MPhil Sports and Exercise Medicine Dissertation

Comparison of sonographic lung comet evaluation by an experienced ultrasonographer and novice in a high-altitude environment

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LIST OF ABBREVIATIONS

AMS:	Acute mountain sickness
CBF:	Cerebral blood flow
COPD:	Chronic obstructive pulmonary disease
CSF:	Cerebral spinal fluid
EVLW:	Extra vascular lung water
HACE:	High altitude cerebral oedema
HAI:	High altitude illness
HAPE:	High altitude pulmonary oedema
HIF-1-a:	Hypoxia-inducible factor 1-alpha
HPV:	Hypoxic pulmonary vasoconstriction
HR:	Heart rate
HVR:	Hypoxic ventilatory response
IQR:	Interquartile range
LLSS:	Lake Louise scoring system
ODC:	Oxyhaemoglobin dissociation curve
PA:	Pulmonary artery
PVR:	Pulmonary vascular resistance
RBCs:	Red blood cells
ULCs:	Ultrasound lung comets
VEGF:	Vascular endothelial growth factor
2,3-DPG:	2,3 Diphosphoglyceric acid

ABSTRACT

Introduction: High altitude illness can be severely debilitating and sometimes fatal to those visiting higher altitudes. The condition is known to develop at altitudes above 2500m and has an incidence of between 50 and 60 percent. High altitude pulmonary oedema (HAPE) presents with signs and symptoms related to the accumulation of extravascular fluid in the lung, and early identification is critical to timeous intervention which in turn improves clinical outcomes. While increases in altitude result in physiological acclimatization, being able to identify when these changes become pathological is vital to early intervention. This process is facilitated with the use of lung ultrasound and the identification of sonographic artifacts called lung comets.

This study was designed to establish whether a novice sonographer can perform effective assessment of lung ultrasound comet scores in comparison to an experienced sonographer in a high-altitude environment. An acceptable limit of agreement of 4 lung comets were identified *a priori*. This value was established based on the work done by Volpicelli et al. in 2006 who defined a positive lung ultrasound test as having at least 3 lung comets present at the time of examination.[49] In addition, various physiological and clinical parameters and their changes at different altitudes, ranging from 950 to 4662 meters above sea level, were assessed to aid the clinical interpretation and relevance of the ultrasound findings.

Methods: Ten participants (six male; four female) underwent daily lung ultrasound scans at varying altitudes on Mount Kilimanjaro according to a standardized 8-zone protocol. One experienced sonographer scanned each participant, with his score then used as the "gold standard" for comparison, followed by a novice sonographer. The two sonographers were blinded to each other's findings during the data collection. Participants also undertook daily Lake Louise Scores, fingertip peripheral oxygen saturation readings and heart rates as part of the safety and clinical monitoring program on the mountain.

Results: An exploratory Bland-Altman analysis revealed that compared to experts, novices showed little bias in identifying lung comets with sonography (mean difference 0,2 comets, 95% CI -0,2 to 0,6). Novice total comet scores typically fell within a range of approximately 3 above and below the expert score. There was a statistically significant difference in the total number of lung comets across the 7 recorded altitude points, χ^2 (6) = 22.05, $p < 0.01$, as

measured by the expert ultrasonographer. In addition, there was an overall statistically significant difference across the 7 recorded altitude points with regards to oxygen saturation (χ^2 (6) = 33.22, $p < 0.001$), heart rate (as a percentage of maximum heart rate) (χ^2 (6) = 12.83, $p < 0.05$) and Lake Louise Scores (χ^2 (6) = 30.59, $p < 0.001$).

Conclusion: Our results suggest that a novice sonographer is able to perform an effective assessment of lung ultrasound comet scores when compared to an experienced sonographer in a high-altitude environment. While the limited sample size of this study advocates for corroboration with future research projects on a larger scale, our preliminary findings encourage the use of a portable ultrasound machine as a potentially useful diagnostic tool in a wilderness expedition kit. The significant effects of high-altitude on physiological parameters are again emphasized, with our results in keeping with the findings of previous authors.

Keywords: High altitude illness, high altitude pulmonary oedema, extravascular lung fluid, lung ultrasound, ultrasound lung comets, high altitude physiology

Chapter 1

LITERATURE REVIEW

1.1 INTRODUCTION

Rapid ascent to high altitude is recognized to cause Acute Mountain Sickness (AMS), as defined by the Lake Louise Consensus (1992 and updated in 2018). This condition may progress to high altitude cerebral oedema (HACE) with raised intracranial pressure, and/or high altitude pulmonary oedema (HAPE).[1] AMS is generally accepted to be an early part of the disease process leading to HACE, whereas HAPE is considered a separate diagnosis.

HAPE is the most frequent cause of death from high altitude illness, generally occurring above 2500m, with an incidence of 0,2 to 6% at 4500m and incidence ranges between 2 and 15% at 5500m, depending upon rate of ascent. The pathophysiology of HAPE relates to the abnormal accumulation of plasma and some red cells in the lung due to a breakdown in the pulmonary blood-gas barrier, triggered by hypobaric hypoxia. This breakdown develops from a number of maladaptive responses to the hypoxia encountered at higher altitudes, including poor ventilatory response, increased sympathetic tone, exaggerated and uneven pulmonary vasoconstriction (pulmonary hypertension), inadequate production of endothelial nitric oxide, and overproduction of endothelin, many of which are genetically determined. The end result is a patchy accumulation of extravascular fluid in the alveolar spaces that impairs respiration and can, in severe cases, prove fatal.[2]

The only effective prevention for AMS, HACE and HAPE is through acclimatization by gradual ascent. Mild AMS can be managed by halting ascent and allowing acclimatization, but severe AMS, HAPE or HACE is managed by supportive treatment and immediate descent to lower altitude.[3]

HAPE has traditionally been diagnosed in the wilderness on the basis of suggestive history, symptoms (dyspnoea at rest, cough, decreased exercise performance and chest tightness), and clinical findings (crackles or wheezing on auscultation, central cyanosis, tachypnoea and tachycardia). Importantly, these findings occur late in the disease process, and may be too late to allow the patient to return to a safe altitude without assistance. However, it is now well established that the onset of HAPE is preceded by increases in extravascular lung water

(EVLW) which are easily detected by the increasing number of sonographic artefacts known as 'lung comets' (also known as sonographic B-lines or comet tail artefacts) on lung ultrasound.[4-8] Results from Yang et al.[51] indicated that lung ultrasound is a reliable method for the diagnosis and surveillance of HAPE. A lung ultrasound is rapidly and non-invasively achieved in the field and has been described in several high-altitude studies.[9-10]

Early recognition of the initial signs of pulmonary oedema before the clinical onset of AMS or HAPE may allow prevention of the condition by allowing changes in the planned ascent profile, commencement of pharmacological prophylaxis, or earlier treatment.[10] Furthermore, sonographic evidence of pulmonary oedema could allow differentiation of HAPE from other conditions causing similar symptoms during an expedition to altitude (such as exhaustion, pneumonia, pneumothorax or pleural effusion).

Recent advances in technology have led to small, highly portable ultrasound machines which can be carried into alpine wilderness environments with little difficulty. The majority of high altitude field studies utilising lung ultrasound have used clinicians who are expert sonographers to perform the ultrasounds, although at least one study has examined the use of lung ultrasound by novices guided in real time using a sophisticated telemedicine system.[11] However, most expeditions do not have access to expert sonographers or real-time telemedicine systems. Fortunately, lung ultrasound is rapidly learnt by novices.[12] We seek to determine whether novices can adequately perform a simple lung ultrasound protocol to detect ultrasound lung comets in a high altitude expedition environment.

1.2 BACKGROUND

1.2.1 HIGH ALTITUDE PHYSIOLOGY

A basic understanding of high-altitude physiology is an essential aid in comprehending the contents of this study and the questions it seeks to answer. The following sections provide the reader with this background knowledge.

1.2.1.1 HYPOBARIC HYPOXIA

The partial pressure of oxygen (PO_2) is the driving force for the diffusion of oxygen down the oxygen cascade. Oxygen moves from inspired air to the alveolar space via the airways and then diffuses across the alveoli into the blood (Figure 1 and Figure 2), where it is carried mainly bound to haemoglobin but also in dissolved form. At the level of the capillaries, oxygen diffuses across vessel walls, through the tissues and into cells, and ultimately into the mitochondria.[60]

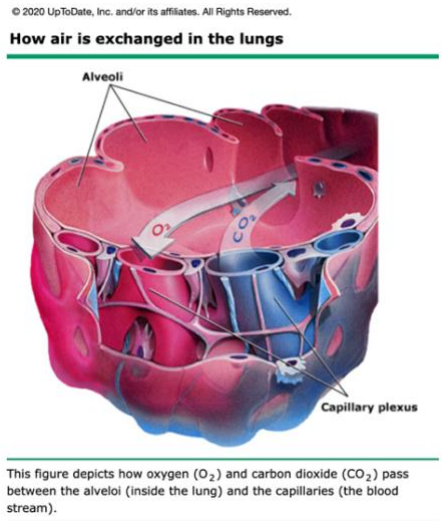


Figure 1: How air is exchanged in the lungs

(Anatomical Chart Co. Copyright © 2008 Lippincott Williams & Wilkins)

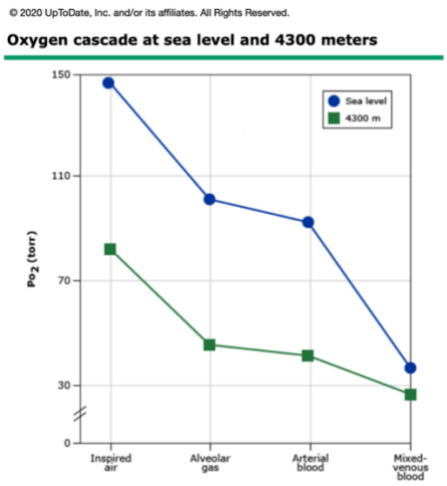


Figure 2: Oxygen cascade at sea level and 4300 meters

(McArdle WD, Katch FI, Katch VL. Exercise Physiology: Nutrition, Energy, and Human Performance, 8th ed, Lippincott Williams & Wilkins, Philadelphia 2014. Copyright © 2014 Lippincott Williams & Wilkins. www.lww.com)

The partial pressure of oxygen of inspired air (PiO2) is given by the equation: $PiO_2 = FiO_2 \times (P_b - 47\ mmHg)$, where FiO_2 is the fraction of oxygen in inspired air, P_b is the barometric pressure, and 47 mmHg is the vapor pressure of H_2O at 37°C. Inspired gas is 100 percent humidified by the time it reaches the alveoli and water vapor pressure is affected by temperature but, unlike other gases, is not dependent on altitude. The proportion of air comprised by oxygen (FiO_2, 20.94 percent) remains constant at the highest terrestrial elevations and even into the upper troposphere. Hence the PiO2 and, therefore, the oxygen cascade, are directly affected by barometric pressure.[61]

Barometric pressure and oxygenation diminish in an exponential fashion with increasing altitude (Table 1 and Table 2 and Table 3). Barometric pressure also decreases with lower temperature, higher latitude, inclement weather, and during winter. Although the effect of these variables upon barometric pressure is not nearly as significant as altitude, it becomes physiologically significant at elevations over approximately 2800m.[13]

Table 1: Acute effect of altitude on oxygen saturation and arterial blood gas values

Acute effect of altitude on oxygen saturation and arterial blood gas values

Population	Altitude (meters)	Altitude (feet)	P_B (mm Hg)	PaO_2 (mm Hg)	SaO_2 (%)	$PaCO_2$ (mm Hg)
Altitude residents	1646	5400	630	73 (65-83)	95.1 (93-97)	35.6 (30.7-41.8)
Acute exposure	2810	9219	543	60 (47.4-73.6)	91 (86.6-95.2)	33.9 (31.3-36.5)
	3660	12,008	489	47.6 (42.2-53)	84.5 (80.5-89)	29.5 (23.5-34.3)
	4700	15,420	429	44.6 (36.5-47.5)	78 (70.8-85)	27.1 (22.9-34)
	5340	17,520	401	43.1 (37.6-50.4)	76.2 (65.4-81.6)	25.7 (21.7-29.7)
	6140	20,144	356	35 (26.9-40.1)	65.6 (55.5-73)	22 (19.2-24.8)
Subacute exposure	6500	21,325	346	41.1 ± 3.3	75.2 ± 6	20 ± 2.8
	7000	22,966	324	–	–	–
	8000	26,247	284	36.6 ± 2.2	67.8 ± 5	12.5 ± 1.1
	8400	27,559	272	24.6 ± 5.3	54	13.3
	8848	29,029	253	30.3 ± 2.1	58 ± 4.5	11.2 ± 1.7
	8848	29,029	253	30.6 ± 1.4	–	11.9 ± 1.4

P_B: barometric pressure; $PaCO_2$: arterial partial pressure of carbon dioxide; PaO_2: arterial partial pressure of oxygen; SaO_2: arterial oxygen saturation.
* Data are mean values and (range) and were obtained in subjects 20 to 40 years of age during the first one to two days of arriving at altitude (acute exposure) and associated with good acclimatization (subacute exposure).

