AN INVESTIGATION OF CHANGES IN TISSUE OXYGENATION IN MILITARY CASUALTIES DURING AEROMEDICAL EVACUATION

by

JUDITH DAWN McLEOD

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College of Medical and Dental Sciences
University of Birmingham
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ABSTRACT

Optimal management of British military personnel injured in Afghanistan is best achieved in the United Kingdom; therefore aeromedical evacuation (AE) is arranged, often within the first 24 hours for the most severely injured casualties. However, early aeromedical evacuation carries its own risks, which must be considered prior to emplaning any casualty. The aim of this study was to investigate whether changes in tissue oxygenation occur in military casualties during aeromedical evacuation. Near infra-red spectroscopy was used in a series of studies designed to test the sensitivity of the tissue oxygen saturation monitoring technique in volunteers exposed to simulated altitude and simulated hypovolaemia. Changes in tissue oxygen saturation readings were detected in the volunteers, so an observational study was undertaken to determine whether changes in tissue oxygen saturation occur in military trauma casualties during aeromedical evacuation. Whilst the majority of casualties did not demonstrate any significant change in readings, some casualties did demonstrate reduced tissue oxygen saturation readings during their flights, although these changes were not reflected in systemic physiological monitoring techniques. Having identified that changes do occur, further work is required to investigate the cause, significance and outcome of these changes in order to fully appreciate the findings of the current study.

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McLeod J, Green N. (2015) An investigation of changes in tissue oxygen saturation in military casualties during aeromedical evacuation [Abstract 86]. (Appendix C)

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List of Abbreviations and Definitions

ADMEM
Academic Department of Military Emergency Medicine

AE
Aeromedical evacuation – the movement of patients under medical supervision to and between medical treatment facilities by air transportation

AECC
Aeromedical Evacuation Control Centre – co-ordinating all aeromedical evacuation requests

AELO
Aeromedical Evacuation Liaison Officer – responsible for requesting aeromedical evacuation flights

CCAST
Critical Care Air Support Team - providing complete intensive care management of casualties in-flight

CO
Cardiac output – calculated as *Cardiac Output = Heart Rate x Stroke Volume*

EMSAC
Experimental Medicine Scientific Advisory Committee

FFP
Fresh frozen plasma

FiO_2
Fraction of inspired oxygen

HAST
Hypoxia altitude simulation test

HR
Heart rate

HUT
Head up tilt – a 70° head up tilt of the tilt table

IED
Improvised Explosive Device

ISS
Injury Severity Score (see Appendix A)

JTTR
Joint Theatre Trauma Registry

LBNP
Lower body negative pressure

MAP
Mean arterial pressure; calculated as:
MAP = diastolic pressure + 1/3 (systolic pressure - diastolic pressure)

MoDREC
Ministry of Defence Research Ethics Committee

NIRS
Near infra-red spectroscopy

NISS
New Injury Severity Score (see Appendix A)

PAO_2
Partial pressure of alveolar oxygen

PEEP
Positive End Expiratory Pressure

PIP
Peak inspiratory pressure

PO_2
Partial pressure of oxygen

RCDM
Royal Centre for Defence Medicine – the main United Kingdom receiving hospital for casualties who have undergone aeromedical evacuation

RR
Respiratory rate

rSO_2
"Regional oxygen saturation of blood. Indicates approximate saturation of oxygen within the region being monitored by the INVOS system" (Somanetics, p89; 2007)

SpO_2
Peripheral arterial oxygen saturation – measured by pulse oximetry

1. INTRODUCTION

Aeromedical evacuation (AE) is defined by the Royal Air Force as the movement of patients under medical supervision to and between medical treatment facilities by air transportation (MoD, 2007). This study focuses on the movement of military casualties from the British Field Hospital at Camp Bastion, in Helmand Province, Afghanistan, back to the Royal Centre of Defence Medicine (RCDM), which is based at the Queen Elizabeth Hospital, Birmingham. British military personnel injured in Afghanistan are initially transferred to a field hospital facility for resuscitation and primary surgical intervention. Once stabilised, optimal management of these patients is best achieved in the United Kingdom (UK), therefore early aeromedical evacuation is arranged, often within the first 12 hours for the most severely injured casualties.

The development of military aeromedical evacuation flights can be traced back to the First World War. A French Medical Officer, Eugene Chassaing, modified military aircraft to operate as air ambulances, transporting wounded soldiers (Coker, 2006). Development of AE continued after the end of the First World War, with the addition of medically trained escorts to provide in-flight care for the evacuated casualties (Vanderburg, 2003).

Since these early beginnings, aeromedical evacuation has continued to advance; contemporary UK military AE flights can be undertaken in a wide range of fixed or rotary wing aircraft, according to the patient load, location and severity of their illness/injuries. Medical escorts for military AE flights will also vary according to the needs of the patient and can range from a Flight Medic (FM), offering minimal intervention, to a full Critical Care Air Support Team (CCAST),

providing complete intensive care management in-flight. Although it is desirable to provide early management of the casualties in the UK medical system, aeromedical evacuation carries its own risks, which must be considered before the patient is emplaned. This study will focus on some of the potential risks associated with aeromedical evacuation of acutely injured military personnel.

