to assess the impact of pulmonary edema susceptibility (PEr, PEs) on each variable ($D_L$co, $D_L$co/V_A, D_M, D_M/V_A, V_C, and V_C/V_A) before and after the maximal exercise task (Pre-D_L-21% and Post-D_L-21%). Tables 3.5 and 3.6 also include the respective values corrected for V_A. Diffusion capacity for CO, D_M, and V_C, corrected for V_A, are shown graphically in Figures 3.6, 3.7, and 3.8, respectively. The change in diffusion capacity (Δ $D_L$co), change in membrane diffusion (Δ D_M), and change in capillary volume (Δ V_C) values are listed in Table 3.7 and plotted in Figure 3.9. Individual data can be found in Table B7. Individual changes in $D_L$co pre- and post-exercise are displayed in Figure B4.

Table 3.5. Pulmonary diffusion capacity of carbon monoxide breathing 21% oxygen (D_L-21%) pre- and post- exercise, diffusion capacity corrected for alveolar volume (D_L-21%/V_A) pre- and post-exercise, and alveolar volume measured breathing 21% oxygen (V_A-21%).

Group	Statistic	D_L-21% ($mL*min^{-1}*mmHg^{-1}$)		D_L-21%/V_A ($mL*min^{-1}*mmHg^{-1}*L^{-1}$)		V_A-21% (L)
		Pre	Post	Pre	Post	
PEs	Mean	32.92	29.43*	4.65	4.27*	6.89
	SD	8.88	9.30	0.79	0.86	1.71
PEr	Mean	33.72	30.05*	5.30	4.65*	6.42
	SD	8.31	8.82	0.85	0.71	1.44
Total	Mean	32.82	29.74*	4.97	4.46*	6.66
	SD	8.39	8.80	0.87	0.79	1.55

*Significantly different from pre-exercise ($p < 0.05$). SD, Standard deviation; PEs, Pulmonary edema susceptible; PEr, Pulmonary edema resistant.

There was no significant interaction effect on $D_L$co between pulmonary edema susceptibility and time, ($F(1, 16) = 1.16$, $p = 0.30$). There was a significant main effect for time, with both groups showing a reduction in D_L-21% in the post-exercise test ($F(1, 16) = 31.49$, $p < 0.001$). The main effect of susceptibility was not significant ($F(1, 16) = 0.085$, $p = 0.77$), suggesting no difference caused by susceptibility to pulmonary edema.

When pulmonary diffusion capacity was corrected for alveolar volume (D_L-21%/V_A), there was no significant interaction effect between pulmonary edema susceptibility and time ($F(1, 16) = 2.31$, $p = 0.15$). There was a significant main effect for time ($F(1, 16) = 33.37$, $p < 0.001$), with both groups showing a reduction in D_L-21%/V_A in the post-test. The main effect of susceptibility was not significant ($F(1, 16) = 1.88$, $p = 0.19$), suggesting no difference caused by susceptibility to pulmonary edema.

Table 3.6. Diffusion capacity of the alveolar membrane (D_M) and capillary blood volume (V_C) components pre- and post-exercise. Values also presented corrected for alveolar volume (D_M/V_A and V_C/V_A).

Group	Statistic	D_M ($mL*min^{-1}*mmHg^{-1}$)		D_M/V_A ($mL*min^{-1}*mmHg^{-1}*L^{-1}$)		V_C (mL)		V_C/V_A ($mL*L^{-1}$)	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post
PE*s*	Mean	42.45	41.96*	6.14	6.07*	92.99	66.64*	13.89	9.77*
	SD	12.21	13.21	0.69	1.04	34.09	21.09	5.36	2.52
PE*r*	Mean	45.10	41.23*	7.01	6.28*	87.26	78.09*	13.98	12.47*
	SD	12.41	15.11	0.99	1.16	25.14	37.08	4.30	6.13
Total	Mean	43.77	41.59*	6.57	6.18*†	90.13	72.36*	13.94	11.12*
	SD	12.02	13.78	0.95	1.07	29.21	29.85	4.71	4.76

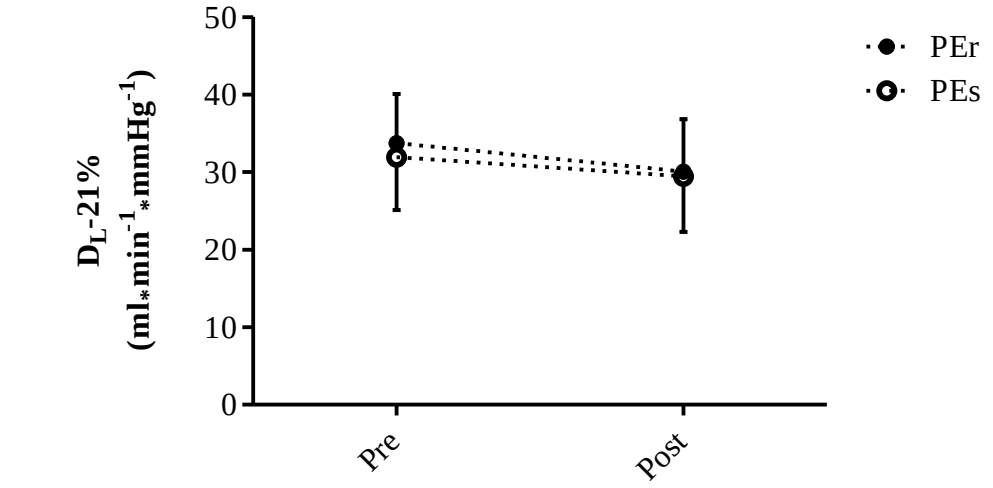
*Significantly different from pre-exercise ($p < 0.05$). †Significant interaction effect found ($p < 0.05$). SD, Standard deviation; PEs, Pulmonary edema susceptible; PEr, Pulmonary edema resistant.

There was no significant interaction effect on D_M between susceptibility group and time ($F(1, 16) = 3.13$, $p = 0.10$). There was a significant main effect for time ($F(1, 16) = 5.20$, $p = 0.04$), with both groups showing a reduction in D_M in the post-exercise test. The main effect of susceptibility was not significant ($F(1, 16) = 0.02$, $p = 0.88$), suggesting no difference caused by susceptibility to pulmonary edema.

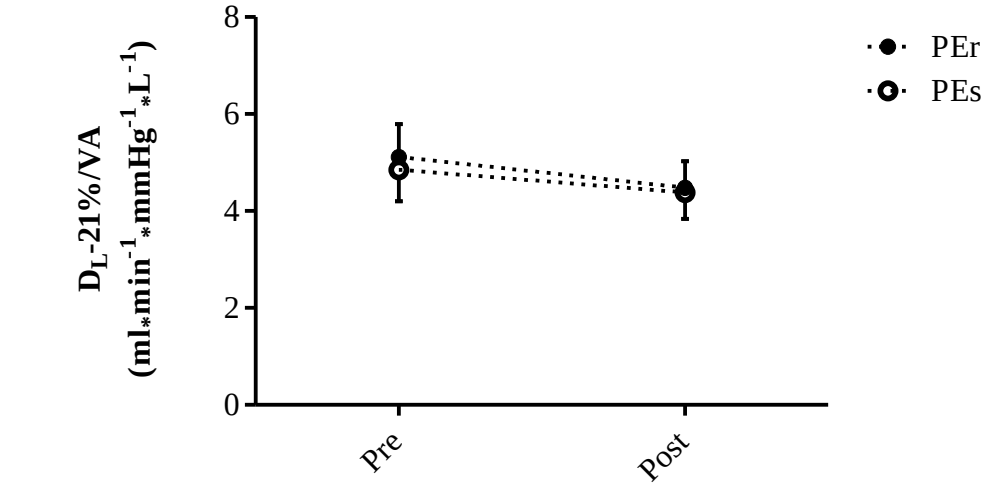
When alveolar membrane diffusion capacity was corrected for alveolar volume (D_M/V_A), there was a significant interaction effect between susceptibility group and time, ($F(1, 16) = 4.66$, $p = 0.04$). There was a significant main effect for time, ($F(1, 16) = 6.76$, $p = 0.02$), with both groups showing a reduction in D_M/V_A in the post-test. The main effect of susceptibility was not significant ($F(1, 16) = 1.54$, $p = 0.23$), suggesting no difference caused by susceptibility to pulmonary edema alone.

There was no significant interaction effect on V_C between susceptibility group and time ($F(1, 16) = 1.97$, $p = 0.18$). There was a significant main effect for time ($F(1, 16) = 8.43$, $p = 0.01$), with both groups showing a reduction in V_C in the post-test. The main effect of susceptibility was not significant ($F(1, 16) = 0.05$, $p = 0.83$), suggesting no difference caused by susceptibility to pulmonary edema.

When pulmonary capillary volume was corrected for alveolar volume (V_C/V_A), there was no significant interaction effect between susceptibility group and time ($F(1, 16) = 1.71$, $p = 0.21$). There was a significant main effect for time ($F(1, 16) = 7.93$, $p = 0.01$) with both groups showing a reduction in V_C/V_A in the post-test. The main effect of susceptibility was not significant ($F(1, 16) = .48$, $p = 0.50$), suggesting no difference caused by susceptibility to pulmonary edema.

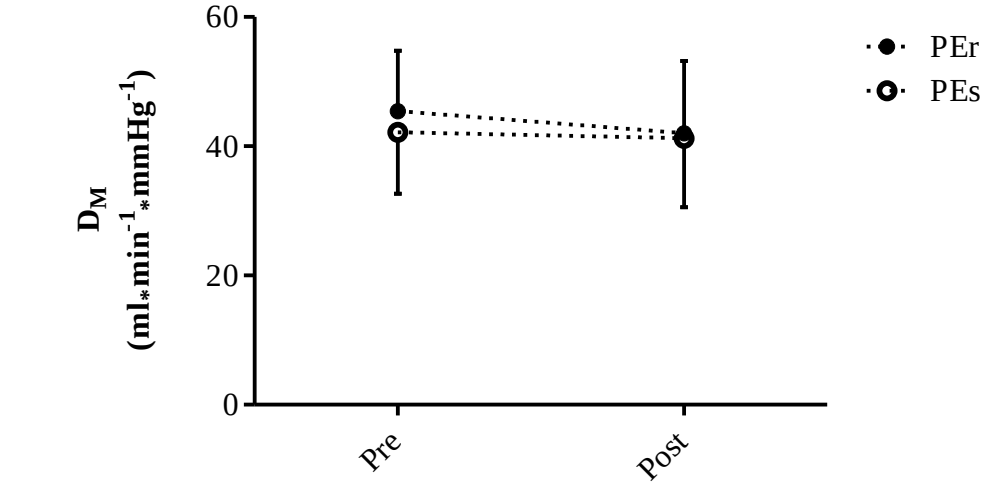


(a)

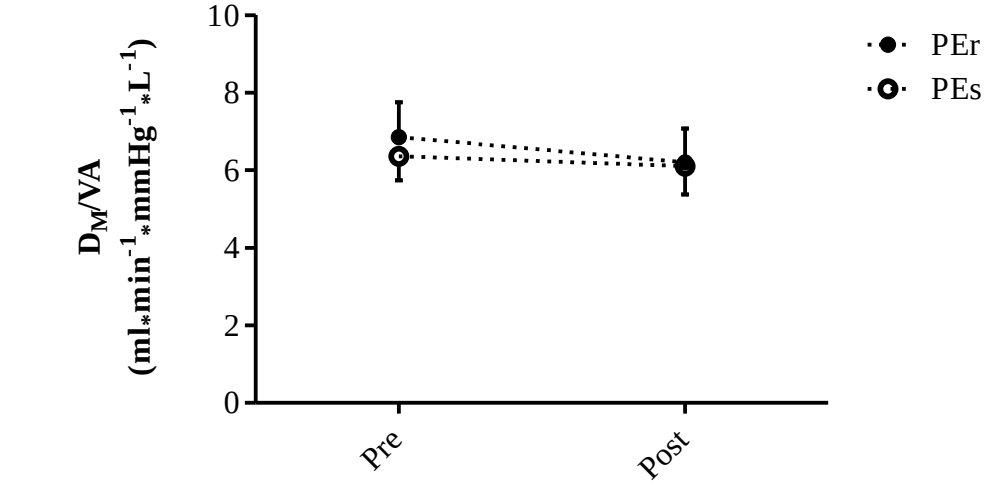


(b)

Figure 3.6. Diffusion capacity of carbon monoxide breathing 21% oxygen (a) and diffusion capacity of carbon monoxide breathing 21% oxygen corrected for alveolar volume (b) pre- and post-exercise in subjects susceptible (PEs) and resistant (PEr) to pulmonary edema.