(Hackett PH, Roach RC. High-altitude medicine and physiology. In: Auerbach PS (Ed). Wilderness Medicine, 6th edition, Elsevier Mosby, Philadelphia, 2012)

Table 2: Physiologic effects of high altitude

Physiologic effects of high altitude

High altitude: 1500 to 3500 m (4921-11,483 ft)
High-altitude illness common with abrupt ascent to above 2500 m (8202 ft)
Decreased exercise performance and increased ventilation
Minor impairment in SpO_2, usually at least 90 percent; PaO_2 significantly diminished 55 to 75 mmHg
Very high altitude: 3500 to 5500 m (11,483-18,045 ft)
Most common range for severe high-altitude illness
Abrupt ascent may be dangerous; requires a period of acclimatization
SpO_2 75 to 85 percent; PaO_2 40 to 60 mmHg
Extreme hypoxia may occur during sleep, exercise and high-altitude illness
Extreme altitude: 5500 to 8850 m (18,045-29,035 ft)
Progressive deterioration of physiologic function eventually outstrips acclimatization
Above the highest permanent human habitation
Abrupt ascent almost always precipitates severe high-altitude illness
A period of acclimatization necessary to ascend to extreme altitude
Severe hypoxia and hypocapnia; SpO_2 58 to 75 percent, PaO_2 28 to 40 mmHg

SaO_2: arterial oxygen saturation; PaO_2: arterial PO_2; PO_2: partial pressure of oxygen.

(Hackett, PH, Roach, RC. High-Altitude Medicine. In: Wilderness Medicine, 5th ed, Auerbach, PS (Ed), Mosby, Philadelphia 2007)

Table 3: High altitude cities and peaks

High altitude cities and peaks

City	Altitude
The 10 highest cities in the world	
1. Lhasa, Tibet, China	12,002 ft./3658 m.
2. La Paz, Bolivia	11,910 ft./3630 m.
3. Cuzco, Peru	11,152 ft./3399 m.
4. Sucre, Bolivia	9331 ft./2844 m.
5. Quito, Ecuador	9249 ft./2819 m.
6. Toluca, Mexico	8793 ft./2680 m.
7. Bogotá, Colombia	8675 ft./2644 m.
8. Cochabamba, Bolivia	8390 ft./2557 m.
9. Addis Ababa, Ethiopia	7900 ft./2408 m.
10. Asmara, Eritrea	7789 ft./2374 m.
Some large cities at high altitude	
Mexico City	2240 meters
Johannesburg	1750 meters
Nairobi	1660 meters
Denver	1610 meters
Guatemala City	1530 meters

Peak	Altitude	Location
The Seven Summits		
Mount Everest	29,035 ft./8850 m.	Asia
Mount Kilimanjaro	19,563 ft./5963 m.	Africa
Mount McKinley	20,320 ft./6194 m.	North America
Puncak Jaya	16,023 ft./4884 m.	Australia/Oceania
Vinson Massif	16,066 ft./4897 m.	Antarctica
Mount Elbrus	18,510 ft./5642 m.	Europe
Aconcagua	22,841 ft./6962 m.	South America
8000m peaks		
Annapurna	26,545 ft./8091 m.	Nepal
Dhaulagiri	26,794 ft./8167 m.	Nepal
Mount Everest	29,035 ft./8850 m.	Nepal
K2	28,253 ft./8612 m.	Pakistan
Kangchenjunga	28,169 ft./8586 m.	Nepal
Lhotse	27,940 ft./8516 m.	Nepal
Makalu	27,765 ft./8462 m.	Nepal
Manaslu	26,758 ft./8156 m.	Nepal
Nanga Parbat	26,658 ft./8125 m.	Pakistan
Broad Peak	26,400 ft./8047 m.	Pakistan
Gasherbrum II	26,360 ft./8035 m.	Pakistan
Shisha Pangma	26,289 ft./8013 m.	Tibet
Gasherbrum	26,470 ft./8068 m.	Pakistan
Cho Oyu	26,906 ft./8201 m.	Nepal

ft: feet; m: meters.

(Gallagher, SA, Hackett, P, Rosen, J.M. 2019. High altitude illness: Physiology, risk factors, and general prevention. In J. Grayzel (Ed.), UpToDate.)

At sea level there is a large pressure gradient for oxygen between inspired air and tissue. However, as barometric pressure falls so does the available oxygen. At high altitudes, especially when tissue oxygen demands are high during athletic or work activities, the marked reduction in the pressure gradient and available oxygen can lead to tissue hypoxia. This form of hypoxia is termed hypobaric hypoxia, and it represents the initial cause of high altitude illness.[14]

1.2.1.2 ACCLIMATIZATION

1.2.1.2.1 OVERVIEW

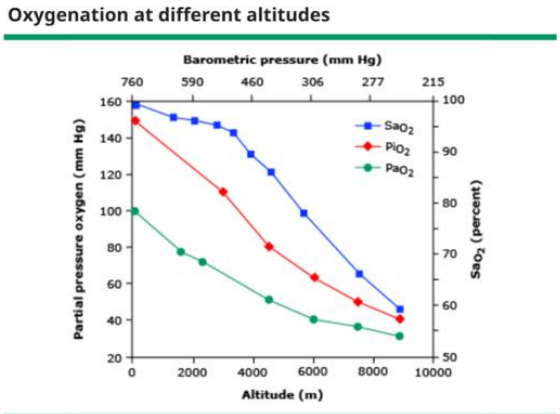
As PiO2 decreases with ascent, the driving pressure of PO_2 along the oxygen cascade diminishes, resulting in progressive hypoxemia and tissue hypoxia (Figure 3).[1, 15] The normal compensatory responses to acute hypobaric hypoxia are termed “acclimatization”; an

incompletely understood, complex series of physiologic changes involving multiple organ systems that occurs over varying periods (from minutes to weeks). Acclimatization improves tissue oxygenation by increasing alveolar PO_2 and the efficiency with which oxygen moves down the oxygen cascade, and by optimizing the utilization of oxygen at the cellular level.

Acclimatization differs from "adaptation," which refers to physiologic changes that take place in response to chronic exposure to hypobaric hypoxia over generations and are observed in some populations permanently situated at high altitude. It should be stressed that the capacity to acclimatize varies greatly among individuals and is dependent upon many factors, including the degree of hypoxic stress (rate of ascent, altitude attained), the intrinsic capacity of the individual to compensate for diminished PaO_2 (genetic and anatomic variation, medical conditions), and extrinsic factors, which may enhance or interfere with compensatory mechanisms (e.g., alcohol, medications, temperature).[16]

The process of acclimatization begins within minutes of ascent but requires several weeks to complete. Hypoxia-inducible factors (HIFs) are transcription factors that respond to decreases in available cellular oxygen. HIF-1-alpha regulates more than 3000 genes in response to hypoxia and plays a major role in activating the cellular mechanisms responsible for acclimatization. Other factors and genes are likely be involved as well.[17]

Although the complex compensatory changes that occur cannot fully restore tissue PO_2 to sea-level values, acclimatization can substantially improve oxygen delivery and utilization. In fact, acclimatization enables some climbers to function with only minor difficulty on the peak of Mount Everest (8848m) without supplemental oxygen.[15]



Increasing altitude results in a decrease in inspired oxygen (PiO_2), arterial oxygen$_2$ (PaO_2), and arterial oxygen saturation (SaO_2). Note that the difference between PiO_2 and PaO_2 narrows at high altitudes because of increased ventilation, and that SaO_2 is well maintained while awake until over 3000 meters.

Figure 3: Oxygenation at different altitudes

(Hackett, PH, Roach, RC. High-Altitude Medicine. In: Wilderness Medicine, 5th ed, Auerbach, PS (Ed), Mosby, Philadelphia 2007)

1.2.1.2.2 VENTILATION, ARTERIAL BLOOD GASES, AND RENAL COMPENSATION

The first and most important step in improving oxygen delivery is an increase in ventilation. Without increased ventilation, humans could not tolerate altitudes higher than 5000m.[1, 15]

Hypoxic stimulation of the peripheral chemoreceptors (in the carotid and aortic bodies) results in increased minute ventilation and is termed the hypoxic ventilatory response (HVR). HVR increases in sensitivity over several days spent at altitude. Overall, minute ventilation increases in a nearly linear fashion with diminishing SaO_2. The increase in ventilation raises alveolar PO_2 and lowers alveolar CO_2, resulting in a respiratory alkalosis. Ventilation reaches a maximum only after four to seven days at the same altitude, as renal compensation for the respiratory alkalosis takes place.[18]

HVR is genetically determined and quite variable among individuals. HVR is not influenced by athletic training but is affected by extrinsic factors, such as respiratory depressants (e.g., alcohol and sedative/hypnotics) and fragmented sleep. Conversely, respiratory stimulants (e.g., progesterone) and sympathomimetics (e.g., coca, caffeine) increase HVR.[19]

While one might assume that a brisk HVR would reduce the degree of hypoxemia and protect against acute mountain sickness (AMS), studies have failed to demonstrate this finding consistently. Some elite climbers, endurance athletes, and high altitude residents (Sherpas and Andean peoples) have low HVR and perform well at altitude. However, a low HVR is associated with an increased risk of HAPE, perhaps because it augments hypoxia-induced pulmonary vasoconstriction, leading to an exaggerated increase in pulmonary artery (PA) pressure.[13, 20]

As ventilation rises in response to hypoxia, $PaCO_2$ falls and pH rises. The central chemoreceptors in the medulla of the brain respond to alkalosis in the cerebral spinal fluid (CSF) by inhibiting ventilation, such that the full hypoxic ventilatory response is attenuated. While peripheral chemoreceptors are sensitive to changes in pH, central chemoreceptors play the major role in this response.

Partial renal compensation for respiratory alkalosis occurs within 24 to 48 hours of ascent as the kidneys excrete bicarbonate, decreasing the pH toward normal, and allowing ventilation to again increase as the alkalosis is reduced. Plasma bicarbonate concentration continues to

drop and ventilation to rise with further increases in altitude. Acetazolamide rapidly facilitates this process.[21]

1.2.1.2.3 CIRCULATORY CHANGES

Circulatory changes following ascent involve the systemic, cerebral, and pulmonary vasculatures. Following a rapid and sustained increase in altitude, increased sympathetic activity transiently increases cardiac output, blood pressure, heart rate, and venous tone. Heart rate remains elevated while stroke volume is diminished due to decreased plasma volume, which can drop as much as 12 percent over the first 24 hours from bicarbonate diuresis, fluid shift from the intravascular space, and suppression of aldosterone.[13] The reduction in plasma volume cannot be offset by increased fluid intake.

The cerebral vasculature is highly autoregulated in response to changes in both oxygen and CO_2. In the brain, oxygen delivery is dependent upon cerebral blood flow (CBF), which in turn depends upon a balance of vasodilation (in response to hypoxia), vasoconstriction (in response to hypocapnia), and changes in autoregulation. While there is considerable variation of cerebral autoregulation and cerebral blood flow among hypoxic individuals, oxygen delivery is generally maintained down to SpO_2 levels of 70 to 80 percent despite marked hypocapnia. Although hypocapnia attenuates hypoxic vasodilation, the net change in response to hypoxia is an increase in CBF. Individual variation in cerebral blood flow is linked to differences in ventilatory responses to hypoxia and hypocapnia. Despite mild regional brain tissue hypoxia revealed by near infrared spectroscopy, overall global cerebral metabolism is well-maintained during moderate hypoxia.[22]

The pulmonary vasculature constricts in response to hypoxia (Hypoxic Pulmonary Vasoconstriction (HPV)), resulting in prompt increases in pulmonary vascular resistance and pulmonary artery (PA) pressure. Increased flow to usually under-perfused areas may augment gas exchange by improving ventilation/perfusion matching. There is marked individual variation of HPV. An exaggerated increase in PA pressure and pulmonary vascular resistance (PVR) is associated with susceptibility to HAPE, as is markedly inconsistent vasoconstriction of pulmonary arterioles.[23]

Increased pulmonary vascular resistance and the accompanying increased pulmonary artery pressures cause a rise in the afterload of the right heart. Initial right ventricular and atrial dilatation due to increased right ventricular and right atrial pressures manifests as mild to moderate regurgitation, which is often detectable on echocardiography at altitude. With prolonged exposure, the eventual sequelae are pulmonary hypertension and right ventricular hypertrophy.

1.2.1.2.4 HEMATOLOGIC CHANGES

Increased haemoglobin concentration ([Hb]) is a well-known component of high altitude acclimatization. A modest increase in [Hb] is beneficial by increasing the oxygen-carrying capacity of blood.