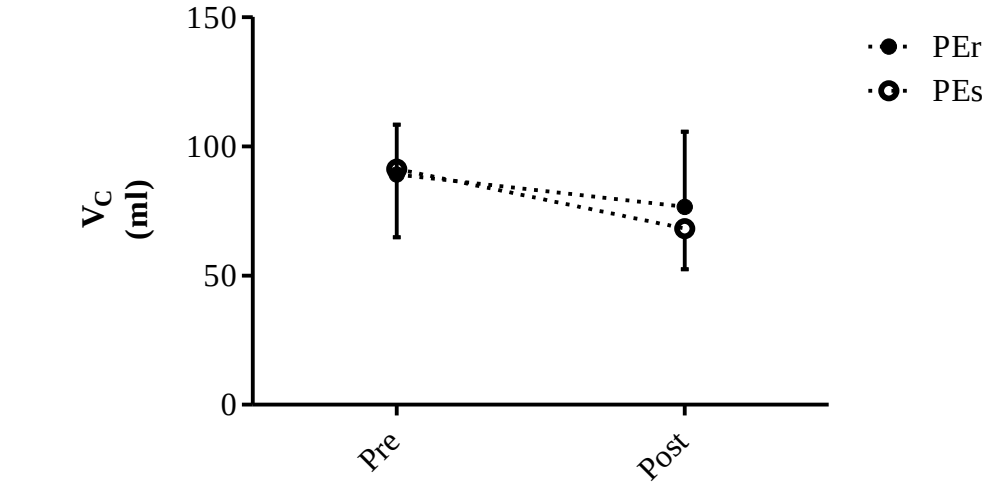


(a)

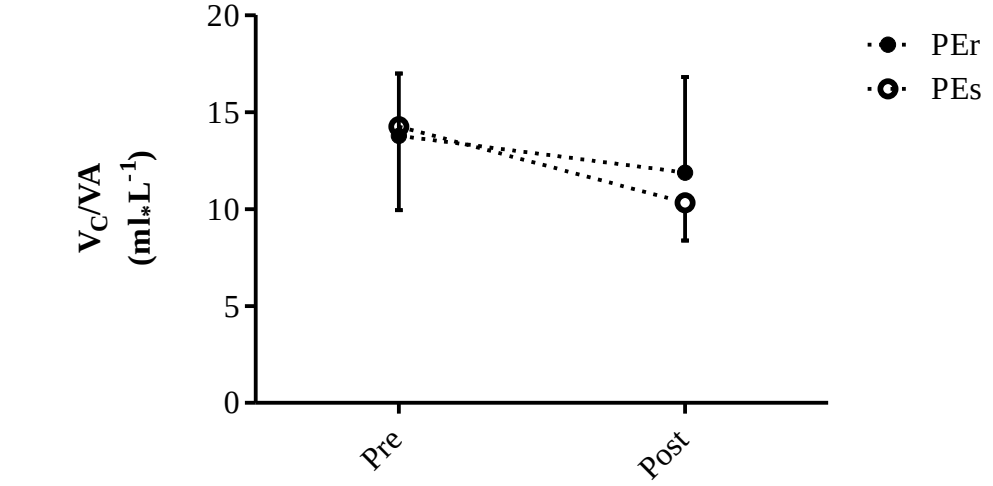


(b)

Figure 3.7. Membrane diffusion capacity (a) and membrane diffusion capacity (b) pre- and post-exercise corrected for alveolar volume in subjects susceptible (PEs) and resistant (PEr) to pulmonary edema.



(a)



(b)

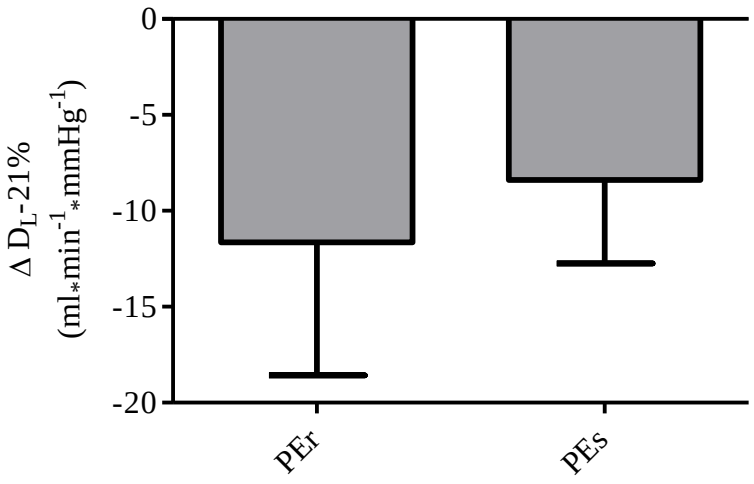
Figure 3.8. Capillary blood volume (a) and capillary blood volume corrected for alveolar volume (b) pre- and post-exercise in subjects susceptible (PEs) and resistant (PEr) to pulmonary edema.

Independent samples t-tests were performed to assess the difference between groups for Δ $D_L$co, Δ D_M, and Δ V_C (Figure 3.9). There was no significant difference for pulmonary edema susceptible and resistant subjects in Δ $D_L$co ($t(16) = 1.51$, $p = 0.169$), Δ D_M, ($t(16) = 2.26$, $p = 0.053$), or Δ V_C ($t(16) = 1.99$, $p = 0.081$).

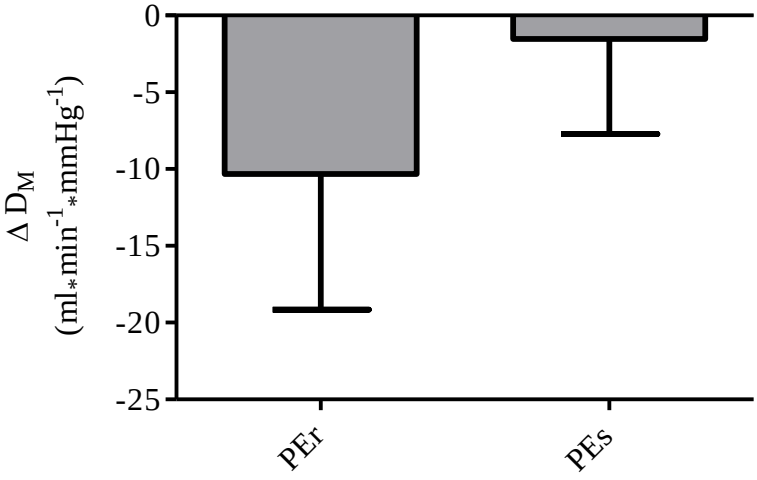
Table 3.7. Mean change in diffusion capacity for carbon monoxide (ΔD_L-21%), change in membrane diffusion (ΔD_M) and change in capillary volume (ΔV_C) calculated for groups of subjects susceptible (PEs) and resistant (PEr) to pulmonary edema.

Group	Statistic	ΔD_L-21% ($mL*min^{-1}*mmHg^{-1}$)	ΔD_M ($mL*min^{-1}*mmHg^{-1}$)	ΔV_C (mL)
PE*s*	Mean	-8.40	-1.54	-25.69
	SD	5.66	8.04	16.30
PE*r*	Mean	-11.64	-10.33	-10.91
	SD	9.03	11.49	25.93

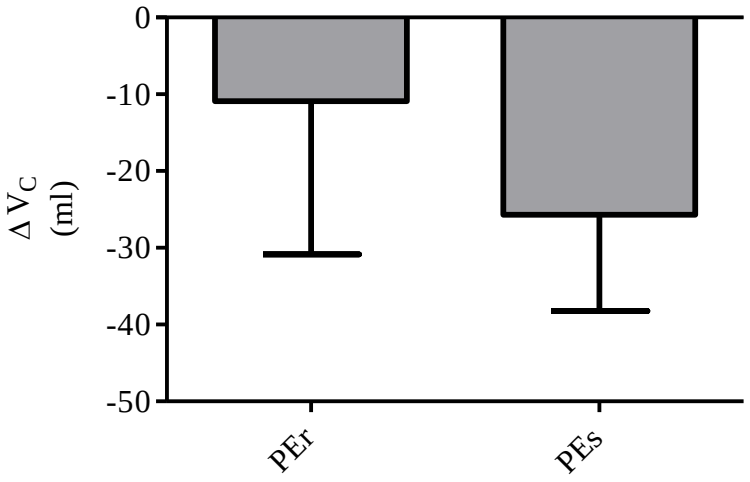
SD, Standard deviation; PEs, Pulmonary edema susceptible; PEr, Pulmonary edema resistant.


0
-5
-10
-15
-20
Δ D_L-21%
(ml*min^-1*mmHg^-1)
PEr
PEs

(a)


0
-5
-10
-15
-20
-25
Δ D_M
(ml*min^-1*mmHg^-1)
PEr
PEs

(b)



(c)

Figure 3.9. Mean change in diffusion capacity for carbon monoxide (Δ D_L-21%) (a), change in membrane diffusion (Δ D_M) (b), and change in capillary volume (Δ V_C) (c) calculated for groups of subjects susceptible (PEs) and resistant (PEr) to pulmonary edema.

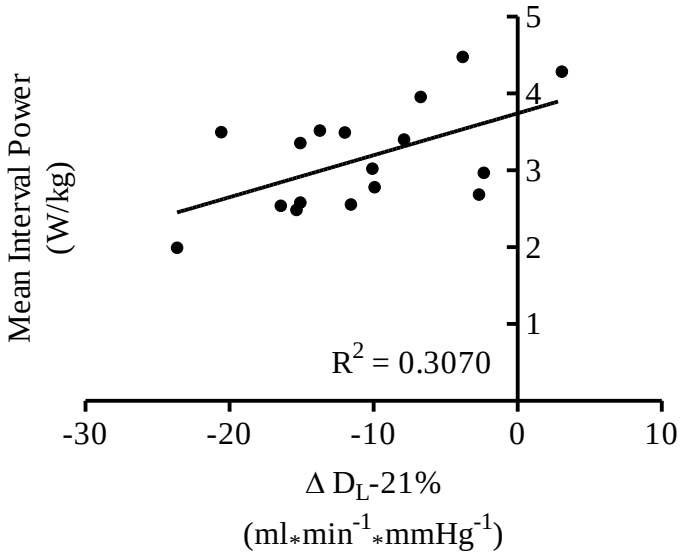


Figure 3.10. The relationship between the change in diffusion capacity for carbon monoxide (Δ D_L-21%) and the mean interval power per kilogram of bodyweight.

The relationship between mean interval power per kilogram bodyweight and Δ $D_L$co was investigated using Pearson product-moment correlation coefficient (Figure 3.10). Preliminary

analyses were performed to ensure no violation of the assumptions of normality. There was a strong, positive correlation between the two variables ($r = 0.55$, $n = 17$, $p = 0.021$) with lower mean power per kilogram associated with greater decreases in D_Lco but ΔD_Lco was not significantly correlated with minimum S_PO_2 ($p = 0.276$).

4. DISCUSSION

4.1 Key Findings

Following exhaustive cycle exercise in HAPE/IPE susceptible and resistant subjects, we observed no change in EVLW, as measured by CT or $D_L$co, in either group. Membrane diffusion and pulmonary capillary volume decreased and lung volume increased post-exercise, but no difference was found between groups for any of these variables. A significant between-groups difference existed for density, unrelated to the maximal exercise task. Participants in the PEs group had a lower lung density than those in the PEr group.

4.2 Extravascular Lung Water

4.2.1 Introduction

Exercise-induced arterial hypoxemia is a common phenomenon; healthy humans, exercising at high intensity, experience a widening of the A-a DO_2 and a resulting decrease in S_PO_2. It has been hypothesized that pulmonary edema may be one of several possible causes of EIAH, but this point remains controversial with a significant amount of conflicting evidence [31, 32] . Pulmonary edema has been shown in healthy humans exercising maximally at sea level; these patients were likely hypoxemic as well [14]. It is possible that EIAH occurs through the same mechanism as HAPE and IPE, and therefore, those susceptible to HAPE and IPE may be more likely to develop EIAH caused by pulmonary edema. Podolsky *et al*. measured V/Q mismatch in HAPE susceptible individuals and found a significant difference compared to the resistant group. The authors concluded this difference was the result of a transient increase in EVLW [33]. The current study is the first to examine the development of EVLW in participants who are susceptible to HAPE or IPE compared to a cohort that has demonstrated resistance to pulmonary

edema in the same environments. This study showed no increase in EVLW after exercise in either group.

4.2.2 Pulmonary Diffusion Capacity

Pulmonary diffusion capacity has previously been shown to decrease after exercise (See Table A2). This study confirms the decrease in $D_L$co following exercise in subjects susceptible and resistant to pulmonary edema. Diffusion capacity of CO was partitioned into its components: D_M and V_C. The results of the partition, significant decreases in both components, were also consistent with previous studies [27]. This suggests a significant limitation in pulmonary diffusion capacity as a result of decreases in both membrane diffusion capacity and capillary blood volume.

Lower power output during the exercise task was correlated with a greater decrease in $D_L$co but not with D_M and V_C. This was unrelated to subject group and seems to suggest that less fit individuals show a greater decrease in $D_L$co than those able to output higher power, similar to trends shown by Sheel *et al*. [27]. It is possible that a diffusion limitation, which manifests during exercise, negatively affects power output. The change in $D_L$co was not significantly correlated with minimum S_PO_2 during exercise, but this diffusion limitation could be an early sign of impending EIAH.

4.2.3 Oxygen Saturation

In both HAPE and IPE, gas exchange impairment caused by fluid buildup can be clearly seen in a patient's decreased S_PO_2 at rest and during exercise. Arterial oxygen saturations below 50% have been reported in HAPE patients at 4,500 meters [34]. Similarly, saturations below 70% have been seen in IPE patients at sea level [11]. EIAH is characterized by a widening of the A-aDO_2 (reflected in a depressed S_PO_2, generally 88 – 93%) due to some combination of the effects

of intrapulmonary shunt, mismatch of ventilation and perfusion within the lung (V/Q mismatch), increased red blood cell transit time, or pulmonary edema [18]. In this study, S_PO_2 at rest in all subjects was 99-100%. Following exercise, S_PO_2 decreased significantly but did not differ statistically between groups. The mean S_PO_2 for the PEs group did appear to be trending lower suggesting some sort of pulmonary gas impairment. While D_M did not differ significantly between groups, this trend could be explained by something other than a diffusion limitation. Eldridge *et al*. proposed a mechanism in which small intrapulmonary arteriovenous shunts act as "pop-off valves" in response to increasing pulmonary pressures [35]. If these shunts were more common in PEs participants, widening of the A-aDO_2 would be likely, resulting in decreased S_PO_2. Conversely, if PEs participants had fewer shunts, higher pressures in the pulmonary capillary network could cause capillary stress failure and increased EVLW, resulting in decreased S_PO_2. Further research is necessary surrounding the existence, onset, and hemodynamic effect of intrapulmonary shunts in patients susceptible to HAPE and IPE.

4.2.4 Lung CT Density, Mass, and Volume

The results of previous studies that use imaging (CT and Magnetic Resonance Imaging (MRI)) to measure exercise-induced lung water have been conflicting. There are a variety of potential reasons for the variation in results. Beginning with exercise intensity and duration, bouts have ranged from 5 to 120 minutes at a variety of intensities (See Table A1). Generally the shorter, higher intensity exercises show no change while medium and longer duration studies find a significant difference. The current study used a medium duration, with subjects maintaining a maximal sustainable power output of approximately 231 ± 57 watts. Extended delays between cessation of exercise and scanning may also have reduced the chance of identifying a change in EVLW. Of the studies reviewed, average time to scan was approximately one hour. According to

Schaffartik *et al*., interstitial edema can clear as quickly as 20 minutes in upright subjects [36]. This study had an average time-to-scan of 11 ± 1 minutes, allowing adequate time for central blood volume to stabilize, while minimizing extravascular fluid reabsorption into the lung.

This study found no difference in the change in lung density between groups. Contrary to previous studies, both groups showed decreased lung density after exercise. Decreased density could be the result of a transient decrease in central blood volume. Several studies have shown decreases in central blood volume and V_C following exercise [27, 37, 38], the timing of which would have a significant effect on lung density. In this study, V_C was significantly reduced, which could explain why lung density did not increase. Further research is needed to determine a more precise time course for the immediate increase and eventual decrease in V_C. In the current study, if a drop in V_C were the cause of the decrease in density post-exercise, we would expect a corresponding decrease in mass. As there was no decrease in mass, a decrease in V_C as the primary cause of decreased density can be ruled out.

Had EVLW been present, volume would be expected to decrease as a result of decreased compliance and increased elasticity caused by fluid stiffening the lung [39], but in this study lung volume increased in both groups after exercise. Several explanations are possible for the observed increase in lung volume. If dilation of the large bronchi were to occur due to exercise, tethering of the large and small airways could increase the size of small bronchioles as well, resulting in increased volume on the scan. It is also possible that the increased volume is a learning effect. Participants were given a relatively brief inhalation time prior to CT image acquisition. Several participants described being surprised at the short amount of time given and described compensating for this during the second scan by inspiring more rapidly. This

explanation is supported by measures of V_A using helium-dilution, which did not change following exercise. Participants were coached to make sure that they inspired the same volume for every scan but no other methods were employed to ensure breath size repeatability. This omission underlines the need for some sort of control in future studies to ensure equal inspiratory volume. A pneumotach measurement or chest restriction using a band would be effective, but a more realistic option would be more extensive familiarization with the auditory cues provided in the CT suite. Finally, volume differences may have resulted from differences in scan areas. The human lung can be represented with the shape of a bell. If slices were imaged slightly lower during the post-exercise acquisition, volume would be artificially increased. This explanation is unlikely due to the systemic nature of the increase in lung volume throughout all subjects. Position errors during scanning would be expected to occur randomly during both scans.

Results from CT scan variables (lung density, mass, and volume) indicate that susceptibility to HAPE or IPE does not increase chances of developing EVLW during sea level exercise.

4.3 Pulmonary Edema Susceptible Lungs

The CT scan estimates of lung water indicate that participants did not develop increased EVLW after exercise, but there was a significant between-group difference in density. There was no between group difference in volume at either time point, but the PEs participants had decreased lung density as compared to PEr subjects. This finding is despite all other spirometric and anthropometric measures not differing between groups, suggesting an inherent disparity in lung density between PEs and PEr participants. Decreased lung density implies less fluid in the slice, less tissue in the slice, or less dense tissue.

While no conclusions can be made regarding the reason for this difference in density, several possible explanations exist. Lower density could be the result of long-term lung damage due to previous HAPE or IPE insults. Potential evidence for a chronic change in lung morphology following HAPE comes from studies involving bronchoscopy of HAPE patients. Broncheoalveolar lavage (BAL) fluid taken from patients with acute HAPE contains significant concentrations of high-molecular-weight protein. The presence of these proteins suggests that the integrity of the alveolar epithelium has been compromised resulting in a "permeability" leak [40]. Follow-up lavage fluid also included inflammatory markers [41], indicating a reaction to lung injury. Schoene *et al*. also noted increased acid proteases in the fluid following HAPE [40]. When these degrading substances are released into the lung, likely by alveolar macrophages, they can break down lung tissue [42]. Over time, especially with multiple incidents of HAPE or IPE, one might expect this protease activity to accumulate, causing chronic degradation of lung tissue that could lower lung density in the susceptible subjects.

Another potential mechanism for the decreased lung density in the PEs group comes from studies of acute respiratory distress syndrome (ARDS). Studies investigating long-term damage from ventilator induced pulmonary edema in patients with ARDS have shown increased lung scarring. In these patients, fibrous sacs of air called bullae form in the alveolar and parenchymal tissue. These sacs are then unable to participate in gas exchange [43, 44]. While the mechanism for lung injury is different in ARDS (ventilator induced *vs.* high altitude or water immersion), it is possible that the PEs participants in this study have similar scarring and bullae as a result of their previous incidents of pulmonary edema. In the current study, although the entire lungs were not

scanned, there was no overt evidence of bulllae or visible scarring in the PEs group when the slices were evaluated.

If the PEs participant's lungs contain fewer blood vessels or the same number of vessels with increased reactivity and decreased recruitment, less fluid would be present in the pulmonary circulation resulting in decreased density measured with CT. Research done by Ghorishi *et al*. examining the pulmonary system of lambs provides a possible explanation for differences in vasculature between PEs and PEr participants. The pulmonary vasculature of fetal lambs is highly sensitive to shear stress within vessels. At birth, these shear stress amplifying characteristics generally fade; however, in some lambs, the fetal characteristics are actually retained. The increased shear stress response could then influence vascular properties including wall thickness and composition [45]. Humans display a similar fetal phenotype, and if PEs individuals were to retain this accentuated shear-stress response after birth, increased remodeling could cause development of smooth muscle and increased pulmonary vasoconstriction or decreased capillary density. The result of pulmonary vascular remodeling would be decreased blood volume within the lung at any given time and increased flow within existing vessels that would in turn increase P_{PA} and potentially cause pulmonary capillary stress failure. This hypothesis is supported by data in previously identified HAPE susceptible subjects, which show P_{PA} is elevated even during rest at sea level [46]. If PEs participants do have fewer vessels or less recruitment, a lower pulmonary blood volume should have been reflected in spirometric V_C measurements. No difference in V_C was found, suggesting that density differences may be the result of fluid or tissue differences elsewhere in the lungs, for example, in the pulmonary lymphatic system.

The pulmonary lymphatic system is responsible for absorption of excess fluid within the lung. When fluid is extravasated from the capillaries into the interstitial and alveolar space, lymphatic capillaries usually reabsorb it. When extravasation of fluid overtakes the reabsorption capacity of the lymph, fluid buildup occurs. This buildup of excess fluid will eventually manifest as clinical pulmonary edema [47]. If PEs individuals have fewer pulmonary lymphatic vessels than those in the PEr group, pulmonary edema would be more likely when exposed to adverse environments such as high altitude or immersion. Fewer lymphatics would require less connective tissue and carry less fluid resulting in lower density. No studies comparing pulmonary lymphatic structure or flow between HAPE susceptible and HAPE resistant participants have been carried out. Further research examining possible differences is needed.

4.4 CT Lung Reconstruction

Computed tomography scans were reconstructed on a computer using B35, B45, and B60 spatial frequency algorithms. CT scans assign voxels density values based on their individual Hounsfield unit value. Air is assigned a value of -1000 HU and bone 1000 HU, with fluid and tissue in between. In lung CT scans, narrowing the range of Hounsfield units can increase resolution. For example, letting -500 represent black and -200 represent white increases resolution when examining details of lung tissue [48]. Image thicknesses of 1mm, 2mm and 5mm were analyzed. Reducing the size of a voxel increases spatial resolution by decreasing the averaging that is required [44], but it also results in increased noise. Statistical tests described in the Results chapter were performed on the results of all algorithms and slice thicknesses. Additionally, all were compared using a one-way ANOVA, and no significant differences were found (See Table B4). During image analysis, it was discovered that the 5 mm slice thickness reconstructions from scans using the Sensation 16 scanner had a gap thickness of 2.2 mm rather

than 5 mm, yielding an effective thickness of 2.2 mm per slice. This error resulted in underestimation of mass and volume but had no effect on density. For this reason, 5 mm image thickness values were not reported.

4.5 Limitations

Several limitations are evident within this study. One of the common mechanisms associated with HAPE and IPE is increased P_{PA}, which causes capillary stress failure. During this experiment, P_{PA} was not measured and therefore cannot be ruled out as a mechanism for the difference in lung density between groups. A second limitation was the availability of volunteers eligible to participate in the study. Due to the relatively low number of people with confirmable cases of HAPE or IPE, it was necessary to create one experimental group rather than two. Because of this, the study assumes that HAPE and IPE are pathophysiologically equivalent phenomena, which has yet to be definitively proven. While this is certainly possible, it cannot be confirmed with this experiment. It is also difficult to confirm cases of HAPE or IPE. Sixteen individuals were identified with possible HAPE or IPE incidents but seven were excluded due to unreliable evidence to support their diagnosis. Finally, several errors occurred during CT scan acquisition. During one testing session, the Sensation 16 scanner used during the study stopped functioning, and scans were completed using a Sensation 64 scanner. This resulted in overestimations of volume and mass for three subjects. A correction factor was applied; however, there is still a slight margin of error that cannot be accounted for due to the bell shape of the lung. Density remained unaffected in all subjects.

4.6 Future Directions

Future studies investigating EVLW and pulmonary edema susceptibility should be focused on confirming and then finding the cause of the density difference between groups. If this difference is the result of differences in the pulmonary lymphatic system, it would be beneficial to employ an imaging technique that can reliably quantify these vessels. It would also be useful to investigate factors such as hypoxia and fluid accumulation that may be acting to trigger lymph flow. Repeating the exercise protocol with a larger sample while measuring P_{PA} would provide more information on differences in vasculature between groups. If differences were found in P_{PA}, another logical step would be to determine if PEs participants were more or less likely to develop intrapulmonary shunts, which might be acting as "pop-off" valves under high pressure. It is possible that individuals susceptible to pulmonary edema might experience the opening of these shunts at higher P_{PA} exposing their pulmonary capillaries to increased stress. Future studies of EVLW should use the Sensation 64 CT scanner, which produces a lower dose of radiation per scan, and during our trials, proved to be more reliable. Finally, separating the HAPE and IPE groups would help define differences in susceptibility within our PEs group.

5. CONCLUSION

This study demonstrated no change in EVLW after exercise. Decreases in D_Lco, D_M and V_C were demonstrated to be consistent with other studies investigating pulmonary diffusion capacity after maximal exercise. This was the first study of EVLW during sea level exercise to include participants who had previously experienced pulmonary edema due to high altitude or immersion. Pulmonary edema susceptible participants did not show any greater changes in lung density, S_PO_2, or D_Lco compared to PEr participants, suggesting that humans with previous HAPE or IPE incidents are not at any greater risk of developing EVLW during maximal exercise at normoxia. A novel finding was that mean lung density was significantly lower in PEs participants at both the pre- and post-exercise time points, suggesting an inherent difference in lung structure possibly as a result of previous pulmonary edema, pulmonary hypertension, or fewer lymphatics. Further investigation is necessary to confirm the existence and nature of this difference.

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APPENDIX A: LITERATURE REVIEW - PULMONARY GAS EXCHANGE

A1. Physiology

Gas Exchange

The primary function of the respiratory system is to provide the tissues with oxygen. At sea level, barometric pressure is 760 mmHg. When air is inspired (and moistened) the P_{O2} is 149 mmHg. At the level of the alveoli, the P_{O2} is approximately 100 mmHg. As the arterial blood delivers oxygen to the tissues, its P_{O2} has decreased further and approaches 1 mmHg in some cells. Maintenance of alveolar P_{O2} (P_AO_2) is crucial to ensure adequate oxygen delivery to all tissues. Hypoxemia is an abnormally low P_aO_2 and can be caused by hypoventilation, shunt, diffusion limitation, or ventilation-perfusion inequality.

A diffusion limitation could be caused by exercise, thickening of the blood-gas barrier, or a low inspired P_{O2}. This decreases the difference between P_AO_2 and P_aO_2, reducing the diffusion gradient which is necessary for gas exchange.

Concentration of O_2 in any airspace of the lung is determined by the rate of ventilation (V_A) to blood flow (Q). In an ideal lung, V_A and Q are matched ($V_A/Q = 1$). By decreasing V_A/Q (decreasing ventilation) P_AO_2 decreases with P_aO_2 and arterial blood will be the same as mixed venous blood. By increasing V_A/Q (decreasing perfusion) P_AO_2 equilibrates with inspired air while P_aO_2 decreases [49].