In the first few days at altitude, [Hb] is increased due to plasma volume contraction. Within a few hours, hypoxemia stimulates increased production of erythropoietin from specialized renal cells, which increases the production of red blood cells (RBCs), resulting in an increased [Hb] within two to four weeks. Up to altitudes of approximately 4000m, this increase is sufficient to balance the reduction in oxygen saturation and restore the oxygen content of arterial blood to sea level values, although now at a lower PO_2.[24]

The oxyhaemoglobin dissociation curve (ODC) plays a crucial role in oxygen transport and delivery (Figure 4). Because of the sigmoid shape of the curve, arterial oxygen saturation (SpO_2) is well-maintained up to 3000 m, despite a significant decrease in arterial PO_2 (PaO_2). This correlates with an oxygen saturation of about 88 to 89 percent. Above that altitude, small changes in PaO_2 result in large changes in SpO_2.[25]

While SpO_2 is the major determinant of blood oxygen content, PaO_2 determines diffusion of oxygen from the capillary to the cell. Intraerythrocytic alkalosis causes a leftward shift of the ODC, but alkalosis is a major stimulus for the production of 2,3-DPG, which shifts the ODC rightward, back toward its normal position. This balance between alkalosis (left shift) and increased 2,3-DPG (right shift) is maintained until sojourners reach very high altitudes. There, the effect of the alkalosis far outstrips the capacity of the RBC to produce more 2,3-DPG, leading to a leftward shift of the ODC.[26]

As an example, in climbers at the summit of Mount Everest the $PaCO_2$ is 8 to 10 mmHg and the pH rises above 7.6. The resulting shift of the ODC to the left facilitates oxygen-haemoglobin binding in the lung, which results in an advantageous rise in SpO_2. Also, animals adapted to high altitude (e.g., yaks, llamas, and bar-headed geese) have left-shifted ODCs compared with their low-altitude counterparts.[26]

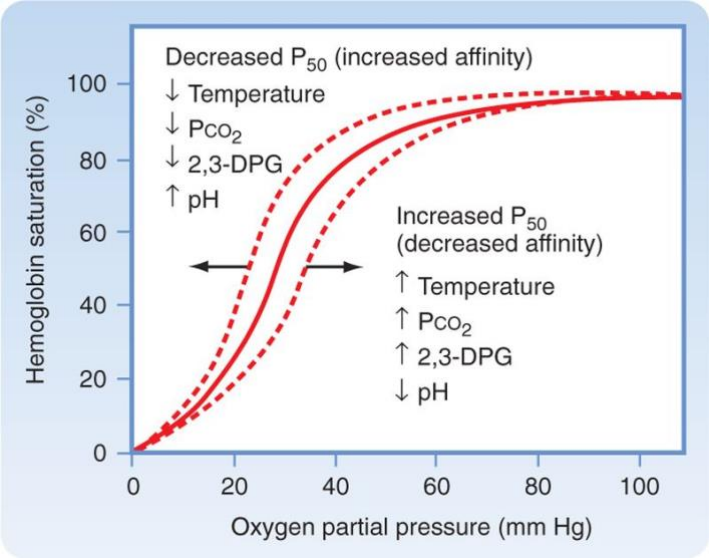


Figure 4: Oxyhaemoglobin dissociation curve

(Koeppen & Stanton: Berne and Levy Physiology, 6th Edition)

1.2.1.2.5 OXYGEN DELIVERY AND UTILIZATION

Diffusion of oxygen from the capillaries to the mitochondria and its subsequent use by these organelles constitutes the final step of the oxygen cascade. Diffusion distance from capillary wall to mitochondria is decreased at high altitude, mainly because of reduction in the diameter of muscle fibers which atrophy during high altitude expeditions. Edwards et al. revealed that there was a 4% decrease in calf muscle cross-sectional area in trekkers following a 14-day expedition to Everest Base Camp.[27] This atrophy occurs due to a net energy deficit and deconditioning effect.[28]

At the tissue level, HIF-1-a stimulates vascular endothelial growth factor (VEGF), which stimulates angiogenesis and nitric oxide synthesis. This results in greater blood flow and oxygen delivery to tissues. Improvements in oxidative metabolism and tissue gas exchange also occur.[29] Using serial measurement of plasma VEGF at 5200 m, following partial

acclimatisation at 3650 m, Dorward et al. demonstrated a highly significant change in VEGF levels ($p < 0.0005$) with a rise in VEGF in approximately 80% of subjects by day 7 at 5200 m.[30]

1.3 HIGH ALTITUDE – MEDICAL CONDITIONS

1.3.1 HIGH ALTITUDE ILLNESS

As increasing numbers of workers, recreational climbers and religious pilgrims ascend to high altitudes around the world, the ability to safeguard these individuals from the risks associated with the hypobaric stress of high-altitude environments become necessary. One of the most common and dangerous sequelae of high altitude is high altitude illness (HAI). High altitude illness (HAI) is the collective term for the unique cerebral and pulmonary syndromes that can occur following an initial ascent to high altitude (generally above 2000 to 2500 m) or following a further ascent while already at high altitude. HAI includes acute mountain sickness (AMS) and high altitude cerebral oedema (HACE), which afflict the brain, and high altitude pulmonary oedema (HAPE), which afflicts the lungs. They are induced by the hypoxic stress of high altitude and are characterized by extravascular fluid accumulation in the brain (AMS/HACE) and lungs (HAPE). All respond to descent, oxygen therapy, or both, if initiated promptly.[31]

The predictability of individual susceptibility to high altitude illness varies widely for reasons that remain largely unexplained. Currently no reliable and easily available physiologic markers are able to predict an individual's risk of developing HAI. It has been established that the following individual factors are associated with an increased risk of developing HAI:[32]

- Past history of HAI (strongly predictive if conditions similar)
- Rate of ascent
- Vigorous exertion at altitude before adequate acclimatization
- Lack of acclimatization
- Substances (e.g., alcohol) or conditions that interfere with acclimatization

- Comorbidities that interfere with respiration or circulation

Comorbid conditions that impair ventilation, respiration, or oxygen-carrying capacity increase the risk for HAI. Examples include neuromuscular disease, chronic obstructive pulmonary disease (COPD), restrictive lung disease, cystic fibrosis, pneumonia, pulmonary hypertension, carotid artery surgery or neck radiation that ablates the carotid bodies, and congenital cardiac anomalies involving right-to-left shunts.[33]

Some individuals seem to be predisposed to developing altitude illness, suggesting an innate contribution to susceptibility. Recent research has looked into the contribution of a genetic background to the efficacy of altitude acclimatization. To date, 58 genes have been investigated for a role in altitude illness. Of these, 17 have shown some association with the susceptibility to, or the severity of, these conditions. No study has demonstrated a clear-cut altitude illness gene, but the accumulating data are consistent with a polygenic condition with a strong environmental component. The genes that have shown an association affect a variety of biological pathways, suggesting that either multiple systems are involved in altitude pathophysiology or that gene–gene interactions play a role.[34]

1.3.2 ACUTE MOUNTAIN SICKNESS AND HIGH ALTITUDE CEREBRAL OEDEMA

Most experts consider AMS and HACE to represent different points of severity along the same pathophysiologic process in the brain. This process may collectively be referred to as AMS/HACE.

AMS is the most common form of high altitude illness and may occur following rapid ascent.[13] It is characterized by headache in combination with other nonspecific symptoms, such as malaise and anorexia.

HACE is the least common form of high altitude illness but is rapidly fatal without prompt recognition and treatment.

Two factors determine the risk of AMS:[35]

1. Rate of ascent, with rapid ascent within 48h being higher risk.

2. The altitude reached, with altitudes above 4500m being at highest risk.

Mountain peaks like Kilimanjaro present with one of the highest number of AMS cases per year when compared to other high-altitude peaks in the world.[36] Mount Kilimanjaro combines easy access with a financial imperative to ascend quickly as the significant national park fees induce climbers to ascend at rates of more than one thousand vertical meters per day. At 5895 m, Kilimanjaro is the world's tallest free standing mountain. This provides less opportunity for climbers to acclimatize before arriving at the park entrance because, unlike other high altitude destinations, travel to the start of the climb usually involves no prior altitude exposure. The ascent of Mount Kilimanjaro is generally not considered difficult amongst travellers to Tanzania. In 2007, 41,760 climbers may have attempted the summit.[36] Climbers on Mount Kilimanjaro are often naive to the risks of altitude exposure, demonstrated by the fact that only 10% of climbers on the mountain have previous high-altitude experience.[37] This combination of large numbers of inexperienced climbers and rapid ascents are major contributing factors to the high AMS incidence rate on Mount Kilimanjaro.[38]

1.3.3 HIGH ALTITUDE PULMONARY EDEMA

High altitude pulmonary oedema (HAPE) is a clinical diagnosis, due to the lack of diagnostic infrastructure in the situations where it is prevalent. It is diagnosed in the setting of a recent increase in altitude above 2500 m on the basis of the presence of at least two symptoms and two clinical signs. Symptoms of HAPE are dyspnea at rest, cough, weakness and/or decreased exercise performance, and chest tightness or congestion. Clinical signs include crackles or wheezing on auscultation in at least one lung field, central cyanosis, tachypnea and tachycardia. It is self-evident from these symptoms and signs that clinical diagnosis is only possible at an advanced stage of the disease, by which time the patient may be unable to descend to an altitude at which the syndrome is reversed.[39,40] However, it is well established that subclinical pulmonary interstitial edema develops well before the clinical manifestation of HAPE.[41] Fortunately, lung ultrasound is effective in detecting interstitial edema.

The clinical relevance of detecting subclinical pulmonary oedema at altitude should be mentioned. As shown by Pratali et al in 2011 and 2012, subclinical pulmonary oedema is

now an accepted phenomenon with altitude gain. Their 2011 Khumbu study showed that all eighteen climbers demonstrated subclinical oedema at 4750 m but only 3 were clinically diagnosed with HAPE. Furthermore, in a study conducted by the same researcher in 2012, the presence of subclinical pulmonary oedema was again found and in addition was associated with exercise limitation in patients with chronic mountain sickness (chronic mountain sickness is defined as a clinical syndrome that occurs in natives or lifelong altitude residents (>2500 m), and it is characterized by excessive erythrocytosis and severe hypoxemia.[42] Whether the acute, reversible increase in lung fluid content is an innocent and benign part of the adaptation to extreme physiological condition or rather the clinically relevant marker of an individual vulnerability to life-threatening pulmonary oedema remains to be established.[43]

These studies have thus demonstrated that Ultrasound Lung Comets (ULCs) are common at altitude in the absence of other classic features of HAPE.[4] It is therefore evident that the exact clinical significance (and the subsequent treatment) of detecting ULCs in a high altitude environment remains to be established, especially in view of ULC values for the prediction and diagnosis of HAPE still being unclear.

1.4 LAKE LOUISE SCORE

As no specific diagnostic or laboratory test for Acute Mountain Sickness exists, the diagnosis is made on the basis of symptoms and clinical signs. The 1991 International Hypoxia Symposium held at Lake Louise in Alberta established an AMS scoring system to assess the severity of disease. A diagnosis of AMS is based upon an increase in altitude above 2500 m within the preceding four days, presence of a headache, and a total score of ≥3 on a self-report questionnaire. The questionnaire grades headache, gastrointestinal symptoms, fatigue and/or weakness and dizziness/lightheadedness on a scale of 0 (absent) to 3 (incapacitating).

The updated 2018 Lake Louise Acute Mountain Sickness Score (Table 4) has removed the sleep component from the diagnostic criteria. Recent studies have shown that disturbed sleep at altitude, previously one of the five symptoms scored for AMS, is more likely due to altitude hypoxia per se, and is not closely related to AMS.[44] A score of 3 to 5 in the presence of recent ascent and headache is considered mild AMS, requiring cessation of ascent. A score of 6 to 9 indicates moderate AMS, while a score of 10 to 12 indicates severe

AMS requiring careful examination for signs of HACE (such as ataxia) or HAPE (such as breathlessness at rest or widespread crepitation on lung auscultation).

Table 4: 2018 Lake Louise acute mountain sickness score

2018 Lake Louise Acute Mountain Sickness Score

Headache
- 0—None at all
- 1—A mild headache
- 2—Moderate headache
- 3—Severe headache, incapacitating

Gastrointestinal symptoms
- 0—Good appetite
- 1—Poor appetite or nausea
- 2—Moderate nausea or vomiting
- 3—Severe nausea and vomiting, incapacitating

Fatigue and/or weakness
- 0—Not tired or weak
- 1—Mild fatigue/weakness
- 2—Moderate fatigue/weakness
- 3—Severe fatigue/weakness, incapacitating

Dizziness/light-headedness
- 0—No dizziness/light-headedness
- 1—Mild dizziness/light-headedness
- 2—Moderate dizziness/light-headedness
- 3—Severe dizziness/light-headedness, incapacitating

AMS Clinical Functional Score

Overall, if you had AMS symptoms, how did they affect your activities?
- 0—Not at all
- 1—Symptoms present, but did not force any change in activity or itinerary
- 2—My symptoms forced me to stop the ascent or to go down on my own power
- 3—Had to be evacuated to a lower altitude

(*Roach et al., 2018. The 2018 Lake Louise Acute Mountain Sickness Score. High altitude medicine & biology, 19(1), 4–6. https://doi.org/10.1089/ham.2017.0164)*

1.5 ULTRASOUND LUNG COMETS (ULCs)

Traditionally, the lung was considered a poor subject of sonographic examination, as ultrasound is intensely reflected by a tissue-air or fluid-air interface. However, more than a decade ago, the usefulness of sonographic artefacts due to increased extravascular lung water (EVLW) was identified.[5-8] This has been extensively correlated with clinical and radiological findings and is both sensitive and specific for pulmonary oedema.[7] The 'comet-tail' artefact, also known as the sonographic B-line or ultrasound lung comet (ULC) is key to this process (Figure 5). This is described as one or many hyperechoic lines fanning out from the pleural interface and is believed to originate from water-thickened interlobular septa due to increased EVLW. It is conceptually equated with the radiological Kerley B-line, which are small, horizontal, peripheral straight lines demonstrated at the lung bases that represent thickened interlobular septa on a chest x-ray. This may be because of lymphatic engorgement or oedema of the connective tissues of the interlobular septa. They usually occur when pulmonary capillary wedge pressure reaches 20-25 mmHg.