Diffusion

Oxygen must move across the alveolar wall to enter the blood stream. This is a passive process called diffusion which uses no energy. The oxygen molecules are only able to move across the wall when going from an area of higher partial pressure to an area of lower partial pressure. This action is described by Fick's law of diffusion. According to Fick's law, a gas' rate of transfer

through a tissue is proportional to the tissue area and the difference in the gas partial pressure on either side. The rate of transfer of the gas is also inversely proportional to the thickness of the tissue. Because the area of the blood gas barrier is so large (up to 100 meters^2) as well as being very thin, conditions for diffusion are ideal [49]. This presents a problem however because the thin barrier provides very little protection from stressors outlined in the next section.

Pulmonary Capillary Stress Failure

Unlike the capillaries of the systemic circulation, [50] the pulmonary capillaries are unsupported by surrounding tissues and are therefore vulnerable to stress failure caused by high pressure. Using rabbit lungs, West *et al.* identified three principle forces which act on the capillary wall [51].

1) Increased wall stress due to circumferential tension on the capillary wall is caused by an increase in capillary transmural pressure. With a capillary transmural pressure gradient of just 22.5 mmHg, disruption of the endothelial and epithelial cells can occur with the basement membrane serving as the only remaining barrier [51].

2) Surface tension at the alveolar lining layer due to surfactant supports the capillary. Increasing lung volume will increase surface tension and compress the endothelial and epithelial layers.

3) Longitudinal tension in the tissue element of the alveolar wall increases wall stress with lung inflation.

These three factors make up the total wall stress which, due to the extreme thinness of the capillary wall, can approach the wall stress found in the aorta. This stress is transmitted through two single epithelial and endothelial layers of cells separated by two (or potentially even one)

very thin basement membranes. It is believed that much of the strength of the thin capillary wall comes from the basement membranes. In cases of stress failure, it is possible to see disruptions in the endothelial and epithelial layers while the basement membrane remains intact. This suggests its apparent greater strength. One study found that the relationship between transmural pressure and diameter of a renal tubule was the same with or without the epithelium suggesting the strength of the basement membrane [52]. When stress failure of the endothelium and epithelium occurs, increased capillary wall permeability is the result and leakage of protein occurs. Studies by West *et al*. suggest that moderate raises in capillary hydrostatic pressure results in leakage of low-protein fluid, while greater raises of hydrostatic pressure results in high-protein fluid leakage due to increased membrane permeability [51].

Pulmonary Pressures

The mean P_{PA} in humans is 15 mmHg. The systolic pressure is usually approximately 25 mmHg. These low pressures allow the walls of the vessels within the pulmonary circulation to be very thin [49]. During maximal exercise breathing room air, Wagner *et al*. estimated that the P_{PA} rose to 35 – 40 mmHg [53]. This is believed to be the range at which interstitial edema can begin to form [28]. Mean P_{PA} has been recorded at much higher values. Hultgren *et al*. gave an example of a 15 year old boy diagnosed with HAPE at an altitude of 3,782 meters with a mean P_{PA} of 110 mmHg [1]. As discussed earlier, at any given moment, not all the pulmonary capillaries are open. To achieve this, West suggests that 37 mmHg would be necessary [54]. According to Starling's law of capillary exchange, vessels subjected to this pressure would experience development of interstitial edema [55, 56].

Left atrial pressure (P_{LA}) is generally around 5 mmHg [49]. Mild elevations in P_{LA} (18 to 25 mmHg) can cause interstitial edema [57, 58]. As P_{LA} increases (>25 mmHg), the lung epithelium is disturbed and fluid can flood the alveoli as well [47].

A2. Pulmonary Stressors

Hypoxia

Exposure to hypoxia causes the pulmonary circulation to respond uniquely when compared to systemic circulation. The response is characterized by increases in P_{PA} and pulmonary vascular resistance as a result of constriction of the small pulmonary vessels [59]. This hypoxic vasoconstriction is an important mechanism which decreases perfusion to poorly ventilated lung units and increases perfusion to better ventilated ones in order to decrease V_A/Q mismatch. When exposed to hypoxia, the small intraparenchymal pulmonary arteries (150-1,600 μm), decreased in diameter up to 25% in a canine model. These vessels were found to contribute significantly to pulmonary vascular resistance [60]. Using small vein micropuncture in cats, it was found that hypoxic vasoconstriction occurs mainly in the small pulmonary arteries (30-50 μm) [61]. This work was confirmed by Kato *et al*. who employed a technique of rapidly freezing hypoxic cat lungs and found pulmonary vasoconstriction to occur in the small muscular pulmonary arteries [62]. In rats, the hypoxic response becomes evident approximately 17 minutes following exposure to hypoxic perfusate and reaches a maximum between 45 and 140 minutes [63].

Repeat exposure to hypoxia has been shown to result in attenuation of this vascular hypoxic response. It is unknown if this is the mechanism for acclimatization to high altitude [64].

The mechanism through which the hypoxic vasoconstrictive response occurs is not completely understood. It is possible that the response is initiated by the release of a vasoactive mediator

from within the lung also known as the mediator hypothesis. Unfortunately, no single agents that have been studied satisfy all the criteria to be considered a mediator; though Endothelian and Endothelial derived relaxing factor (nitric oxide) may be involved. It is also possible that hypoxia acts directly on pulmonary vascular smooth muscle to cause vasoconstriction without a mediator [59].

Inhibition of the hypoxic response has been successful using calcium channel blockers. Nifedipine is an effective pulmonary vasodilator which is successful in lowering P_{PA} and pulmonary vascular resistance while maintaining systemic vascular resistance and Q [59, 65]. Nifedipine is used as a preventative agent for individuals susceptible to HAPE.

Hydration

Hydration levels can influence P_{PA} through increases in plasma volume which would be reflected in increases of V_C. Jimenez *et al*. measured plasma volume using injected Evans blue dye after subjects had ingested a solution containing 128 g glycerol diluted with water to make a total volume of 256 ml. At regular time intervals, subjects drank a mean volume of 465 ml of water containing 1.2 $g*l^{-1}$ NaCl. The total ingested volume was 21.4 $ml*kg^{-1}$. Plasma volume was found to increase significantly (7.5%) [66]. Shifts in the vascular fluid compartment have been found to be caused by changes in hydration level [67-69]. Hydration status should be carefully considered when investigating increases in V_C as a mechanism for increased EVLW. Hydration may also be an issue for athletes in austere environments trying to find the balance between proper hydration for exercise and hypohydration, which could put them at risk for HAPE or IPE.

Body position

The distribution of blood flow within the human lung is determined primarily by gravity and can have significant effects on P_{PA}. In the upright human lung, perfusion decreases from the base to

the apex where it reaches very low levels. Because venous pressure is less than alveolar pressure in the upper lung, blood flow is determined by the gradient between arterial and alveolar pressure. In the dependent lung zones, flow is determined by the arterial-venous pressure difference [49]. When posture is changed to sitting, redistribution of perfusion is such that flow to the base of the lung remains the same while flow increases at the apex to a nearly uniform distribution. Marshall *et al*. found a significant increase in P_{PA} between sitting (upright) and standing positions. While sitting, P_{PA} was 7.4 ± 0.8 mmHg and increased to 11.2 ± 0.7 mmHg when standing. It is also recognized that when changing from sitting to supine position, the $D_L$co increases significantly [28, 70]. This increase is likely because of the increase in perfusion which allows a greater surface area to be available for diffusion. These data demonstrate that P_{PA} is not an appropriate estimation of pulmonary perfusion. It also demonstrates that when in the supine position, V_A/Q mismatch is decreased [28]. The effect of body position on EVLW development may not significantly affect humans during upright cycling but could have a profound effect on the development of IPE. Swimmers and divers, primarily in the prone position, are exposing larger percentages of their lungs to increased perfusion, possibly increasing likelihood of IPE. Further research is necessary to determine if individuals susceptible to IPE have an exaggerated response to changes in body position.

Cold

Cold elicits a number of physiological responses in the human body. The greatest effect of cold on the development of IPE is peripheral vasoconstriction. Blood is redistributed from the peripheral to thoracic vessels causing an increase in preload and afterload. Keatinge *et al*. studied the cardiopulmonary response of an ice cold shower on humans. Subjects were sprayed with 0 - 2.5° C water for 2 minutes at 6 L/min. All subjects experienced a significant increase in the rate

and depth of breathing and Pa_{CO_2} decreased. There was also a significant increase in blood pressure and HR. Cardiac output was measured in two subjects and was found to increase significantly (7.9 and 6.5 to 12.4 and 13.0 L/min) [71]. Subjects who have previously experienced IPE show an increased vasoconstrictive response to cold when compared to control subjects. The vasoconstrictive response results in increased preload and afterload [72]. Peripheral vasoconstriction may cause a redistribution of blood increasing P_{PA}. Wester *et al*. found an increase in HR and Q when subjects were immersed in cold water compared to warm water. Central venous pressure (CVP) and P_{PA} increased significantly when immersed in cold water compared to warm water [8]. When water temperature is 1° - 2°C below body temperature it may be considered warm for diving but still results in a decreased core temperature and central pooling of blood [73]. Many swimmers and divers report unzipping their wetsuit to reduce constriction following feelings of dyspnea. While it may provide temporary relief, this reaction may exacerbate IPE by eliminating the insulative effects of the wetsuit [74]. Decreasing body temperature has also been shown to be related to increased pulmonary vascular resistance [75]. Increases in Q and central blood volume caused by cold induced vasoconstriction make it likely a major factor in IPE. Further research is warranted to investigate the cold response in individuals with repeat episodes of IPE.

Immersion

Increased hydrostatic pressure due to immersion causes a redistribution of blood from the periphery to the core associated with an increase in intrathoracic blood volume of 700 mL. This shift can result in P_{PA} increasing up to 12 mmHg [76]. Begin *et al*. found a 20 to 40% increase in Q with no increase in HR on immersion to the neck, confirming Arborelius' findings. Q

increases reached these levels within 30 minutes of seated immersion [77]. At rest, immersion in warm water has been shown to significantly increase Q, P_{PA}, pulmonary artery wedge pressure (PAWP), and CVP. Increases in HR and mean arterial pressure (MAP) also occurred. During cold-water immersed exercise trials, P_{PA} was reported as high as 37 mmHg [8]. Dujic *et al*. studied divers during a single open sea dive to 30 msw and found an increase in P_{PA} from 25 ± 3 to 33 ± 2 mmHg [78] which is well above the P_{PA} which Wagner *et al*. suggested could lead to pulmonary capillary stress failure [53]. The likely cause of increased P_{PA} is the increased intrathoracic blood volume and Q contributing to increased preload and afterload on the heart. As the depth of the dive increases, so does hydrostatic pressure. Immersion causes a sudden and temporary rise in cardiac output [79] as well as a negation of the effects of gravity on blood flow, which enhances venous return, increasing preload. Immersion can also increase sympathetic activity causing peripheral vasoconstriction and an increase in afterload [80].

Immersion can cause a decrease in the functional residual capacity of the lung. Begin *et al*. reported a 33-40% decrease, similar to the 46% decrease reported by Agostoni [77, 81]. It is believed to be caused primarily by a decrease in expiratory reserve volume. Immersion has been found to decrease D_Lco in the lung following SCUBA dives. Koehle *et al*. measured D_Lco in divers following a 60-minute dive to 4.5 msw in a swimming pool and found a significant reduction in D_Lco at 30 and 90 minutes post dive. This has been suggested to be caused by an increase in extravascular lung water, which impairs D_Lco [6]. A study by Prediletto *et al*. on breath-hold divers found mixed results when measuring D_Lco following a series of four dives from between 10 and 30 msw. They found a significant increase in D_Lco two minutes following the dives that subsequently decreased towards baseline. In four divers, D_Lco continued to

decrease >10% below baseline. It was concluded that extravascular lung water may impair $D_L$co following breath-hold diving [82]. The increase in P_{PA} during water immersion, likely the result of increased CO and central blood volume, appears to be sufficient a stimulus to cause development of sub-clinical EVLW and decrease $D_L$co.

Exercise

Physical exertion is unavoidable in many of the situations that mountaineers, swimmers, and divers face. Exercise induces increases in oxygen consumption, ventilation, heart rate and stroke volume which result in increased Q. When Q increases, peripheral vascular resistance must decrease to avoid a large increase in systemic blood pressure. Despite this change in resistance, blood pressure does increase with the majority of the increase in systolic and mean blood pressure. Pulmonary artery pressure is elevated minimally (approx. 10 mmHg) due to a low resistance to flow [83]. With the onset of metabolic acidosis, it is possible that changes in respiratory patterns could also cause an increase in P_{PA} [84]. A redistribution of blood flow is seen which involves vasoconstriction in organs such as the brain, gut, and kidneys. This blood is directed to exercising muscles that can go from receiving 15% of Q at rest to 80% of Q during maximal exercise [83]. Using a double indicator-dilution technique, supine exercise at 150 kg/m caused an increase in EVLW from 126 ± 15 ml sitting to 229 ± 22 ml. Cardiac output was found to increase in relation to increasing EVLW. Diffusion capacity increased from 22.6 ± 1.6 to 32.9 ± 1.9 $ml*min^{-1}*torr^{-1}$. Exercise also caused a significant increase in pulmonary capillary blood volume [70]. While exercise causes redistribution of blood towards working muscles and the resultant increase in P_{PA} is low, it is still sufficient to exacerbate stress on capillaries making exertion a major risk factor when in environments where HAPE or IPE are likely.