An increasing total number of ULCs obtained by the sum of each sonographic view is associated with increasing lung edema in a linear relationship.[6] It is important to note, however, that at the time of data collection for this study, it was still not known what number of ULCs were diagnostic for HAPE as opposed to the presence of subclinical edema.

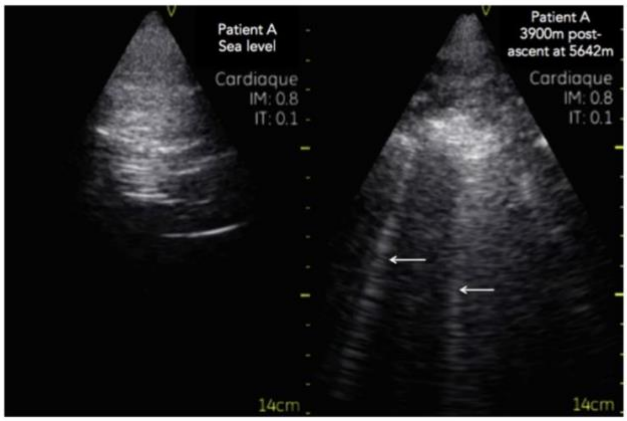


Figure 5: Ultrasound lung comets

Two lung ultrasound images from the same expedition member at 160m AMSL in Moscow (left) and 3900m AMSL on Mount Elbrus after returning from the 5642m summit (right). In the high-altitude image, two ultrasound lung comets (ULCs) can be seen, indicated by the arrows.

(Page et al., 2015)

Numerous studies have shown a progressive increase in ULC counts with increasing exposure to hypobaric hypoxia due to increases in altitude.[45,10]

It has been well established that development of pulmonary interstitial oedema always precedes onset of pulmonary alveolar oedema.[5] ULCs are detectable at a very early stage in the development of pulmonary oedema, as they are a sensitive test for interstitial oedema.[6] Detection of ULCs may be of particular value in the high altitude expedition context, and could in the future be used to guide intervention before onset of clinically relevant HAPE, once their exact clinical significance and proven predictive values become more clear.

1.6 AIMS AND OBJECTIVES

The primary aim of this study is to establish whether a novice sonographer can perform effective assessment of lung ultrasound comet scores in comparison to an experienced sonographer in a high-altitude environment. An acceptable limit of agreement of 4 lung comets were identified *a priori*. This value was established based on the work done by Volpicelli et al. in 2006 who defined a positive lung ultrasound test as having at least 3 lung comets present at the time of examination.[49]

The secondary aim is the interpretation of various physiological and clinical parameters (including saturation, heart rate and Lake Louise Score Questionnaire) at different altitudes, ranging from 950 to 4662 meters above sea level, and whether this is clinically significant.

Chapter 2

METHODS

2.1 STUDY DESIGN

The study was conducted as a prospective, blinded, observational study. The study recorded daily lung comet scores by both an experienced and a novice sonographer using a standardized protocol. The two sonographers were blinded to each other's findings during the data collection.

2.2 SETTING AND PARTICIPANTS

This study took place during a financial institution's staff expedition to Mount Kilimanjaro in Tanzania. This was an 8-day expedition from the 5th to the 13th of October 2018. Twenty-five individuals and one expedition doctor spent two nights in the town of Moshi (950 m), before starting the climb (7 October 2018) to Uhuru Peak (5895 m) on Kilimanjaro over 6 days using the Umbwe Route. The group was also accompanied by staff from a tour operating company which included experienced porters and mountain guides with mountain medicine training. All members of the expedition were invited to participate. A training session on the standardized lung ultrasound protocol was held during the time spent at Moshi, prior to the start of the climb.

This research protocol was approved by the Health Sciences Research Ethics Committee of the University of Cape Town (Reference number: 045/2016). Written informed consent was obtained from all participants prior to commencement of the research study. This research trial strictly followed the principles of good clinical practice and ethical conduct as delineated in the Declaration of Helsinki (2013).

2.3 INTERVENTION

Of the 25 individuals on the expedition, 10 participants were identified to enroll in the study. Of this group, 6 were male and 4 were female with an age distribution ranging from 35 to 60 (mean 45.2, SD 9.163). All participants were previously healthy with no previous history of HAI. The study size of 10 allowed daily scans to be completed on all individuals before depletion of the portable ultrasound machine battery. Participants undertook daily Lake Louise Scores, fingertip pulse oximeter readings and heart rates as part of the safety and clinical monitoring program on the mountain. Daily lung ultrasounds were performed according to a standardized 8-zone protocol.[4,10,46] One experienced sonographer scanned each participant, with his score then used as the "gold standard" for comparison. A member of the expedition group was identified and acted as the novice sonographer. This person was not a medical doctor and had no prior ultrasound experience and received training at Moshi one day before the start of the climb. The expedition medical doctor acted as the experienced sonographer, having received appropriate and adequate skills training. The two sonographers were blinded to each other's findings during the data collection.

2.4 EXCLUSION CRITERIA

All expedition participants were screened prior to the expedition and any significant underlying medical conditions were excluded which would preclude high altitude trekking. The use of acetazolamide as prophylaxis to aid acclimatization did not constitute an exclusion criterion and was used by the majority of the expedition members, including all 10 participants that enrolled in this study. One participant had an incomplete dataset as they were only excluded from data collection on 11/10/2018 at 3800 m during the descent, due to early evacuation off the mountain for suspected heat exhaustion. Where statistically appropriate, this individual's data was omitted from the data analysis in order to prevent non-compliance with the assumptions of the chosen statistical test, to maintain validity and accuracy of the results.

2.5 DATA COLLECTION

2.5.1 GENERAL MEASURES

Data collection on the mountain was completed on a daily basis between 16:00 and 18:00 (after arrival at the camp site following the day's trek), with the exact altitude at the time of measurement being recorded. This resulted in 7 data sets per participant at varying altitudes: 950 m (6/10/2018: hotel, Moshi); 2944 m (7/10/2018: Umbwe Cave Camp); 3986 m (8/10/2018: Barranco Camp); 4034 m (9/10/2018: Karanga Camp); 4662 m (10/10/2018: Barafu Camp); 3800 m (11/10/2018: Millennium Camp); 950 m (12/10/2018: hotel, Moshi). All participants were protected from environmental exposure with ultrasound examinations being done in a tent or screened area to preserve privacy and dignity.

2.5.2 SPECIFIC MEASURES

Participant Lake Louise Scores, resting heart rates and fingertip pulse oximetry measurements (Contec CMS50D (Contec, USA)) were recorded concurrently with sonographic examinations. These variables are regularly assessed as part of the standard high-altitude expedition precautions and form part of the routine care provided to members of the expedition party

2.5.2.1 LAKE LOUISE SCORE

Daily Lake Louise Scores were performed on all participants (n = 10). The Lake Louise Scoring System (LLSS), as explained previously, was designed to evaluate adults for symptoms of acute mountain sickness (AMS). The system uses an assessment questionnaire and a scorecard to determine whether an individual has mild, moderate or severe AMS. The Lake Louise AMS score for an individual is the sum of the score for the four symptoms (headache, nausea/vomiting, fatigue, and dizziness/light-headedness). For a positive AMS definition, it is mandatory to have a headache score of at least one point, and a total score of at least three points (Table 4).[44]

2.5.2.2 RESTING HEART RATE

Daily heart rate recordings were performed using a fingertip pulse oximeter (Contec CMS50D (Contec, USA)). The accuracy of this model has been established by the work done by Smith et al. in 2018.[58] A 30-minute resting period was provided at the end of each day's hike prior to data collection to minimize the effect of exercise and exertion on resting heart rate values.

Heart rate data is represented as a percentage of maximum heart rate. This was done to accommodate for the effect of age on absolute heart rate values. Predicted maximum heart rates were calculated with the following formula: 220 – age.[59]

2.5.2.3 PULSE OXIMETRY

Pulse oximetry readings were concurrently recorded with resting heart rate values using the same pulse oximeter as mentioned above by placing the participant's index finger within the placement area of the meter for a minimum duration of 30 seconds.

2.5.2.4 ULTRASOUND RECORDINGS

Daily lung ultrasounds were performed according to a standardized 8-zone protocol (Figure 6)[47] for 7 consecutive days. This was achieved using the *Vscan™ with Dual Probe* from *General Electric Healthcare* (2014 model). This battery powered portable ultrasound machine allowed clear visualization of lung comets, as previously described. Battery capacity allowed 10 participants to be screened daily. Solar power was used to recharge the battery after the daily examinations.

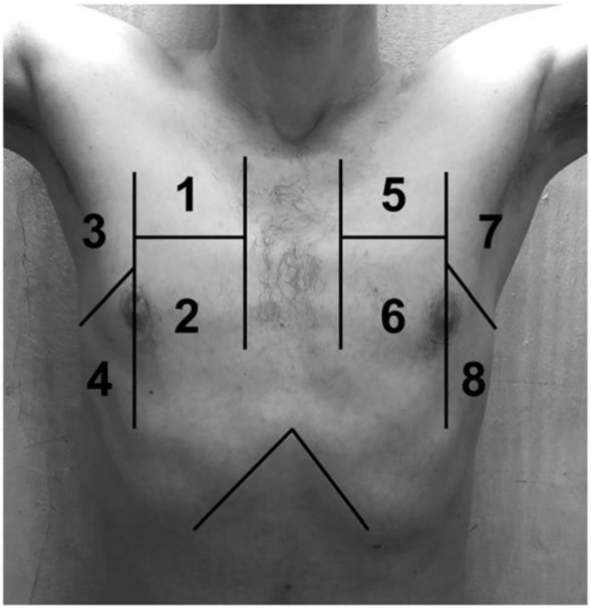


Figure 6: 8-zone ultrasound protocol

(Brainin et al., 2020)

Each participant was scanned by an experienced ultrasonographer followed by a novice ultrasonographer with the results being unknown to each other during data collection. All 8 lung zones were systematically scanned with the number of visible lung comets in each zone documented. The sequence of each scan remained the same with the order being: Left lung: 1) Anterior superior; 2) Anterior inferior; 3) Lateral superior; 4) Lateral inferior; Right lung: 5) Anterior superior; 6) Anterior inferior; 7) Lateral superior; 8) Lateral inferior. Participants were scanned in the sitting position.

2.6 STATISTICAL ANALYSIS

2.6.1 ULTRASOUND DATA

Lung comet scores between the expert and novice ultrasonographer were compared using an explanatory Bland-Altman analysis. Comparison between total number of lung comets over time / altitude were analysed using Friedman's test.

2.6.2 PHYSIOLOGICAL PARAMETERS

While data were normally distributed, due to the small sample size, non-parametric data analyses were applied. Physiological parameters measured over time (and hence altitude) were analysed using Friedman's test, with differences in specific time points determined by means of the post hoc analysis (i.e. Dunn's multiple comparisons test). The Mann-Whitney test was utilized to compare sex based differences. Data were analyzed with IBM® SPSS® Statistics Version 27. Statistical significance was accepted as $p < 0.05$.

Statistical analyses were performed by Doctor F. Wilhelm Vogts, Associate Professor Ross Hofmeyr and Doctor Caroline D'Alton.

Chapter 3

RESULTS

3.1 ULTRASOUND DATA

3.1.1 COMPARISON BETWEEN EXPERT AND NOVICE ULTRASONOGRAPHER

An exploratory Bland-Altman analysis comparing expert versus novice lung comet scores was performed, taking into account the modest sample size for this method (69 paired recordings). Compared to experts, novices showed little bias (mean difference 0,2 comets, 95% CI -0,2 to 0,6) with upper and lower limits of agreement (95% CI) of 3,2 (2,5 to 3,8) and -2,8 (-3,4 to -2,2) respectively. Thus, novice total comet scores typically fell within a range of approximately 3 above and below the expert score (Figure 7).

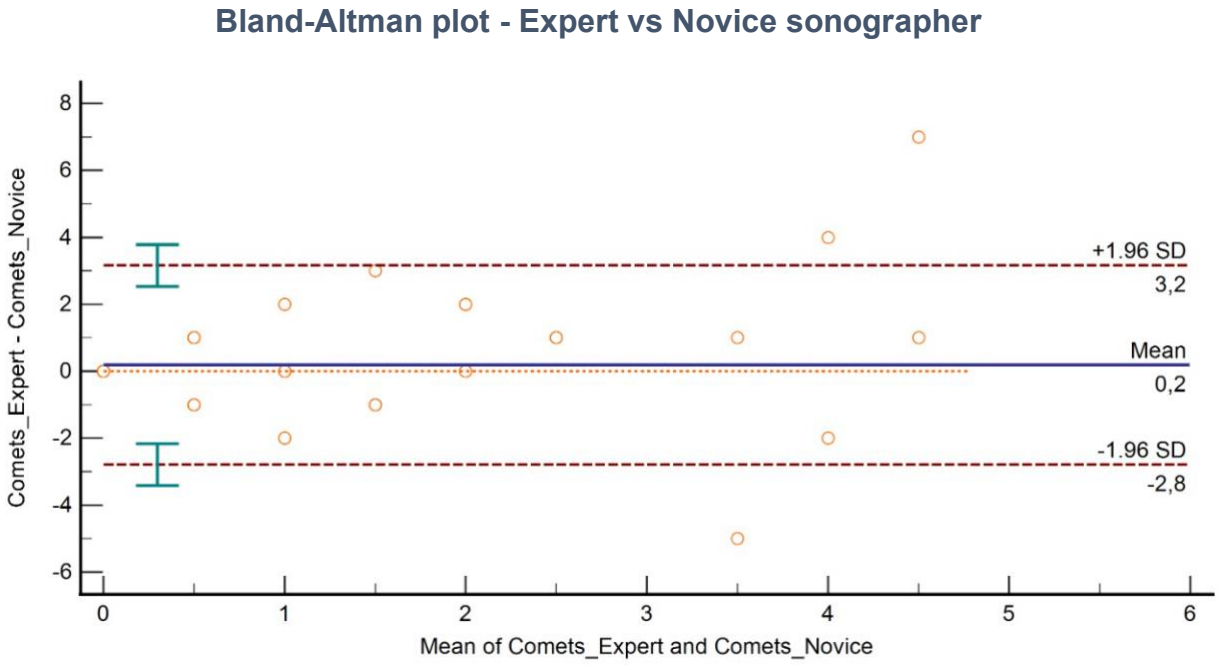


Figure 7: Bland-Altman plot - Expert vs Novice sonographer

3.1.2 DESCRIPTIVE

Total cumulative lung comets for all participants at varying altitudes are depicted in Figure 8 (expert and novice sonographer). The highest number of comets (i.e. 19 lung comets) were observed by the expert sonographer at 4034 m above sea level. Figure 9 and 10 respectively indicates the median (IQR) lung comets and scatter plot of all recorded lung comet values at varying altitudes (expert sonographer). There was a statistically significant difference in the total number of lung comets across the 7 recorded altitude points, χ^2 (6) = 22.05, $p < 0.01$, as measured by the expert ultrasonographer.

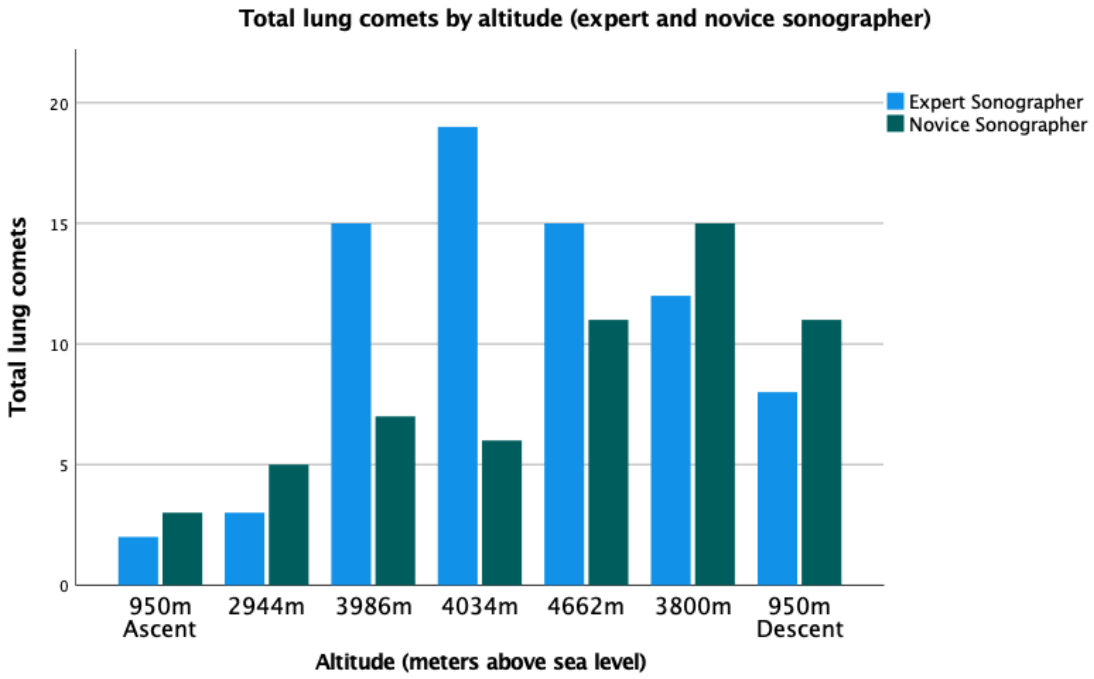


Figure 8: Total lung comets by altitude (expert and novice sonographer)

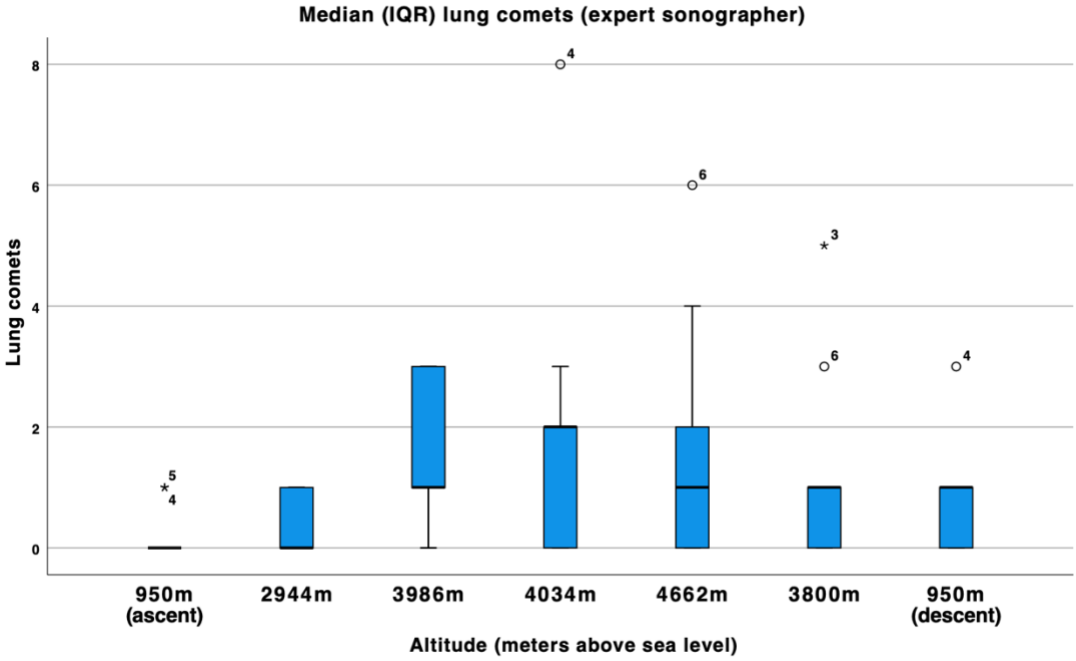


Figure 9: Median (IQR) lung comets by altitude (expert sonographer)

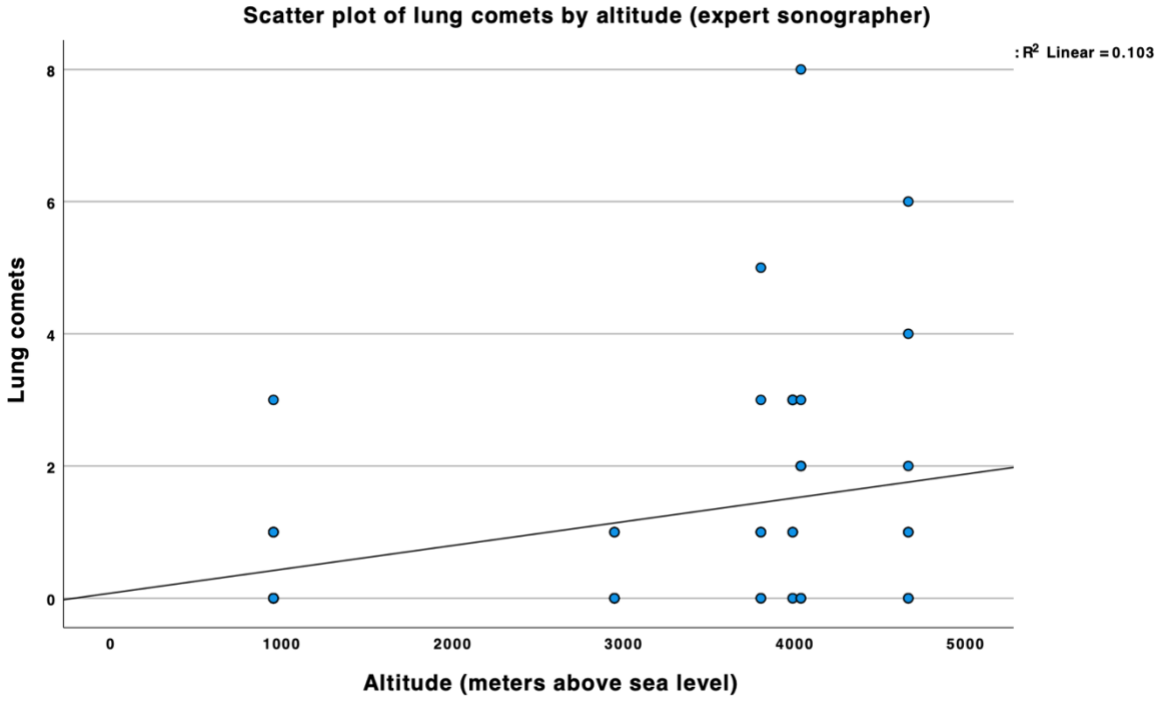


Figure 10: All recorded lung comet values by altitude (expert sonographer)

3.2 PHYSIOLOGICAL PARAMETERS

3.2.1 OXYGEN SATURATION

There was a statistically significant difference in saturation percentages across the 7 recorded altitude points, χ^2 (6) = 33.22, $p < 0.001$, with oxygen saturations decreasing with increasing altitudes and with the lowest saturation values recorded at altitudes greater than 3900 m (refer table 5).

Significant changes in oxygen saturations with changing altitudes were shown between the lowest recorded altitude at 950 m and the higher altitudes i.e. 3986 m ($p < 0.005$), 4034 m ($p < 0.005$) and 4662 m ($p < 0.05$) respectively. These significant differences were evident during both the ascent and descent legs of the expedition.

Median and interquartile range (IQR) oxygen saturation percentages at each recorded altitude are depicted in Figure 11 with statistically significant differences between specific altitude points as indicated on the graph. Median oxygen saturations remained very similar at 950 m for both the ascent and descent. (i.e. 95% vs 96% respectively) (Figure 11).

Table 5: Oxygen saturation percentages

Oxygen saturation percentages

	N	Minimum	Maximum	Percentiles 25th	50th (Median)	75th
Sats 950m (ascent)	9	92	99	92.00	95.00	97.50
Sats 2944m	9	85	99	86.50	88.00	94.00
Sats 3986m	9	78	91	84.00	86.00	89.50
Sats 4034m	9	76	91	80.00	87.00	89.00
Sats 4662m	9	81	91	81.50	86.00	89.00
Sats 3800m	9	79	93	88.50	90.00	92.50
Sats 950m (descent)	9	88	99	94.00	96.00	97.00

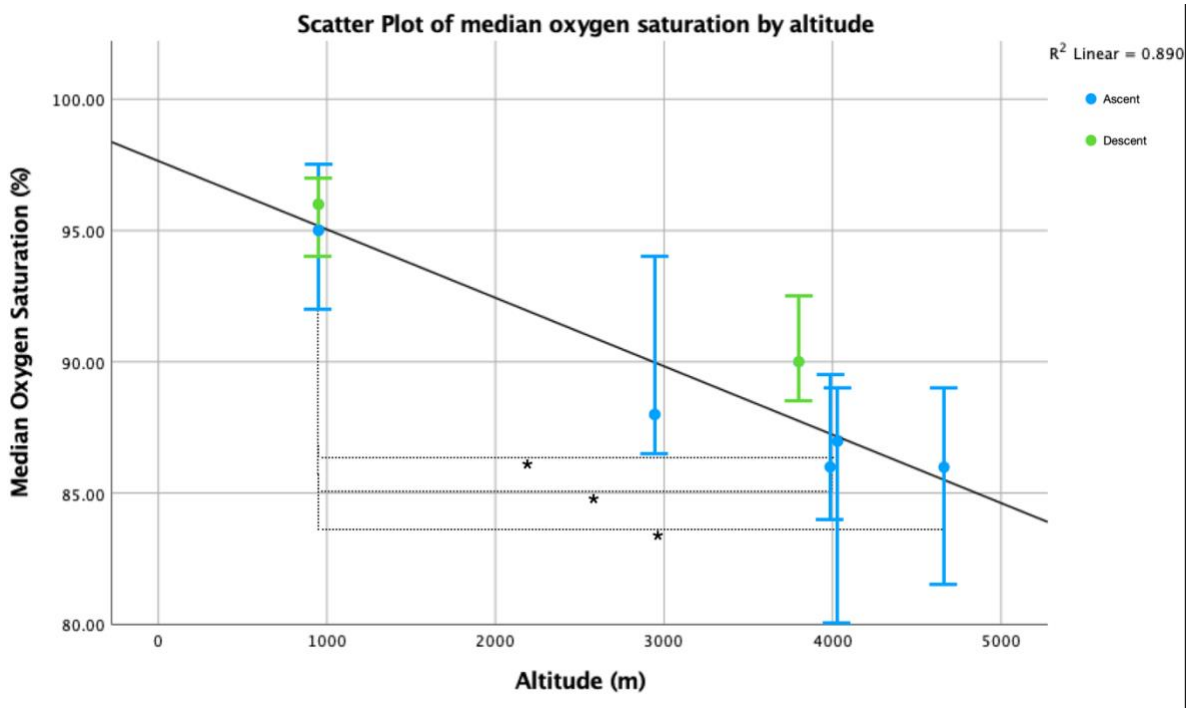


Figure 11: Median (IQR) oxygen saturation by altitude

($p < 0.01$)*

While oxygen saturations decreased with increasing altitudes, median oxygen saturation percentages varied between males and females at different altitudes.