A3. High Altitude Pulmonary Edema

High altitude pulmonary edema is a severe type of altitude illness in which the interstitial space and alveoli of the lungs fill with fluid, impairing gas exchange.

Signs and Symptoms

Onset of HAPE is generally 2-3 days after arrival [85]. Symptoms may include dyspnea, weakness, cough, chest congestion, nausea, vomiting and headache which may worsen at night. Signs include tachypnea, tachycardia, pulmonary rales, and cyanosis [1]. Investigation will reveal low oxygen saturation and decreases in PaO_2 and $PaCO_2$ which are characteristic of arterial hypoxemia. In cases where oxygen delivery to the brain is severely impaired, confusion and coma may result. If left untreated, the outcome is death. Confusion and delirium may be compounded by symptoms of high altitude cerebral edema [86]. Pulmonary hypertension is constantly present. Pulmonary artery wedge pressure can be normal or slightly decreased and Q is generally low [1].

At elevations above 2,500 metres, it is generally established that HAPE is the result of acute hypoxia that causes nonuniform pulmonary vasoconstriction throughout the pulmonary bed. The unprotected arterioles and capillaries receive excess blood flow and pressure. This excess pressure results in capillary stress failure and eventual leakage out of the capillary into the alveolus. This EVLW interferes with gas exchange at the level of the alveolus, causing the hypoxemia (and resultant shortness of breath) that is characteristic of HAPE [1].

Prevalence

A critical factor in HAPE is the rate of ascent; HAPE is most common in cases where the subject did not properly acclimatize [2]. Of those who have a prior history of HAPE, some have demonstrated an abnormal elevation of P_{PA} during acute hypoxia [87]. Children are more

susceptible to HAPE than adults. Hultgren *et al*. found that between age 13 and 20, the incidence of HAPE is 17% while in ages 21 and older the incidence is only 3% [88]. The risk of developing HAPE after a rapid ascent to 3,600 metres is about 0.5% in adults [86]. Occurrence of HAPE is rare below 2,500 metres [89]. Sub-clinical HAPE occurs 6 to 10 times more commonly than clinical HAPE [90, 91]. It is possible for susceptible individuals to ascend to high altitude without developing HAPE with a slow rate of ascent. Similarly, HAPE has been shown to occur in individuals with a successful history at high altitude [34]. Although no conclusive evidence exists, it is likely that HAPE susceptibility is represented on a continuum and that no individual could be completely resistant depending on rate of ascent, exertion, and final altitude [2].

Diagnosis

At the 1991 International Hypoxia Symposium, a proposal for the diagnosis of HAPE required that two of the following criteria be met following a recent gain in altitude: dyspnea at rest, cough, weakness or decreased exercise performance, chest tightness, plus two of the following signs: rales or wheezing in at least one lung field, central cyanosis, tachycardia, or tachypenia [92]. When obtained, a chest radiograph will display three general abnormalities including vascular congestion without an infiltrate, patchy infiltrates, either localized or distributed throughout both lung fields and/or homogenous diffuse infiltrates, usually bilateral [93]. Infiltrates may show up for several days after symptoms abate. Weakness and fatigue accompanying symptoms may continue up to two weeks [86].

Pathophysiology

Mortality is primarily dependent on access to medical care, specifically the ability to use supplemental oxygen and descend quickly. For this reason, mountaineers who are in remote

locations have the highest mortality rates. In one study of 166 cases of HAPE, the mortality rate was 11.4% however, in those patients who descended or were given oxygen, only four died (6%) [21]. Bronchoalveolar lavage fluid from climbers at 4400 m with HAPE contained significant amounts of high-molecular-weight proteins, erythrocytes, and leukocytes as well as increased leukotriene B_4 indicating a "large pore leak" in capillary-alveolar interface. Also of note was the lack of neutrophil accumulation which accompanies other lung injury [40]. On autopsy, lungs show diffuse pulmonary edema with foamy fluid filling the airways. A small percentage of cases had pulmonary emboli or cerebral edema present. In 24 cases, histological studies were carried out and it was found that 46% of small pulmonary arteries and capillaries contained thrombi, 75% had infiltration with leukocytes, and 58% had alveolar hemorrhages [1].

Treatment

The easiest and most effective treatment for HAPE is descent to a lower altitude. A descent of 600 to 900 meters is often sufficient to provide relief from symptoms [86] and other methods of treatment should only be considered as supplementary, not substitutions [1]. Oxygen administration is also an effective means to decrease the effect of HAPE. Portable hyperbaric bags such as the Gamow bag are useful if immediate descent is not possible. Their small size and no need of electricity makes them useful in remote situations. A study by Kasic *et al*. showed that a Gamow bag will give greater improvements in signs and symptoms of HAPE when compared with oxygen administration [94]. Nifedipine has shown to be effective at decreasing P_{PA} and increasing SaO_2 [95, 96]. Nifedipine also has potential to prevent HAPE. When taken upon ascent and continued, nidefipine prevented HAPE in 9 of 10 patients while a placebo prevented HAPE in 7 of 11 patients, all of whom had previously experienced HAPE [97]. Sildenafil is hypothesized to decrease P_{PA} in HAPE patients and has been shown effective in

reducing pulmonary hypertension through its vasodilator effects [98]. Snyder *et al*. showed an attenuation of the increase in P_{PA} during hypoxia exposure when patients were given 100 mg sildenafil [99]. Some patients have been given furosemide in order to reduce fluid volume however this has been shown to cause a potentially severe fall in systemic blood pressure which can delay recovery [100]. Maggiorini *et al*. has used both tadalafil and dexamethasone as a prophylactic in a study investigating HAPE prevention in 29 HAPE susceptible patients traveling to altitude. Dexamethasone, a steroid used to prevent acute mountain sickness, has been shown to induce vasodilatation. None of the ten participants who took dexamethasone before travelling to 4559 m in 24 hours developed HAPE. Dexamethasone is believed to reverse endothelial dysfunction and stimulate the production of cyclic guanosine monophosphate as well enhancing nitric oxide availability in the pulmonary vessels. Only one of eight participants who were given tadalafil developed HAPE. Tadalafil is effective at restoring nitric oxide in subjects with decreased bioavailability [101]. While prophylactic drugs have a place in the prevention of HAPE, the most effective strategy is a slow rate of ascent.

A4. Immersion Pulmonary Edema

Immersion Pulmonary Edema (IPE) is a rare but potentially life threatening condition where patients immersed in water develop pulmonary edema. First reported in otherwise healthy SCUBA divers by Wilmshurst *et al*. in 1984, an increasing number of cases have been published in long distance swimmers and breath-hold divers [72, 102]. Onset of symptoms is rapid [4, 11], and the reasons patients develop IPE are not well understood.

Signs and Symptoms

Symptoms include dyspnea, respiratory distress, cough, hemoptysis, chest tightness, expectoration of froth, weakness, and tachypenia. The most severe symptoms include loss of

consciousness, seizures, and cardiopulmonary arrest. Signs include cyanosis and rales upon chest auscultation [4, 11].

Diagnosis

Chest radiograph is most commonly performed and used to confirm immersion pulmonary edema. Chest auscultation and CT are also successfully used. While radiographic measures may provide an easy method of diagnosis at the hospital, the use of ultrasound is emerging as a reliable field measure. A technique called ultrasound lung comets has already been used to identify individuals suffering from high altitude pulmonary edema [103]. Ultrasound machines are ultra-portable, ranging in size from a laptop to a large cellular phone. This could allow their use on a dive or rescue boat immediately after an incident occurs, eliminating the confound of an investigation that takes place significantly after the participant leaves the water. Ultrasound evaluation also allows the ability to rule out other differential diagnoses such as pneumothorax. Pulse oximetry provides a quick indication of the presence of pulmonary edema which has been shown to range from 76 % to 94 % [4].

Pathophysiology

To allow gas exchange through passive diffusion, the pulmonary blood-gas barrier must be extremely thin however it must be strong enough to withstand high stress when capillary pressure increases. Acute pulmonary edema may be caused by either an increase in pulmonary capillary permeability (noncardiogenic) or when pulmonary capillary pressure becomes greater than plasma oncotic pressure (cardiogenic). Pulmonary capillary stress failure occurs when increased P_{PA} disrupts the blood-gas barrier membrane allowing fluid to leak into the interstitial and alveolar space [79]. Sudden increases in preload and afterload can cause blood displacement into the lungs which reduces FRC and, when combined with the increase in pulmonary closing

volume and decreased lung compliance caused by immersion, results in ventilation-perfusion mismatch, hypoxemia, and pulmonary capillary vasoconstriction. Non-uniform capillary vasoconstriction results in exposure of unprotected vessels to high pressures, facilitating stress failure. Because gravity has an effect on regional distribution of blood flow in the lung, dependent areas are more highly perfused and therefore more likely to accumulate fluid.

This vascular explanation for immersion pulmonary edema would explain why three subjects swimming in the lateral decubitus position would develop edema only in the dependent lung [80] while hypoxic vasoconstriction explains the patchy presentation of EVLW on radiograph and CT.

It is possible that the garment swimmers and divers choose may affect P_{PA}. In moderate water temperatures, many people choose to use a wetsuit. These suits are perceptibly tight and a diver who gains weight over the course of time but continues to use the same suit may compound increased hydrostatic pressure. Tight wetsuits are also attributed to the feelings of dyspnea during the onset of IPE though when unzipped, patients report little or no relief.

It is also possible that these individuals are exposed to some degree of hypoxia before the onset of pulmonary edema. Certainly breath hold divers become hypoxic during a dive, even if just for a few seconds. It is also conceivable that long distance swimmers, especially in rough, choppy, open water could have breathing irregularities that result in slight hypoxia. Hypoxia could induce uneven pulmonary capillary vasoconstriction similar to the mechanism proposed in high altitude pulmonary edema.

Terminology

Early case reports describe breath hold divers who lost consciousness underwater and surfaced without equalizing. These fatalities were attributed to "thoracic squeeze". While their deaths could be explained as barotrauma, their loss of consciousness and expectoration of bloody froth underwater was unexplained. It is now believed that these patients initially suffered from IPE which caused them to lose consciousness after which they suffered fatal thoracic squeeze. The term swimming induced pulmonary edema (SIPE) was coined to describe pulmonary edema in triathletes and military trainees. The term SIPE implies that patients must be exerting themselves by swimming in order to develop pulmonary edema however, while exertion is a risk factor, pulmonary edema is also possible in divers who attain great depths in cold water while moving very little. Cold-induced pulmonary edema has also been used to describe IPE but recent cases in relatively warm water have also made this term misleading [104, 105]. For these reasons, the term immersion pulmonary edema is preferable to describe the development of pulmonary edema in an individual immersed in water regardless of activity type.

Other Factors

Excessive hydration before immersion can increase preload and pulmonary venous pressure [74]. Only a small number of patients [104] reported water overload. Acetylsalicylic acid (asprin) is taken frequently by breath hold divers in order to increase performance. While acetylsalicylic acid is not known to cause spontaneous hemorrhage, pulmonary edema may be aggravated by its anti-platelet effect [106]. Voluntary diaphragmatic contractions (VDC) are a maneuver used by breath-hold divers to increase their time underwater. The diver makes a forceful inspiratory effort against an obstructed airway which tricks mechanoreceptors into the illusion of breathing. Voluntary diaphragmatic contractions result in negative intrapulmonary pressures which increase

venous return, pulmonary blood volume, and pulmonary capillary hydrostatic pressure [107]. Each of these factors are reported in a small number of cases and should not be considered major contributing factors to the development of IPE but should not be discounted as they each may provide an additive effect in increasing P_{PA} or aggravation of pulmonary edema.

Treatment

Primary treatment of IPE involves immediate removal of the patient from water immersion. Other factors to consider depending on the conditions include cessation of physical activity, treatment of hypothermia, and administration of oxygen. Diuretics may reduce plasma volume and decrease P_{PA} [11].

A5. Exercise induced Arterial Hypoxemia

Recent research has indicated that some humans develop pulmonary edema during maximal exercise [12-14, 108]. This pulmonary edema has been hypothesized to be the cause of a phenomenon called exercise induced arterial hypoxemia (EIAH). EIAH is characterized by a widening of the alveolar-to-arterial P_{O_2} difference ($A\text{-}a\ D_{O_2}$) and a reduction in arterial O_2 saturation. It is estimated that EIAH occurs in 52% of highly trained athletes [15] and has been shown to impair exercise performance. For example, Koskolou *et al*. found a significant decrease in maximal exercise capacity in highly trained cyclists when EIAH was induced (% S_aO_2 = 87 ± 1%) [16]. Furthermore, the detrimental effects of EIAH on performance can be reversed with hyperoxia [17]. The transient increase in EVLW demonstrated in these studies could be the cause of impaired gas exchange and hypoxemia in EIAH [18]. Table A1 summarizes all the studies examining lung density before and after exercise looking for an increase in EVLW. The proposed mechanism of this transient pulmonary edema with exercise is believed to be increased

capillary leakage caused by an elevated pulmonary arterial pressure, the very same mechanism proposed in both IPE and HAPE [19, 20].

Table A1. Extravascular lung water as measured using different subject populations and exercise types. Maximal oxygen consumption (VO_{2max}), duration of exercise protocol, intensity of exercise protocol, type of measure, gender of participants, pre and post protocol result, and significance of change in EVLW.