3.2.2 HEART RATE

There was an overall statistically significant difference between recorded heart rates (as percentage of maximum heart rate) across the 7 recorded altitude points, χ^2 (6) = 12.83, p = 0.0458, with heart rates increasing in comparison to the first recording at 950 m above sea level.

Median (IQR) heart rates (as percentage of maximum heart rate) are depicted in Figure 12. While not statistically significant when compared to the first %HR measure at the starting altitude of 950 m, it was interesting to note that the greatest median percentage increase in HR was observed once back in the town of Moshi at 950 m above sea level following descent (in spite of very similar oxygen saturations recorded for both these time points).

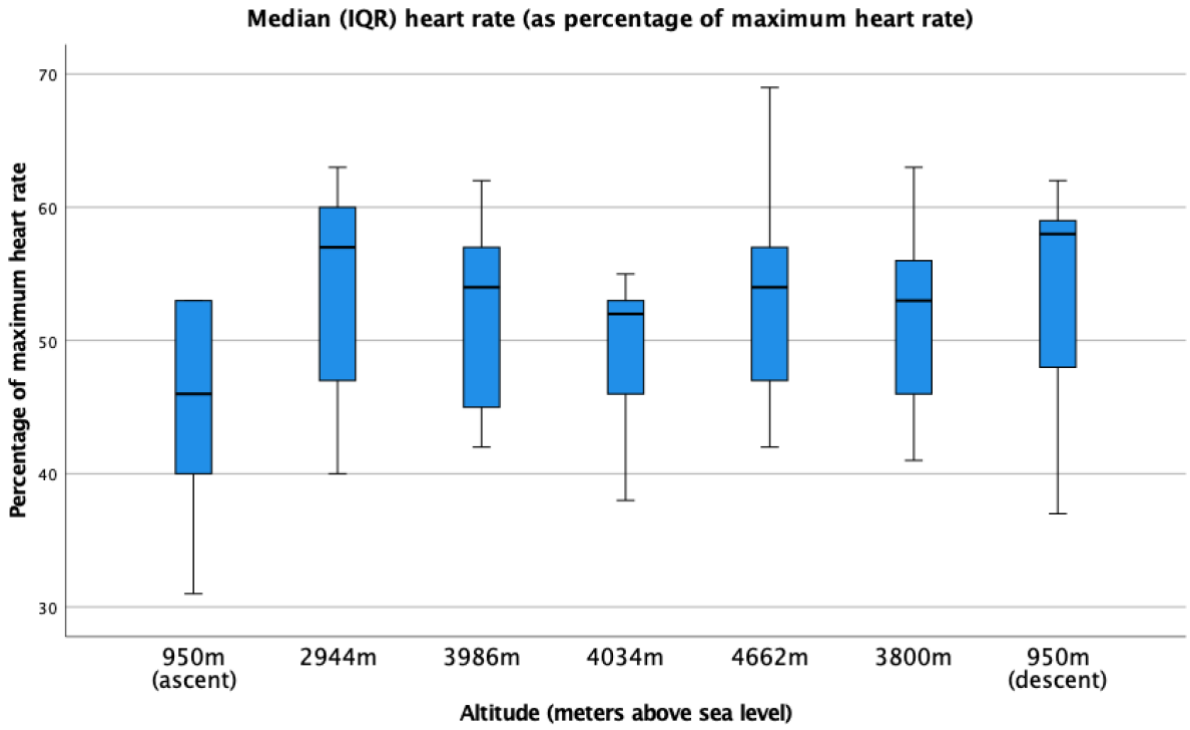


Figure 12: Median (IQR) heart rate (as percentage of maximum heart rate)

Similar to oxygen saturations, actual differences of median heart rates (as percentage of maximum heart rate), although a very small sample, varied between males and females. While not statistically significant, these observed differences could be more robustly tested in a larger data set.

3.2.3 LAKE LOUISE SCORE

There was an overall statistically significant difference between Lake Louise scores across the 7 recorded altitude points, χ^2 (6) = 30.59, $p < 0.001$. The highest Lake Louise scores were recorded at 3800 m during the descent (Table 6).

Table 6: Lake Louise scores

LLSQ

	N	Minimum	Maximum	Percentiles 25th	50th (Median)	75th
LLSQ 950m (ascent)	9	0	0	.00	.00	.00
LLSQ 2944m	9	0	2	.00	1.00	1.00
LLSQ 3986m	9	0	2	.00	.00	2.00
LLSQ 4034m	9	0	1	.00	1.00	1.00
LLSQ 4662m	9	0	1	.00	.00	1.00
LLSQ 3800m	9	0	4	2.00	2.00	3.00
LLSQ 950m (descent)	9	0	2	.00	.00	.00

Median Lake Louise scores differed statistically significantly between the following recorded altitude points: 950 m (during the ascent) (0 points) and 3800 m (2 points) ($p < 0.01$); 3800 m (2 points) and 950 m (during the descent) (0 points) ($p < 0.05$).

While females recorded higher median Lake Louise scores than males at all altitudes (except at 950 m during the ascent and descent where males and females were equal), these differences did not prove to be statistically significant, but again a larger sample size would be of value.

Chapter 4

DISCUSSION

The main finding of this study established that a novice sonographer was able to perform effective assessment of lung ultrasound comet scores (as defined by an acceptable limit of agreement of 4 lung comets) in comparison to an experienced sonographer. This was in keeping with the work done by Chiem et al. in 2015 who concluded that novice sonographers (emergency medicine resident physicians) could identify sonographic B-lines with similar accuracy compared to an expert sonographer in patients with acute heart failure syndrome.[48] Key differences to note is that our study was the first of its kind to be conducted in a high-altitude environment and that the novice ultrasonographer in our research had no prior medical training or background.

Novice total comet scores typically fell within a range of approximately 3 above and below the expert score. An acceptable limit of agreement of 4 lung comets were identified *a priori*. This value was established based on the work done by Volpicelli et al. in 2006 who defined a positive lung ultrasound test as having at least 3 lung comets present at the time of examination.[49] Using this cut-off value as reference, our results fall within the acceptable degree of error.

While the exact clinical significance of the presence of lung comets at altitude remain to be fully elucidated,[4] if found to be a valuable screening method to identify those at risk of developing HAPE or AMS during expeditions at altitude, being able to rely on relatively novice ultrasonographers may ultimately lead to better medical care of adventurers. It is already well recognized that early intervention for those suffering from altitude-related illnesses results in better outcomes.[50]

However, when interpreting these results, it has to be taken into consideration that the modest sample size for this comparison (69 paired recordings) and the small number of comets visualized advocates for future studies to be undertaken where a larger sample size can support this finding.

Despite the presence of lung comets in the participants of this study, none developed HAPE during the course of the expedition. Yang et al determined that the best critical value for the diagnosis of HAPE was the visualization of a minimum of 6.5 lung comets on an ultrasound examination.[51] In the majority of participants in our study, observed lung comets did not exceed this critical value of 6.5 (median value of comet scores for the participants' on this expedition were highest at 4034 m above sea level, i.e. 2 lung comets). This may support why none developed the clinical symptoms of HAPE. However, it is interesting to note that a total lung comet score of 8 was observed in one individual at 4034 m (expert sonographer). Despite this value being greater than the best critical value of 6.5, the participant had no other clinical signs or symptoms of HAPE and was allowed to continue with the expedition with no adverse events. This once again emphasizes the importance of taking all signs and symptoms into account when diagnosing HAPE instead of solely relying on an absolute lung comet value.

Although an increase in altitude corresponded with a decrease in saturation and a higher number of lung comets (expert sonographer), there was no clear correlation between median lung comets and saturation percentages observed at varying altitudes in our study. This is in contrast to the findings of Fagenholz et al. in 2007 where regression analysis showed comet-tail scores were predictive of oxygen saturation ($p < 0.001$), and for every 1-point increase in comet-tail scores, oxygen saturation fell by 0.67% (95% confidence interval, 0.41 to 0.93%, $p < 0.001$). Possible explanations for this discrepancy could be related to 1.) the small sample size and 2.) the fact that the majority of participants in the above mentioned study were clinically diagnosed with HAPE prior to undergoing lung ultrasound. A relatively high number of lung comets with lower than normal saturation levels were observed in these patients. In our setting, a smaller number of lung comets were observed in patients who did not develop HAPE during any point of the expedition.

It has to be noted that lung comets are not only a sign of pulmonary oedema but also a sign of interstitial pneumonia and severe pulmonary fibrosis, which may generate diffuse intensive lung comets. Therefore, when interpreting their significance, LUS should be integrated with other clinical information, including symptoms, physical signs, and medical history. In fact, nearly all routine diagnostic methods need to be interpreted with other clinical information to arrive at the correct diagnosis. Even typical X-ray signs can lead to a misdiagnosis of HAPE if the findings are not integrated with other medical information including physiological parameters..[51]

The physiological findings of this study support previously documented responses to altitude. Firstly, a decrease in median oxygen saturation levels with increasing altitude were demonstrated in this study. This is in keeping with the findings of Lorente-Aznar et al. where a decrease in arterial oxygen saturations were observed with acute and subacute altitude exposure caused by a decrease in barometric pressure and a subsequent decrease in the arterial partial pressure of oxygen.[52] It is interesting to compare the median saturation percentages for participants in our study with the values obtained by the predictive arterial oxygen saturation equation developed by Lorente-Aznar et al. in 2016 (i.e. Blood Oxygen Saturation = 103.3 – (altitude ×0.0047) + (Z), with (Z)=0.7 in men and 1.4 in women, respectively).[52] All median saturation values for participants were equal to or higher than the predicted values calculated by the aforementioned equation (except at 950 m during the ascent and descent). The ability of participants to maintain higher saturation percentages than predicted could be a possible contributing factor to the reason that none of the participants in our study developed AMS as exaggerated hypoxemia in asymptomatic climbers prior to further ascent has been found to correlate with subsequent AMS.[53]

While the sample size was quite small and comparison results are viewed with caution, sex does not seem to play a role when comparing saturation levels of males against females at different altitude points. This result is in keeping with the findings of Botek et al which showed that there were no significant differences in saturation percentages during hypoxia between males and females in a simulated altitude environment.[54]

It is interesting to note the difference in median %HR at the starting altitude of 950 m above sea level when compared with the final day of the expedition at the same altitude (46% vs 58% respectively), with the final day in fact representing the highest %HR for the entire expedition. This is despite similar baseline oxygen saturation values recorded . While it is possible that fatigue, fluid status and temperature may play a contributing role, this phenomenon might be explained by the findings of Attias et al in 2017 where they postulated that a persistent increased heart rate associated with high-altitude exposure and acclimatization is caused by cardiac parasympathetic withdrawal. This was concluded to be the dominating cardio-acceleratory mechanism, owing to the finding that an increased heart rate was persistent when β -adrenergic, but not when muscarinic receptors were inhibited.[55]

Furthermore, the highest median Lake Louise scores were recorded at 3800 m during the descent which is a significant increase when compared to Lake Louise Scores measured at

950 m. It is thought-provoking to note that the highest Lake Louise Scores occurred during the descent as opposed to any other altitude during the ascent or even the highest recorded altitude of 4662 m. The rationale for this distribution has been debated extensively in the literature. In our setting the most likely reason for this relates to the relatively high fatigue scores recorded by participants. This can be explained by the fact that the recordings done at Millennium Camp (3800 m) were preceded by the longest and most challenging trekking session of the expedition – i.e. starting the summit attempt from base camp at midnight (4662 m) and then subsequently descending down to 3800 m in one session. The short duration of ascent to the summit followed by immediate descent may also result in symptoms which are slow to develop only manifesting or being measured after the participants have descended during the course of the summit day. Despite these higher scores, none of the participants were diagnosed with AMS. The specificity of the Lake Louise scoring system has been questioned by previous authors. The findings by Moore et al. supported the recent removal of sleep quality from the LLS, but also demonstrated that fatigue had an equal part to play in the misdiagnosis of AMS. These data highlighted the poor specificity of the LLS and suggest that the measurement of illness at altitude undergo further review.[56]

Though again not statistically significant, it is interesting to note that females recorded higher median Lake Louise scores than males at all altitudes (except at 950 m during the ascent and descent where males and females were equal). A meta-analysis to determine sex-based differences in the prevalence of AMS using the Lake Louise Scoring System revealed that Acute Mountain Sickness was more common in women than men (*RR* = 1.24, 95% CI 1.09–1.41).[57] This finding could be a possible explanation for the sex distribution of Lake Louise scores in our study, although again we acknowledge the small sample size and interpret the findings with caution. The pathological mechanism behind this apparent female predisposition has yet to be established.

On a clinical note, while the participants of this study demonstrated expected physiological changes to exposure to exercise at altitude, the fact that none developed severe forms of AMS or HAPE might be attributed to the implementation of preventative measures during the expedition. This included a gradual ascent profile, daily clinical monitoring, adequate education to all expedition members regarding the early symptoms and signs of AMS and HAPE, the avoidance of sedative-hypnotics and moderate to heavy alcohol intake, the maintenance of sufficient hydration levels and the use of acetazolamide to aid acclimatization.

One participant was diagnosed with heat exhaustion during the descent on the sixth day of the expedition. He was safely evacuated and responded rapidly to medical care. Clinical signs and symptoms were in keeping with heat-related illness and were not related to AMS or other altitude-related illness.

Limitations of this study include a small sample size that was dictated by the restricted battery life of the portable ultrasound machine. Battery capacity was especially influenced by the cold environment experienced in a high-altitude setting.

Chapter 5

SUMMARY AND CONCLUSIONS

Our findings conclude that a novice sonographer can perform an effective lung ultrasound (as defined by an acceptable limit of agreement of 4 lung comets) and identify lung comets when compared to an experienced sonographer in a high-altitude environment. Although further studies with a larger sample size are warranted to confirm these results, the preliminary findings of this research project advocates for the inclusion of a portable ultrasound machine in a wilderness expedition kit as a potentially useful diagnostic tool.

It is clear that complex interactions exist between the external environment and the various organ systems in an attempt to maintain physiological homeostasis at increasing altitudes. The recording and analysis of physiological parameters in this study contribute to the growing pool of literature with the aim to comprehend and fully understand the numerous effects of altitude on the human body and subsequently also aid in the monitoring of the wellbeing of these individuals.

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SUPPLEMENTARY DOCUMENTATION

- Ethics approval letter
- Ethics Annual Progress Report / Renewal
- Approved Protocol

UNIVERSITY OF CAPE TOWN
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Human Research Ethics Committee

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08 October 2018

HREC REF: 045/2016

A/Prof R Hofmeyr
Department of Anaesthesia
D-23 OMB

Dear A/Prof Hofmeyr

PROJECT TITLE: COMPARISON OF SONOGRAPHIC LUNG COMET EVALUATION BY AN EXPERIENCED ULTRASONOGRAPHER AND NOVICE IN A HIGH-ALTITUDE ENVIRONMENT:

Thank you for your response letter dated 19 September 2018, addressing the issues raised by the Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 October 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on

2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95 and FDA Code Federal Regulation Part 50, 56 and 312.

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☐ Approved	Annual progress report	Approved until/next renewal date	30.01.23
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	2/4/2022

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	31/03/2022		
HREC REF Number	045/2016	Current Ethics Approval was granted until	30/01/2022
Protocol title	Comparison of sonographic lung comet evaluation by an experienced ultrasonographer and novice in a high-altitude environment		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?		☐ Yes	✓ No
If yes, could you please provide the HREC Reference number for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Dr F. Wilhelm Vogts		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Department / Office Internal Mail Address	Division of Exercise Science and Sport Medicine (Email: wilhelmvogts@gmail.com)

1.1 Does this protocol receive US Federal funding?	☐ Yes	✓ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval? **Note:** Any annual approvals for **Full Committee** review MUST be submitted on the monthly HREC submission dates. (Please send electronic copy for full committee review to hrec-submission@uct.ac.za)	☐ Yes	☐ No

If yes in 1.2 please complete section 1.3 below for invoicing purposes

1.3 Ethics Renewal Fee

Please **(tick ✓)**appropriate box for billing purposes:

Submission Type	***Description***	***New fee (Vat Incl.)***	***tick ✓***
Research funded solely from UCT departmental/ divisional/group budget	Annual evaluation of research progress report for re-certification	**R0,00**	☐
Non-sponsored student research for degree purposes at UCT/Other Universities & Colleges	Annual evaluation of research progress report for re-certification	**R0,00**	☐
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Full Committee Approval	**R7000,00**	☐
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Expedited review	**R3 710.00**	☐
Annual re-certification / Progress report (FHS016 Form)	National grant funded research - Annual evaluation of research progress report for re-certification for Full Committee Approval	**R6000.00**	☐
Annual re-certification / Progress report (FHS016 Form)	National Grant funded research for Annual evaluation of research progress report for re-certification for Expedited review	**R1 500,00**	☐

NB: Protocols funded by UCT (e.g. departmental funding / student research) and by certain grant funding organizations (e.g. MRC, NRF, CANSA,) are exempt from these charges.

Please provide details for Invoicing, either complete section 1 or 2 :

1. Invoice billing – Directly to Sponsor

Sponsor's name	
Billing Address of Sponsor:	
Vat Number:	

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Contact person	
Telephone number	
Email Address	
2. **Internal Journal Billing:**	
Fund Number:	
Cost Centre Number:	
Account Holder Name:	
Division of Account Holder:	

2. List of documentation for approval

FHS016

3. Protocol status (tick ✓)

☐	Open Enrolment
☐	Closed to enrolment (tick ✓)
☐	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
✓	Research-related activities are complete, data analysis only
☐	Main study is complete but sub-study research-related activities are ongoing
☐	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

Number of participants enrolled to date	10
Number of participants enrolled, since last HREC Progress report (continuing review)	10
Additional number of participants still required	-

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	-

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

6. Cumulative summary of participants

Total number of participants who provided consent	10
Number of participants determined to be ineligible (i.e. after screening)	-
Number of participants currently active on the study	-
Number of participants completed study (without events leading to withdrawal)	10
Number of participants withdrawn at participants' request (i.e. changed their mind)	-
Number of participants withdrawn by PI due to toxicity or adverse events	-
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	-
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	-
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	-

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:
The completed thesis was successfully submitted for examination on 13/02/2022. Once marked, the paper will be published. Thereafter the study will be formally closed.

8. Protocol violations and exceptions (tick ✓ all that apply)

☐	No prior violations or exceptions have occurred since the original approval
✓	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved
☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

9. Amendments (tick ✓ all that apply)

☐	No Prior amendments have been made since the original approval
✓	Prior amendments have been reported since the last review and have already been approved

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

☐	New protocol changes/ amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006).
Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.
None

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?		
☐ Yes	☐ No	✓ Not applicable
If yes, please describe:		

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. SAHPRA, FDA)?		
☐ Yes	☐ No	✓ Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report?		
☐ Yes	☐ No	✓ Not applicable

11.3 If yes, please identify the agency and attach a summary of the findings.					
Agency Name		Report attached	☐ Yes	☐ No	☐ Not applicable
		DSMB report attached	☐ Yes	☐ No	☐ Not applicable

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
☐ Yes	✓ No
If yes, please explain:	

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

12. Level of risk (tick ✓)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
☐	Increased
☐	Decreased
✓	Shown no change
If there has been a change, please explain:	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.
N/A

13. Insurance

Please confirm that valid no fault insurance is still in place? **(tick ✓)**			
As per initial ethics application, this was an observational study only. The thesis has already been submitted on 13/02/2022. Once published, the study will be formally closed.			
☐ Yes		☐ No	
If yes, please complete the following:			
Insurer's name:			
Policy no.		*Coverage Period:	
For UCT sponsored studies please liaise the Insurance office via fhs.sponsorship@uct.ac.za regarding the required documentation and information required obtain a renewed UCT No-fault Insurance Certificate.			

14. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
☐ Yes	✓ No
If yes, please explain and if necessary, attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):	

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

15. Signature

My signature certifies that the above is complete and correct.			
Signature of PI		Date	31/03/2022

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Protocol

Comparison of sonographic lung comet evaluation by an experienced ultrasonographer and novice in a high-altitude environment

Wilhelm Vogts, Ross Hofmeyr, Caroline D'Alton

Principal Investigator: Dr F. Wilhelm Vogts
Candidate: MPhil Sport and Exercise Medicine, Division of Exercise Science and Sport Medicine, Department of Human Biology, Faculty of Health Sciences, University of Cape Town.

Date: September 2018

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1. Overview

Rapid ascent to high altitude is recognized to cause Acute Mountain Sickness (AMS), as defined by the Lake Louise Consensus (1992). This condition may progress to high altitude cerebral edema (HACE) with raised intracranial pressure, and/or high altitude pulmonary edema (HAPE)(Gallagher and Hackett, 2004). AMS is generally accepted to be an early part of the disease process leading to HACE, whereas HAPE is considered a separate diagnosis. HAPE is the most frequent cause of death from high altitude illness, affecting 0,2 to 15% of individuals ascending to between 2500 and 5000 m. The pathophysiology and progression of HAPE is not well understood, but increased pulmonary artery pressures secondary to hypoxic pulmonary vasoconstriction and subsequent alveolar capillary membrane leakage during hypobaric hypoxia are believed to be responsible for development of the condition. The only effective prevention for AMS, HACE and HAPE is through acclimatization by gradual ascent. Mild AMS can be managed by halting ascent and allowing acclimatization, but severe AMS, HAPE or HACE is managed by supportive treatment and immediate descent to lower altitude (Luks et al., 2014).

HAPE has traditionally been diagnosed in the wilderness on the basis of suggestive history, symptoms (dyspnea at rest, cough, decreased exercise performance and chest tightness), and clinical findings (crackles or wheezing on auscultation, central cyanosis, tachypnea and tachycardia). Importantly, these findings occur late in the disease process, and may be too late to allow the patient to return to a safe altitude without assistance. However, it is now well established that onset of HAPE is preceded by increases in extravascular lung water (EVLW) which are easily detected by the increasing number of sonographic artefacts known as 'lung comets' (also known as sonographic B-lines or comet tail artefacts) on lung ultrasound (Wimalasena et al., 2013, Lichtenstein et al., 1997, Agricola et al., 2005, Jambrik et al., Picano et al.). This is rapidly and non-invasively achieved in the field, and has been described in several high-altitude studies (Fagenholz et al., 2012, Pratali et al., 2010).

Early recognition of signs of pulmonary edema before the clinical onset of AMS or HAPE may allow prevention of the condition by allowing changes in the planned ascent profile, commencement of pharmacological prophylaxis, or earlier treatment (Pratali et al., 2010). Furthermore, sonographic evidence of pulmonary edema could allow differentiation of HAPE from other conditions causing similar symptoms during an expedition to altitude (such as exhaustion, pneumonia, pneumothorax or pleural effusion).

Recent advances in technology have led to small, highly portable ultrasound machines which can be carried into alpine wilderness environments with little difficulty. The majority of high altitude field studies of lung ultrasound have used clinicians who are expert sonographers to perform the ultrasounds, although at least one study has examined the use of lung ultrasound by novices guided in real time using a sophisticated telemedicine system (Otto et al., 2009). However, most expeditions do not have access to expert sonographers or real-time telemedicine

systems. Fortunately, lung ultrasound is rapidly learnt by novices (Heiberg et al., 2015). We seek to determine whether novices can adequately perform a simple lung ultrasound protocol to detect ultrasound lung comets in a high altitude expedition environment.

2. Objective

The primary aim of this study is to establish whether a novice sonographer can perform effective assessment of lung ultrasound comet scores in comparison to an experienced sonographer.

3. Background

As increasing numbers of workers, recreational climbers and religious pilgrims ascend to high altitudes around the world, the ability to safeguard these individuals from the risks associated with the hypobaric stress of high altitude environments becomes necessary. One of the most common and dangerous sequelae of high altitude is AMS. This syndrome is thought to be due to hypobaric hypoxia causing leaky capillaries. The consequent clinical picture is that of increasing cerebral and pulmonary edema. Patients often complain of headache, increased drowsiness, dyspnea and increased fatigability. Late diagnosis and treatment can lead to severe disability and death. The treatment of AMS is rapid descent to lower altitude; prevention by gradual ascent and prophylaxis with the carbonic anhydrase inhibitor acetazolamide is the advisable course.

Two factors determine the risk of AMS.