Study	VO_{2max}	Duration	Intensity	Measure	Gender	Pre	Post	Time to scan	Result
Unit	($l*min^{-1}$)	(min)	(watts)	(type)	(m/f)	($g*ml^{-1}$)	($g*ml^{-1}$)	(min)	($p < 0.05$)
McKechnie et al.(1979) [14]	Trained	90 km	Race	CXR	M	N/A	N/A	N/A	yes
Caillaud et al. (1995) [108]	4.8 ± 0.12	120	Race	CT	M	0.21 ± 0.009	0.25 ± 0.01	95 ± 25	yes
McKenzie et al. (1998) [109]	4.5 ± 0.2	5	435 ± 19.9	MR	M	0.23 ± 0.02	0.22 ± 0.01	N/A	no
Anholm et al. (1999) [110]	Trained	70-90 km	Race	CXR	N/A	0.8 ± 1.2**	1.8 ± 1.6	immediate	yes
Manier et al. (1999) [111]	66.4 ± 4.7‡	120	75% max	CT	M	0.373 ± 0.044	0.352 ± 0.027	< 30	no
McKenzie et al. (2005) [13]	4.8 ± 0.14	45	300 ± 8.8	MR	M	0.22 ± 0.008	0.24 ± 0.018	90	yes
Snyder et al. (2006) [112]	38 ± 8‡	Ramp	To max	CT	M/F	N/A	-103 ± 20††	N/A	yes†
Zavorsky et al. (2006) [25]	3.12 ± 0.42	15	236 ± 27	CXR	F	1.3 ±1.6**	1.9 ± 2.0**	33.2 ± 6.1	yes

Study	VO_{2max}	Duration	Intensity	Measure	Gender	Pre	Post	Time to scan	Result
Unit	($l*min^{-1}$)	(min)	(watts)	(type)	(m/f)	($g*ml^{-1}$)	($g*ml^{-1}$)	(min)	($p < 0.05$)
Hodges et al. (2007) [113]	65 ± 7.5‡	60	race	MR	M	0.177 ± 0.019, 0.178 ± 0.021*	0.173 ± 0.019, 0.176 ± 0.019*	50	no
Guenette et al. (2007) [22]	3.3 ± 0.4	5 x 3 km	335 ± 33*	CT	F	0.138 ± 0.014	0.137 ± 0.011	44	no
MacNutt et al. (2007) [23]	4.65 ± 0.32	5 x 3 km	451 ± 29*	CT	M	0.18 ± 0.04	0.18 ± 0.04	76	no
Present Study (2011)	3.75 ± 1.12	15	231 ± 57	CT	M/F	0.2057 ± 0.034	0.1956 ± 0.031	11 ± 1	no

*Indicates test was performed under hypoxic (15% O_2) conditions. **Units are overall edema score. †Decrease in lung water volume. ††Units are EVLW in mL. ‡Units are $ml*min*^{-1}kg^{-1}$.

A6. Methods of Evaluating EVLW

Radiologic

X-Ray Production

X-rays are produced within a sealed glass vacuum that contains two electrodes. A high potential difference between electrodes allows electrons produced at the cathode to be accelerated towards the anode. When the electron is suddenly decelerated by the anode, an energy conversion occurs. The quantity of x-rays produced is dependent on the number of electrons that flow from cathode to anode. The current (in milliamperes) applied to the cathode equals the number of electrons flowing per second to the anode target. The voltage applied to the cathode provides the potential difference that accelerates the electrons.

Most of the energy in the electrons is converted into heat; less than 1% become x-rays. The heat generation of an x-ray tube is a product of peak kilovoltage (kVp), current (mA) and exposure time (sec). This is expressed as a heat unit or joule.

When electrons are accelerated towards the target anode of an x-ray tube, they lose energy which produces x-rays. Two different interactions between electrons and the target anode cause x-ray production.

General radiation is the result of electrons passing near the nucleus of an atom of the target anode (usually tungsten). A photon of radiation is emitted when the electron is attracted toward the nucleus which causes it to deflect and decelerate, losing energy. An electron may be decelerated repeatedly, losing a small amount of energy with each interaction before coming to rest. It is also possible for the electron to collide directly with the nucleus. In this case, all the energy of the electron is emitted as one photon. The energy of a photon (and quality of the x-ray

beam) is related to the energy (keV) of the electron, which is the result of the potential difference (kVp) applied across the x-ray tube. In other words a photon could have an energy as high (though not always) as the keV of the electron produced by the potential difference kVp across the x-ray tube.

Characteristic radiation is the result of an electron that ejects an electron from the inner orbit of the target tungsten atom. This results in an excess positive charge on the atom which must expel energy. This energy can be expelled by producing radiation. The x-rays produced are characteristic of the atom that has been ionized. If the potential is below 70 kVp, characteristic radiation is nonexistent (greater than 70 kV is needed to ionize the atom). Between 80 and 150 kVp, 10% to 28% overall radiation is due to characteristic radiation. Beyond 150 kVp, characteristic radiation begins to decrease, becoming negligible above 300 kVp.

Intensity of the x-ray beam is dependent on the number of photons in the beam times the energy within each proton. Intensity is measured in roentgens per minute (R/min). Intensity can be affected by the tube kilovoltage, current, target material, and filtration of the beam.

When x-ray photons interact with matter they can either be absorbed or scattered. When a photon is scattered, it is deflected in a random direction and is no longer useful. If a photon is absorbed, it no longer exists and is removed from the x-ray beam. Scattering is represented as black on an x-ray film and contributes to the noise of the x-ray, which may partially or totally obscure an image.

Attenuation

If intensity of an x-ray beam is the product of quality and quantity, attenuation is the loss of intensity of the beam as it cross matter caused by absorption or scattering of photons. Four

factors affect the attenuation of x-rays. An increase in radiation energy results in decreased attenuation but increasing the density, atomic number, or electrons per gram of the tissue will result in increased attenuation.

Energy can affect the contrast seen on the x-ray film. If two tissues have significantly different attenuation coefficients, a low energy x-ray beam will display lots of contrast while a higher energy beam will reduce contrast and hopefully make the image more useful.

Attenuation and density have a linear relationship because an increase in density means an increase in the electrons present to absorb x-rays.

The linear attenuation coefficient is the expected amount of attenuation per thickness of tissue. The linear attenuation coefficient is specific to monochromatic radiation. It depends on the energy of the x-ray beam as well as the type of tissue. Tissues of different densities will attenuate more or less energy.

The mass attenuation coefficient is independent of the density of the absorber and is the same even if the physical state of the material differs.

Patient exposure is measured in roentgens (R) or coulombs per kilogram ($C_{*}Kg^{-1}$). The unit of absorbed dose is the rad or gray (Gy). One Gy equals 100 rads.

Computed Tomography

Computed Tomography (CT) was first demonstrated by G.N. Hounsfield in April 1972. Using a computer to reconstruct multiple projections of an object, CT allows differentiation between various soft tissues which make up the internal structure of a patient.

Using a rotate-rotate scanner, the patient is held stationary while a gantry holding an x-ray tube opposite a detector array rotates. The x-ray beam is collimated (accurately made parallel) into a fan beam in order to image the entire patient in each scan. Sometimes up to 700 detectors are necessary to image the entire object. As the gantry rotates, successive projections are made, sometimes up to 1000 in less than 1 second. These projections are then combined to form a single image. This image is also known as a slice. A rotate-fixed scanner is one where the detectors (sometimes more than 2000) completely surround the patient while the x-ray tube rotates around, allowing faster scans. Speed is necessary to image moving objects such as vessels and the heart.

Image reconstruction is completed using a computer, which represents the tissue as a matrix of tiny blocks called voxels. These boxes are then each assigned a number according to the tissues attenuation for x-rays using the equation for exponential attenuation:

$$N = N_0 e^{-(\mu_1 + \mu_2 + \ldots \mu_n)x}$$

Where e is known as the base of the natural logarithm, the initial number of photons (N_0), transmitted photons (N) and voxel thickness (x) are all known so the attenuation coefficient (μ) is the only unknown. By combining the projections from each different angle, the equation can be solved for each individual attenuation coefficient.

Image quality of a CT scan is a combination of factors including noise, patient exposure, and resolution. Noise is the result of a statistical fluctuation caused by a variation in the number of x-ray photons absorbed by a detector and is reduced by increasing the number of projections in a slice. Resolution is composed of spatial resolution and contrast resolution. Spatial resolution is

the scans ability to differentiate between two small objects that sit near each other. Contrast resolution is the ability to differentiate between two objects with very similar densities (and therefore similar attenuation coefficients). Spatial resolution is improved through the scanner design, computer reconstruction and display output. Contrast resolution is increased by reducing noise [114].

CT and Exercise

Several studies have used CT to investigate development of EVLW during exercise at sea-level or in hypoxia (See Table A1). In female subjects exercising maximally in normobaric hypoxia (15% O2), Guenette *et al.* found no change in lung density. Lung density at 44 min post exercise (0.137 ± 0.011 $g_{*}ml^{-1}$) was not significantly different than baseline (0.138 ± 0.014 $g_{*}ml^{-1}$) [22]. MacNutt *et al.* measured lung density in males exercising maximally in normobaric hypoxia. There was no change in lung density between baseline (0.18 ± 0.02 $g_{*}ml^{-1}$) and post-exercise (0.18 ± 0.04 $g_{*}ml^{-1}$) [23]. Caillaud *et al*. measured lung density in eight male subjects after a triathlon. Lung density increased significantly from 0.21 ± 0.009 g/cm^3 at baseline to 0.25 ± 0.01 g/cm^3 [108]. In nine trained runners who ran at 75% of their VO_{2max} for two hours, no change in lung density was observed (0.37 ± 0.04 vs. 0.35 ± 0.03, not significant) [111]. While results are conflicting, it is possible that the increase in lung density after exercise occurs in only a small sub-sample of the population. It is possible that individuals susceptible to HAPE or IPE are more likely to be included in this sample.

Spirometric

Pulmonary Diffusion Capacity

According to the laws of diffusion, we know that the amount of gas which crosses a tissue is proportional to the area of the tissue, the difference in partial pressure, a constant, and inversely proportional to the thickness of the tissue. This is Fick's equation:

$$\dot{V}gas = \frac{A}{T} \times D \times (P1 - P2)$$

Because it is not possible to measure these parameters in vivo, the equation is rewritten so that D_L is the diffusion capacity of the lung which includes the area, thickness and constant of the tissue and gas.

$$\dot{V}gas = \mathrm{D_L} \times (\mathrm{P1} - \mathrm{P2})$$

Because factors other than just tissue area and thickness can affect the diffusion capacity of oxygen, carbon monoxide (CO), with its high affinity for hemoglobin, is used in its place. The diffusion capacity for carbon monoxide ($D_L$co) is shown below:

$$\mathrm{D_L} = \frac{\dot{V}co}{P1-P2}$$

[49]

Using the single-breath method, a mixture of gas including a small amount of carbon monoxide (0.3%) is inhaled during a single inspiration. The inhalation must be within 10% of the largest previously measured vital capacity. The patient is instructed to hold their breath for 10 seconds while the carbon monoxide is allowed to diffuse across the barrier. The breath hold must involve no Valsalva or Muller maneuvers and the exhalation must be quick and smooth. On exhalation,

the remaining carbon monoxide is calculated by the spirometer and compared to the inhaled concentration to give the diffusion capacity in $ml*min^{-1}*mmHg^{-1}$. A minimum of two tests are necessary and averaged to find the mean $D_L$co. Tests should be five minutes apart and are included when within 3 $ml*min^{-1}*mmHg^{-1}$ of each other [29, 115].

$D_L$co is normally separated into its two components which act as resistances in series to diffusion. The "extra-Hb resistance" refers to the passage of gas by way of passive diffusion from the alveolar space through the epithelial cells, the basement membrane, the capillary endothelium, the plasma, red blood cell membrane and red blood cell cytoplasm. This pathway is termed the membrane diffusion component (D_M). The second resistance is related to the capillary blood volume (V_C) that is exposed to alveolar air and the conductance of the blood for CO transfer (Ø) [116]. The D_M and V_C are combined to determine $D_L$co using the equation:

$$1/ D_Lco = 1/D_M + 1/(Ø V_C)$$

[30]

In order to partition these two components, it is necessary to make a second measure of single breath $D_L$co using a gas at a different P_AO_2 (10% He, 0.3% CO, Balance O_2). These are plotted on a graph and a line is fitted. The y-intercept is equal to $1/ D_M$ and the slope is equal to $1/ V_C$. Because Ø and therefore $D_L$co are directly related to the concentration of hemoglobin (Hb) in the blood, it is necessary to measure Hb during each test [116].

Normal diffusion capacity at rest is 25 $ml*min^{-1*}mmHg^{-1}$ and can increase with exercise [49]. Stewart *et al*. found that $D_L$co in the supine position was significantly higher than in the seated position [28]. Several studies have looked at the effect of exercise on $D_L$co, D_M, and V_C; these

are summarized in Table A2. Exercise was found to cause a depression in $D_L$co, specifically in the membrane diffusion component, following maximal exercise [27]. This is believed to be caused by a thickening of the alveolar-capillary membrane which causes a decrease in the rate of gas transfer. This could be caused by the onset of pulmonary edema. The higher $D_L$co in the supine position could be due to increased pulmonary lymph flow which serves to remove and fluid which has accumulated in the alveolar-capillary membrane. It is also thought that the depressed $D_L$co in the seated position could be due to redistribution of perfusion which is concentrated primarily in the lower parts of the lung. This would be more evenly spread out in the supine position and result in less of a depression in $D_L$co [28].

Table A2. Changes in pulmonary diffusion capacity as measured in different populations performing different types of exercise. Maximal oxygen consumption (VO_{2max}), duration of exercise protocol, type of exercise, gender of participants, and significant change in pulmonary diffusion capacity ($D_L$co), membrane diffusion (D_M), and capillary blood volume (V_C).

Study	VO_{2max}	Duration	Type	Gender	Time to Test	$D_L$co	D_M	V_C
Unit	($l*min^{-1}$)	(min)		(m/f)	(min)	($p < 0.05$)	($p < 0.05$)	($p < 0.05$)
Filley et al. (1954)[117]	Healthy	6	Treadmill	M/F	During	Increase	N/A	N/A
Ross et al. (1959) [118]	Healthy	N/A	Leg Flexion	M	During	Increase	N/A	N/A
Miles et al. (1983) [119]	Trained	210	Run	M	5-10 min	Decrease	Decrease	N/C
Rasmussen et al. (1986) [120]	N/A	6-10	Canoe	N/A	130	Decrease	N/A	N/A
Manier et al. (1991) [121]	Trained	180	Run	M	28 ± 14	Decrease	Decrease	Decrease
Rasmussen et al. (1992) [122]	N/A	6	Rowing	N/A	120-180	Decrease	N/A	N/A
Manier et al. (1993) [123]	Professional	20-22	Handball	M	Post	Decrease	Decrease	N/C
Hanel et al. (1994)[124]	Trained	6	Rowing	M	360	Decrease	N/C	Decrease

Study	VO_{2max}	Duration	Type	Gender	Time to Test	$D_L$co	D_M	V_C
Unit	($l*min^{-1}$)	(min)		(m/f)	(min)	($p < 0.05$)	($p < 0.05$)	($p < 0.05$)
Caillaud et al. (1995) [108]	4.8 ± 0.12	120	Run	M	Post	Decrease†	N/A	N/A
McKenzie et al. (1999) [125]	67 ± 3.6‡	2 x 60	Cycle	M	60	Decrease	Decrease	Decrease
Sheel et al. (1998) [27]	3.73 ± 0.37	Ramp	Cycle	M	60	Decrease†	Decrease	Decrease
“	4.45 ± 0.5	Ramp	Cycle	M	60	Decrease†	Decrease	Decrease
“	4.93 ± 0.34	Ramp	Cycle	M	60	Decrease†	Decrease	Decrease
McKenzie et al. (2005) [13]	4.8 ± 0.14	45	Cycle	M	60	Decrease	No Change	Decrease
Snyder et al. (2006) [112]	38 ± 8‡	Ramp	Cycle	M/F	N/A	Increase*	Increase*	Increase*
Present Study (2011)	3.75 ± 1.12	3 x 5	Cycle	M/F	23 ± 4	Decrease†	Decrease†	Decrease†

*Indicates test was performed under hypoxic (reduced F_IO_2) conditions. †Change also significant when corrected for V_A. ‡Units are $ml*min*^{-1}kg^{-}$

APPENDIX B: INDIVIDUAL DATA

Table B1. Individual anthropometric and spirometric characteristics of 18 subjects.

Subject	Age (years)	Height (cm)	Weight (kg)	FVC (L)	FEV_1 (L)
1	40	187	87.6	5.69	4.23
2	53	189	91.6	6.35	4.5
3*	27	187	78.1	8.81	7.01
4*	46	179	79.9	4.98	4.06
5*	55	160	54.7	4.9	3.37
6‡	30	179	85.9	4.83	4.21
7‡	22	164	54.5	3.87	3.62
8	30	167	64.3	4.66	3.62
9*	55	171	83.3	4.66	3.8
10*	21	169	65.9	6.85	4.4
11*	46	174.5	89.5	6.87	4.36
12	21	171	76.5	5.92	4.04
13	24	180	73.2	5.95	4.89
14	27	183	93.3	4.99	3.7
15	52	175	78.3	5.08	4.29
16	28	166	65.1	4.25	3.49
17‡	40	165	54.9	3.95	1.99
18	61	164	66.6	3.16	2.5

*Indicates susceptibility to HAPE; ‡ indicates susceptibility to IPE.

Table B2. Maximal oxygen consumption (VO_{2max}), peak power, maximum heart rate (MHR) and minimum arterial oxygen saturation (S_PO_2).

Subject	VO_{2max} ($L_{*}min$)	VO_{2max} ($mL_{*}min_{*}kg$)	Peak Power (watts)	MHR (bpm)	Min S_PO_2 (%)
1	5.38	56.4	432	185	88
2	3.97	43.4	322	152	99
3*	5.40	69.2	442	187	99
4*	3.34	41.9	284	183	95
5*	2.81	51.4	270	169	78
6‡	3.00	35.0	344	187	98
7‡	2.29	41.9	234	191	98
8	3.07	47.7	311	183	79
9*	3.37	40.4	280	181	98
10*	3.71	56.2	335	189	98
11*	4.65	51.9	373	188	92
12	5.29	69.2	362	175	98
13	4.94	68.6	410	189	98
14	4.80	55.2	389	184	93
15	4.31	55.2	343	170	98
16	2.55	39.2	235	181	65
17‡	2.60	47.3	270	183	79
18	2.12	32.1	202	174	98

*Indicates susceptibility to HAPE; ‡ indicates susceptibility to IPE.

Table B3. Maximum heart rate (MHR), minimum arterial oxygen saturation (S_PO_2), during third interval, mean interval power (INT Power), mean percent maximal power (INT Intensity).

Subject	MHR (bpm)	Min S_PO_2 (%)	INT Power (watts)	INT Intensity (%)
1	182	88	N/A	N/A
2	160	98	236	73.41
3*	188	94	350	79.12
4*	185	88	204	71.91
5*	171	92	186	68.94
6‡	188	99	260	75.44
7‡	200	86	146	62.54
8	179	N/A	226	72.78
9*	188	98	232	82.73
10*	188	97	261	77.81
11*	190	79	266	71.20
12	179	98	267	73.81
13	194	98	314	76.51
14	179	92	237	60.90
15	176	99	263	76.63
16	197	91	162	68.79
17‡	193	88	192	71.15
18	180	98	133	65.76

*Indicates susceptibility to HAPE; ‡ indicates susceptibility to IPE.

Table B4. Individual CT reconstruction algorithms and slice thicknesses for lung density pre- and post- exercise.

Sub #	Density ($g_{*}mL^{-1}$) For Each Spatial Frequency Reconstruction Algorithm															
	B35 1mm		B35 2mm		B45 1mm		B45 2mm		B45 5mm		B60 1mm		B60 2mm		B60 5mm	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	0.178	0.177	0.178	0.178	0.173	0.172	0.175	0.174	0.178	0.177	0.177	0.175	0.178	0.176	0.174	0.174
2	0.198	0.205	0.198	0.205	0.193	0.200	0.194	0.201	0.198	0.203	0.195	0.202	0.196	0.202	0.194	0.200
3*	0.217	0.188	0.217	0.189	0.213	0.184	0.214	0.185	0.215	0.186	0.211	0.182	0.213	0.184	0.213	0.183
4*	0.249	0.215	0.249	0.216	0.243	0.210	0.244	0.211	0.254	0.215	0.246	0.214	0.249	0.215	0.251	0.213
5*	0.156	0.161	0.157	0.161	0.151	0.155	0.152	0.156	0.154	0.159	0.149	0.154	0.150	0.155	0.151	0.155
6‡	0.208	0.200	0.208	0.200	0.203	0.195	0.204	0.196	0.210	0.202	0.206	0.198	0.206	0.200	0.205	0.197
7‡	0.185	0.157	0.186	0.158	0.184	0.148	0.181	0.153	0.185	0.155	0.170	0.144	0.172	0.150	0.181	0.151
8	0.250	0.249	0.251	0.250	0.248	0.246	0.249	0.247	0.251	0.249	0.249	0.246	0.251	0.249	0.257	0.255
9*	0.151	0.156	0.152	0.157	0.146	0.151	0.147	0.152	0.151	0.156	0.150	0.154	0.150	0.155	0.147	0.152
10*	0.234	0.205	0.234	0.206	0.234	0.201	0.235	0.203	0.237	0.205	0.237	0.199	0.240	0.202	0.243	0.211
11*	0.160	0.152	0.161	0.153	0.158	0.150	0.159	0.151	0.163	0.153	0.165	0.153	0.165	0.154	0.160	0.149
12	0.237	0.250	0.238	0.250	0.233	0.246	0.234	0.247	0.237	0.251	0.236	0.250	0.238	0.251	0.235	0.250
13	0.238	0.216	0.238	0.217	0.234	0.212	0.235	0.213	0.238	0.215	0.233	0.210	0.235	0.212	0.237	0.213
14	0.260	0.240	0.260	0.240	0.257	0.237	0.258	0.237	0.258	0.239	0.262	0.241	0.263	0.241	0.257	0.237
15	0.193	0.187	0.193	0.188	0.187	0.181	0.188	0.182	0.193	0.187	0.190	0.184	0.190	0.185	0.190	0.184
16	0.227	0.208	0.227	0.208	0.224	0.204	0.224	0.205	0.226	0.208	0.226	0.207	0.228	0.209	0.232	0.214
17‡	0.179	0.189	0.180	0.189	0.174	0.183	0.175	0.184	0.176	0.186	0.170	0.179	0.172	0.180	0.173	0.183
18	0.183	0.167	0.184	0.168	0.178	0.163	0.179	0.164	0.182	N/A	0.177	0.163	0.179	0.162	0.179	0.162

*Indicates susceptibility to HAPE; ‡ indicates susceptibility to IPE; Sub, subjects.

Table B5. Individual CT reconstruction algorithms and slice thicknesses for lung mass pre- and post- exercise.

	Mass (g) For Each Spatial Frequency Reconstruction Algorithm											
Sub #	B35 1mm		B35 2mm		B45 1mm		B45 2mm		B60 1mm		B60 2mm	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	157.856	162.483	118.033	163.462	153.740	158.879	154.719	160.051	157.298	161.178	157.677	161.679
2	164.583	166.096	164.571	165.678	160.707	162.908	161.708	163.140	162.763	164.553	163.005	164.535
3*	176.977	163.212	176.715	163.690	174.230	159.725	174.368	160.702	173.506	158.925	173.948	160.122
4*	138.302	124.223	136.424	124.487	134.618	121.938	134.028	122.323	136.129	124.446	136.851	124.372
5*	101.949	103.420	102.210	103.586	98.443	100.277	99.052	100.744	97.688	99.877	98.046	100.117
6‡	160.560	143.987	159.866	143.692	157.934	140.779	157.283	141.041	158.833	143.166	158.323	143.562
7‡	120.624	107.934	120.774	108.111	117.328	101.459	118.006	104.896	110.487	98.877	111.333	103.100
8	131.044	133.301	131.276	133.896	130.622	132.453	128.034	132.980	131.531	132.635	132.186	134.054
9*	116.730	118.294	116.914	118.681	112.567	114.823	112.689	114.791	116.070	117.199	115.278	116.738
10*	125.665	125.629	125.863	125.893	127.133	123.195	127.896	124.051	129.490	121.575	131.084	123.326
11*	129.327	133.730	129.161	133.619	128.588	132.869	128.764	133.422	131.162	134.021	131.309	133.750
12	156.577	157.641	156.238	155.392	154.369	154.781	154.444	155.144	156.886	158.213	157.088	157.373
13	154.157	150.642	153.789	150.756	152.187	148.062	152.087	148.426	151.881	146.982	146.647	148.038
14	168.962	178.466	168.405	177.809	167.546	176.524	167.338	176.238	171.572	180.071	171.283	179.636
15	127.494	131.868	127.288	131.300	124.774	128.221	124.424	128.183	125.847	129.494	125.818	129.462
16	126.566	120.939	126.522	118.065	125.489	119.324	125.512	119.790	127.073	121.342	127.935	122.433
17‡	113.850	124.926	114.217	125.183	110.685	121.995	111.347	122.191	108.565	119.562	109.559	119.855
18	107.041	105.902	107.494	105.979	104.275	103.448	105.105	103.727	104.320	103.681	104.961	102.819

*Indicates susceptibility to HAPE; ‡ indicates susceptibility to IPE; Sub, subjects.

Table B6. Individual CT reconstruction algorithms and slice thicknesses for lung volume pre- and post- exercise.