1. Rate of ascent, with rapid ascent within 48h being higher risk.
2. The altitude reached, with altitudes above 4500m being at highest risk.

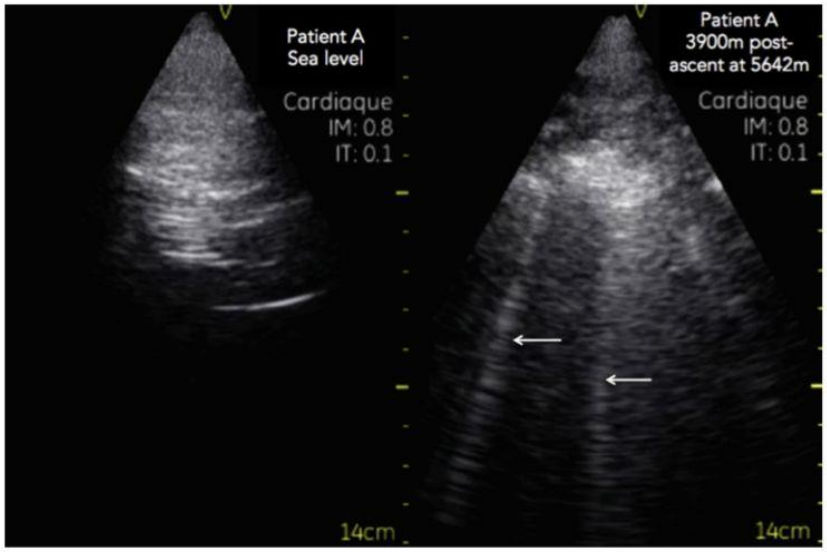
Mountain peaks like Kilimanjaro present with the highest number of AMS cases per year due to its altitude of close to 6000m and the ease of climbing with ascent to elevations above 4500m reached within 48 hours by many parties. The sheer number of climbers also account for the caseload. Fitness and background medical history does not appear to play a role in AMS, and genetic predisposition appears to play a major role in selection for the disease.

High Altitude Pulmonary Edema (HAPE) is a clinical diagnosis, due to the lack of infrastructure in the situations where it is prevalent. It is diagnosed in the setting of a recent increase in altitude above 2500 m on the basis of presence of at least two symptoms and two clinical signs. Symptoms of HAPE are dyspnea at rest, cough, weakness and/or decreased exercise performance, and chest tightness or congestion. Clinical signs are crackles or wheezing on auscultation in at least one lung field, central cyanosis, tachypnea and tachycardia. It is self-evident from these symptoms and signs that clinical diagnosis is only possible at an advanced stage of the disease, by which time the patient may be unable to descend to an altitude at which the syndrome is reversed. However, it is well established that subclinical pulmonary interstitial edema develops well before the clinical manifestation of HAPE. Fortunately, lung ultrasound is effective in detecting interstitial edema. The

clinical relevance of detecting subclinical pulmonary at altitude should be mentioned. As shown by studies done by Pratali et al in 2011 and 2012, subclinical pulmonary edema is now an accepted phenomenon with altitude gain. Their 2011 Khumbu study showed that all climbers demonstrated subclinical edema at 4750 m but only 3 were diagnosed with HAPE. This presence of subclinical pulmonary edema was further shown in a study conducted in 2012 where it was associated with exercise limitation in patients with chronic mountain sickness. These studies have demonstrated that Ultrasound Lung Comets (ULCs) are common at altitude in the absence of other classic features of HAPE (Wimalasena et al., 2013). It is therefore evident that the clinical significance (and the subsequent treatment) of detecting ULCs in a high altitude environment remains to be established. Especially in view of ULC values for the prediction and diagnosis of HAPE still being unclear.

4. Ultrasound Lung Comets (ULCs)

Traditionally, the lung was considered a poor subject of sonographic examination, as ultrasound is intensely reflected by a tissue-air or fluid-air interface. However, more than a decade ago, the usefulness of sonographic artefacts due to increased extravascular lung water (EVLW) was identified (Agricola et al., 2005, Jambrik et al., Picano et al., Lichtenstein et al., 1997). This has been extensively correlated with clinical and radiological findings and is both sensitive and specific for pulmonary edema (Jambrik et al.). The 'comet-tail' artefact, also known as the sonographic B-line or ultrasound lung comet (ULC) is key to this process. This is described as one or many hyperechoic lines fanning out from the pleural interface, and is believed to originate from water-thickened interlobular septa due to increased EVLW. It is conceptually equated with the radiological Kerley B-line. An increasing total number of ULCs obtained by the sum of each sonographic view is associated with increasing lung edema in a linear relationship (Agricola et al., 2005). It is important to note, however, that it is still not known what number of ULCs is diagnostic for HAPE as opposed to the presence of subclinical edema.



1. Two lung ultrasound images from the same expedition member at 160m AMSL in Moscow (left) and 3900m AMSL on Mount Elbrus after returning from the 5642m summit (right). In the high altitude image, two ultrasound lung comets (ULCs) can be seen, indicated by the arrows. Source: Page et al, 2015(Page et al., 2015)

Numerous studies have shown a progressive increase in ULC counts with increasing exposure to hypobaric hypoxia due to increases in altitude (Page et al., 2015, Pratali et al., 2010).

It has been well established that development of pulmonary interstitial edema always precedes onset of pulmonary alveolar edema (Lichtenstein et al., 1997). ULCs are detectable at a very early stage in the development of pulmonary edema, as they are a sensitive test for interstitial edema (Agricola et al., 2005). Detection of ULCs may be of particular value in the high altitude expedition context, and could in the future be used to guide intervention before onset of clinically relevant HAPE, once their exact clinical significance and proven predictive values become more clear.

5. Lake Louise Score

As no specific diagnostic or laboratory test for Acute Mountain Sickness exists, the diagnosis is made on the basis of symptoms and clinical signs. The 1991 International Hypoxia Symposium held at Lake Louise in Alberta established an AMS scoring system to assess the severity of disease. A diagnosis of AMS is based upon an increase in altitude above 2500m within the preceding four days, presence of a headache, and a total score of ≥3 on a self-report questionnaire. The questionnaire grades headache, gastrointestinal symptoms, fatigue and/or weakness and dizziness/lightheadedness on a scale of 0 (absent) to 3 (incapacitating). The updated 2018 Lake Louise Acute Mountain Sickness Score has removed the sleep component from the diagnostic criteria. Recent studies have shown that disturbed sleep at altitude, previously one of the five symptoms scored for AMS, is more likely due to altitude hypoxia per se, and is not closely related to AMS (Roach et al., 2018). A score of 3 to 5 in the presence of recent ascent and headache is considered mild AMS, requiring cessation of ascent. A score of 6 to 9 indicates moderate AMS, while

a score of 10 to 12 indicates severe AMS requiring careful examination for signs of HACE (such as ataxia) or HAPE (such as breathlessness at rest or widespread crepitation on lung auscultation).

6. Methods

a. Study Design

This study will be a prospective, blinded, observational study. The study will record daily lung comet scores by both an experienced and a novice sonographer using a standardized protocol. All sonographers will be blinded to each other's results.

b. Setting and Participants

This study will take place during the October 2018 Old Mutual Finance (OMF) Kilimanjaro Expedition on Mt Kilimanjaro in Tanzania. This is an 8-day expedition for employees of the Old Mutual Finance company. The dates for the expedition are 5 to 13 October 2018. Twenty-five participants and one expedition doctor (Dr F. Wilhelm Vogts) will spend two nights in the town of Moshi (700m – 950m), before starting the climb (7 October 2018) to Uhuru Peak (5895m) on Kilimanjaro over 6 days using the Umbwe Route. The group will also be accompanied by staff from Wild Frontiers which include experienced porters and mountain guides with mountain medicine training. All members of the expedition will be invited to participate. A training session on the standardized lung ultrasound protocol will be held during the time spent at Moshi, prior to the start of the climb.

c. Intervention

All members of the expedition will be undertaking daily Lake Louise Scores and fingertip pulse oximeter readings as part of the safety program on the mountain. Daily lung ultrasound will be performed according to a standardized 8-zone protocol (Pratali et al., 2010, Edsell et al., 2014, Wimalasena et al., 2013) by blinded ultrasonography operators. One experienced sonographer will scan each participant, with his score used as the "gold standard" for comparison. The participant will then be a novice sonographer. Dr F. Wilhelm Vogts will act as the experienced sonographer, having received appropriate and adequate skills training. We are aiming to scan a minimum of 10 separate participants daily.

d. Exclusion Criteria

All expedition participants will have been screened prior to the expedition and any significant underlying medical conditions excluded which would preclude high altitude trekking. Participants will be excluded if:

- Pregnant or thought to be pregnant
- Exhibiting signs or symptoms of AMS, HACE or HAPE on commencement of the study (This will also preclude them from participation in the expedition)

Use of diuretics, steroids, acetazolamide, or nonsteroidal anti-inflammatory drugs in the fortnight leading up to the study or while taking part in the expedition will not constitute an exclusion criterion, but will be recorded for later subset analysis.

Decisions regarding continued ascent and prophylaxis or treatment will be made on the basis of standard best practices by the experienced expedition leaders (Luks et al., 2014, Page et al., 2015).

Data from each sonographer will be excluded should they develop severe AMS or other clinical illness, as this biases or precludes the ability to perform an adequate examination. The research project will cease to continue if the affected party happens to be the Principal Investigator.

e. Data collection

Participant Lake Louise Scores, resting heart rates and fingertip pulse oximetry measurements will be recorded concurrently with the sonographic examinations. These variables are regularly assessed as part of the standard high-altitude expedition precautions and forms part of the routine care provided to members of the expedition party.

f. Sample size and data analysis

The sample size for this study is 10. At the time of writing, there are 25 trekkers involved in the expedition. We are aiming to recruit 12 volunteers within the group to consent to the trial. The decision to recruit 2 extra participants (with the sample size being 10) was to account for the possible withdrawal of individuals from the research study for whatever reason. A minimum of ten subjects will be scanned on each of the expedition's 6 days (2 days in the town of Moshi, 5 days ascent and 1 day descent). This will generate a minimum of 60 data sets, which is sufficient for the Bland-Altman analysis (see below). Further scans will be obtained as far as determined by the available time and battery life of the portable ultrasound machine.

The primary outcome (reliability of a novice versus an experienced expedition medic to accurately perform field lung ultrasound) will be assessed using a Bland-Altman limits-of-agreement analysis on the ultrasound lung comet counts. Although the same participants will be scanned at multiple instances across the duration of the expedition, significant changes in the number of ULCs is expected from day to day, rendering each investigation a discrete sample. However, we will perform the test for repeated measures using the method described by Bland and Altman and correct if any effect is found (Bland and Altman, 1986).

(The authors are grateful to Dr Carl Lombard at the MRC for advice regarding the statistics)

7. Ethical Considerations

This protocol and any amendments has been submitted to the University of Cape Town Human Research Ethics Committee for formal approval of the study conduct. As this is an observational study using a purely non-invasive measurement, no

additional risks to participants as a result of the study is anticipated. All members of the expedition are cognizant of the risks of high altitude trekking, but this study in no way influences their attendance or participation in the expedition, or their medical monitoring or treatment.

The study will be performed in accordance with the ethical principles of the Helsinki Declaration of 2013 (latest version) and the South African Good Clinical Practice Guidelines.

a. Adverse events

There are no foreseeable adverse events as a consequence of study participation. All participants are already taking part in the expedition of their own volition. The presence of the ultrasound equipment on the expedition confers a safety advantage to all participants, as it can also be used to detect other clinical conditions such as spontaneous pneumothorax, pneumonia, pleural effusion, deep vein thrombosis, etc. However, all decisions regarding medical care will be based on standard wilderness medicine practice guidelines and gold standard treatment protocols. Experienced expedition medicine providers will be on site to provide treatment for AMS or HAPE should it be diagnosed.

b. Patient confidentiality and consent

Participation in the study will only take place after completion of written, informed consent process. Ultrasound examinations do not require full exposure of the chest and will be undertaken in a tent or screened area to preserve privacy and dignity of the participants.

Participants may withdraw from this study at any time with immediate effect. All data collected will remain strictly confidential and securely stored and if utilized in published form, anonymity will be ensured. All data hardcopies will be stored in a secure facility within the Division of Exercise Science and Sports Medicine.

8. Funding

A private company will provide the ultrasound machine for the duration of the expedition. Costs of the expedition are borne by the individual participants and Old Mutual Finance. No conflict of interest is foreseen.

9. Outcomes

The results of the research study will be published in an appropriate medical journal and the information disseminated at a relevant congress if found to be of value. If the results are found to be of benefit to the management of altitude associated illnesses, the inclusion and use of an affordable portable ultrasound as part of a standard high altitude medical kit will be advocated.

10. Acknowledgements

We would like to acknowledge the following co-investigators who laid the initial groundwork for this study in 2016:

- Sr. Niki Rogala
- Dr. Chanel Rossouw
- Dr. Sian Gerarty
- Dr. Bonny Bulajic
- Dr. Clemens Ortner
- Dr. Vijay Krishnamoorthy
- Prof. Justiaan Swanevelder

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