Sub #	Volume (mL) For Each Spatial Frequency Reconstruction Algorithm											
	B35 1mm		B35 2mm		B45 1mm		B45 2mm		B60 1mm		B60 2mm	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	881.539	916.721	673.509	914.326	883.163	918.722	880.231	916.345	884.798	921.403	881.437	917.656
2	831.143	809.525	829.549	806.499	832.598	811.471	830.746	808.607	835.080	814.070	832.421	810.859
3*	819.859	868.433	816.862	866.397	822.098	870.490	819.065	868.450	824.146	872.293	820.676	870.414
4*	551.724	587.025	546.991	585.707	552.322	589.280	549.438	587.439	554.112	591.548	551.096	588.905
5*	652.715	642.298	650.837	640.407	654.359	644.141	652.321	642.255	656.164	646.254	653.888	644.217
6‡	766.002	722.231	761.763	718.463	768.558	724.324	764.116	720.675	767.173	725.588	763.208	722.289
7‡	652.303	693.467	651.198	692.357	653.756	691.757	652.763	693.772	650.541	692.556	649.068	695.157
8	404.466	412.090	375.094	382.772	249.630	414.524	222.349	384.306	251.076	415.812	232.829	385.752
9*	774.203	763.844	770.830	761.152	775.167	765.658	771.353	762.079	776.377	766.705	772.434	763.125
10*	414.644	468.279	384.649	434.411	418.925	469.345	388.864	435.593	421.071	467.949	390.950	434.315
11*	799.139	874.008	795.573	870.369	804.204	879.121	800.497	875.903	801.606	876.673	798.551	873.330
12	659.327	635.051	655.685	628.980	661.387	636.408	657.684	633.047	663.783	640.124	659.679	634.897
13	649.892	697.505	647.726	696.326	652.956	699.645	650.225	698.264	655.228	701.410	627.155	700.369
14	651.023	742.249	648.189	739.489	653.373	744.943	650.596	742.216	655.908	747.822	652.509	744.340
15	647.753	694.844	645.246	691.427	650.409	696.469	646.664	693.029	651.652	698.378	648.535	695.156
16	427.614	447.027	396.656	404.779	429.839	449.089	398.330	416.658	431.437	450.712	400.041	418.206
17‡	634.379	662.541	632.822	661.205	636.003	664.703	634.301	662.948	637.849	666.142	636.113	664.100
18	585.003	632.999	584.370	631.015	586.971	635.359	586.024	633.240	589.144	637.685	587.980	634.353

*Indicates susceptibility to HAPE; ‡ indicates susceptibility to IPE; Sub, subjects.

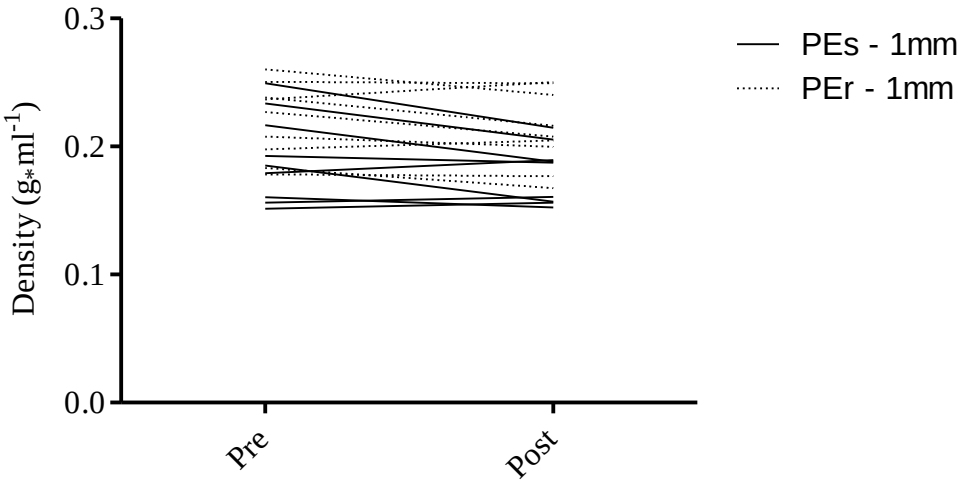

Figure B1. CT lung density pre and post exercise. B35 spatial frequency reconstruction algorithm, 1mm slice thickness.

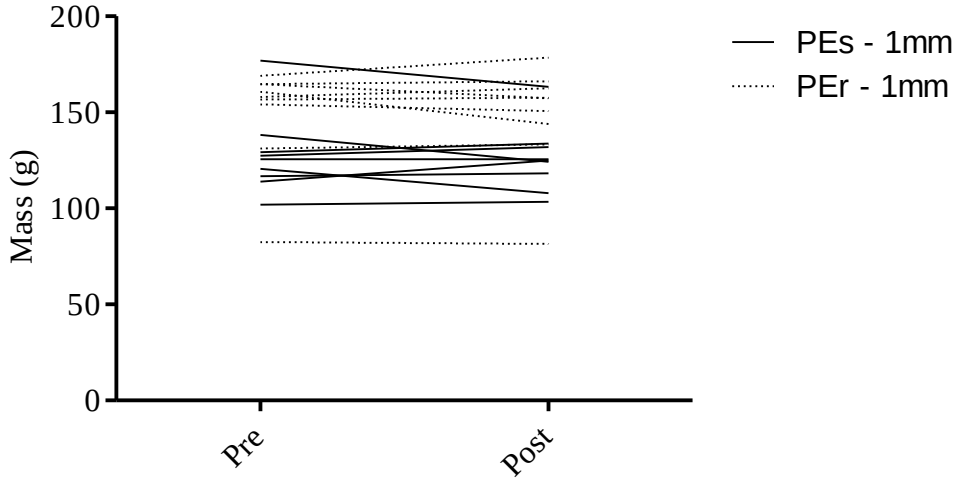

Figure B2. CT lung mass pre and post exercise. B35 spatial frequency reconstruction algorithm, 1mm slice thickness.

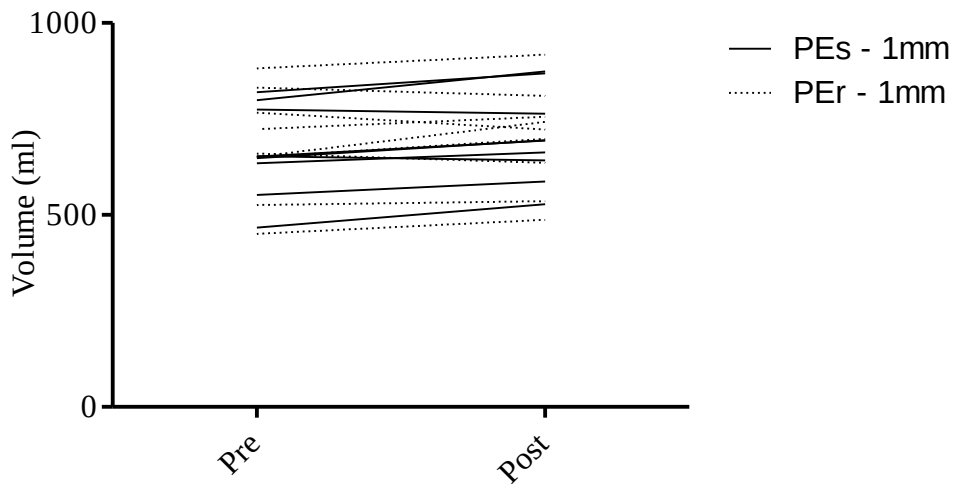

Figure B3. CT lung volume pre and post exercise. B35 spatial frequency reconstruction algorithm, 1mm slice thickness.

Table B7. Pulmonary diffusion capacity of carbon monoxide breathing 21% oxygen (D_L-21%), alveolar volume measured breathing 21% oxygen (VA), diffusion capacity of the alveolar membrane (D_M) and capillary blood volume (V_C) in each participant, pre and post exercise.

Subject	D_L-21% ($mL*min^{-1}*mmHg^{-1}$)		V_A (mL)	V_C (mL)		D_M ($mL*min^{-1}*mmHg^{-1}$)	
	Pre	Post	Mean	Pre	Post	Pre	Post
1	36.23	37.47	8.13	84.56	83.16	49.35	51.29
2	40.99	34.81	7.89	122.48	74.11	52.23	51.15
3	47.42	45.61	10.73	81.88	80.22	67.82	68.39
4	31.59	27.94	6.42	105.85	87.49	39.84	34.44
5	22.94	21.13	5.25	69.63	45.51	29.02	29.93
6	29.35	26.39	7.06	66.87	50.15	42.48	42.42
7	24.19	23.54	5.48	56.24	44.68	34.09	37.05
8	26.88	23.19	4.84	85.41	63.98	34.31	29.94
9	23.89	21.52	6.05	67.17	62.46	31.43	27.42
10	36.98	34.49	5.77	144.74	69.46	43.34	45.75
11	43.46	42.44	8.22	148.46	105.98	54.99	56.44
12	49.36	43.44	7.12	108.46	94.84	67.58	60.49
13	37.76	38.92	8.26	67.57	59.34	58.45	63.47
14	32.34	27.02	6.09	110.90	166.42	40.36	30.19
15	30.88	26.23	5.10	79.71	67.44	36.31	28.95
16	22.88	19.37	5.49	38.77	35.66	34.45	28.89
17	27.48	21.83	7.05	96.11	53.80	39.03	35.82
18	26.14	19.97	4.87	87.47	57.83	32.86	26.76

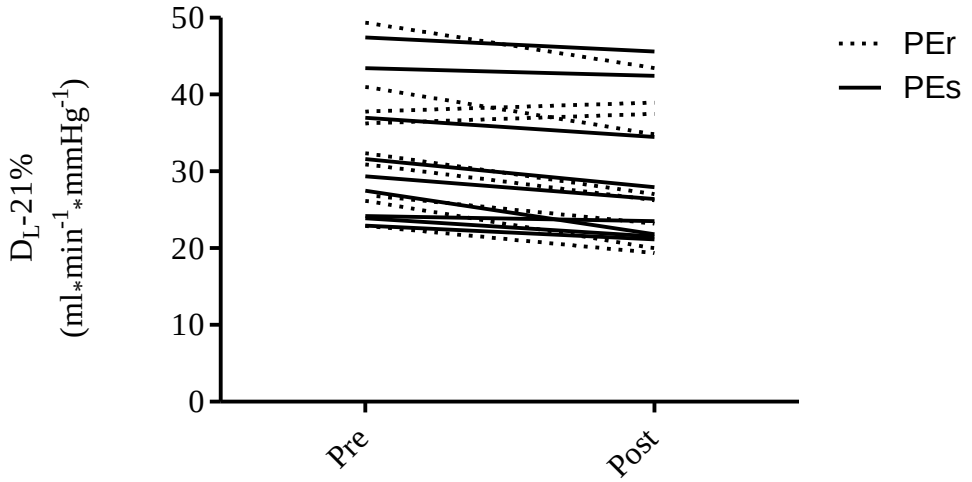

Figure B4. Pulmonary diffusion capacity of carbon monoxide breathing 21% oxygen (D_L-21%) in each participant, pre and post exercise.

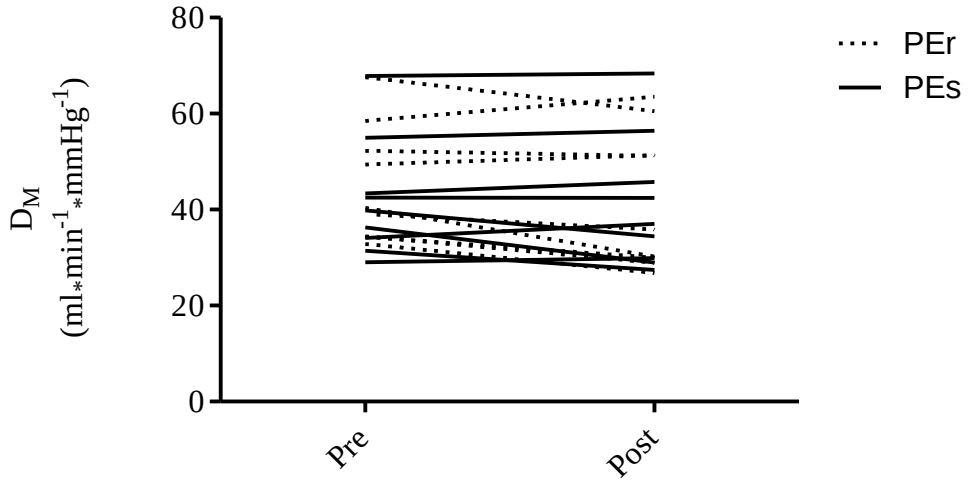

Figure B5. Pulmonary membrane diffusion capacity of carbon monoxide breathing 21% oxygen (D_M) in each participant, pre and post exercise.

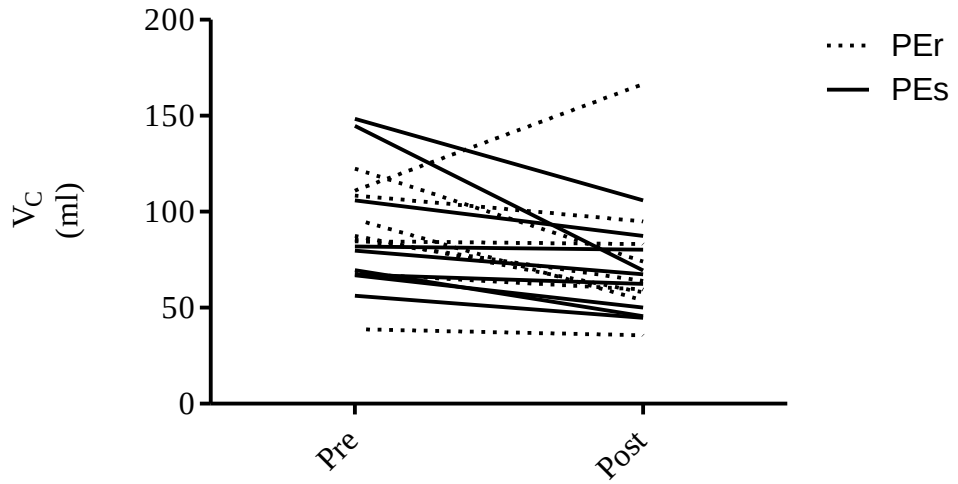

Figure B6. Pulmonary capillary blood volume (V_C) in each participant, pre and post exercise.