1.1. Hypobaric Hypoxia

Military aeromedical evacuation from the current operational settings may be undertaken in a variety of fixed wing aircraft. Irrespective of aircraft type, the cabin will be pressurised to an altitude between 6,000 and 8,000 feet (ft) (1829 to 2438 metres (m)), unless there is a specific medical reason for a ground level cabin altitude[1]. Although the aircraft is actually cruising at a much higher altitude (>30,000 feet or 9144m), the physiological effects on the crew and passengers at these altitudes would be fatal; 8,000 feet is commonly the maximum permitted cabin pressurisation in military and commercial passenger aircraft, to ensure the safety and well-being of all on board.

At sea level, barometric pressure is approximately 760mmHg (101kPa). Barometric pressure falls with increasing altitude; at 8,000 feet, barometric pressure is reduced to 565mmHg, which is significant because the partial pressure of oxygen also decreases as a result. According to Dalton's Law, the pressure of a mixture of gases is equal to the sum of the partial pressures of the individual gases in the mixture. Oxygen forms approximately 21% of ambient air, so at sea level,

[1] In locations above sea level, a ground level cabin altitude is used, as the casualty is already accustomed to this altitude. As an example, Camp Bastion is at an altitude of 3,000ft, so casualties requiring a cabin altitude restriction for medical reasons will be transported at or above 3,000ft cabin altitude (equal to ground level), not at sea level.

the approximate partial pressure of oxygen (PO_2) is 160mmHg (21.3kPa) (PO_2 = 21/100 x 760). At 8,000 feet, the partial pressure of oxygen falls to 118mmHg (15.7kPa). Consequently, at altitude, the partial pressure of oxygen in alveolar air also falls, which is significant for oxygen carriage throughout the body. Haemoglobin binds easily with oxygen to form oxyhaemoglobin and, at sea level, is almost completely saturated with oxygen when it leaves the lung. Lower PO_2 in the tissues causes the oxygen to dissociate from the haemoglobin, freeing the oxygen for use by the tissues. At altitude, the lowered partial pressure of alveolar oxygen (PAO_2) results in less saturated molecules of haemoglobin, which results in less oxygen availability in the tissues. Reduced barometric pressure at altitude causes a decrease in the partial pressure of oxygen, which, in turn, results in less saturated molecules of haemoglobin, which is demonstrated by the oxyhaemoglobin dissociation curve at Figure 1. At sea level, PO_2 is 95mmHg, which (in healthy individuals) will result in 97% oxyhaemoglobin saturation (Gradwell, 2006). Ascent to an altitude of 8,000ft causes a reduction in PO_2 to 56mmHg and a subsequent fall in oxyhaemoglobin saturation.

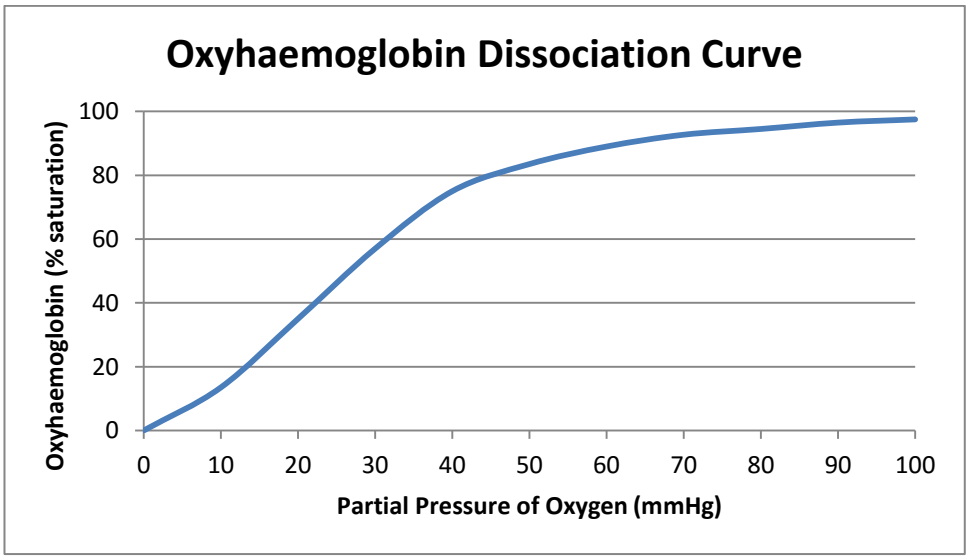

Figure 1. Oxyhaemoglobin dissociation curve, demonstrating fall in % saturation with decreased partial pressure of oxygen which occurs at altitude

Factors affecting the uptake of oxygen by haemoglobin at the alveolar level and the off-loading of oxygen at the tissue level include temperature and acidosis/alkalosis. A right shift of the curve at Figure 1 indicates factors such as acidosis, a raised body temperature or hypercapnia, which reduces the uptake of oxygen by haemoglobin but increases oxygen release at the cellular level. A left shift of the curve at Figure 1 indicates alkalosis, hypothermia, hypocapnia or lower levels of 2,3 diphosphoglycerate (2,3 DPG) in red blood cells. These conditions increase the affinity of haemoglobin to oxygen but the release of oxygen at the cellular level consequently occurs at much lower partial pressures (Holleran, 1996). 2,3 DPG is a glucose metabolite which assists with the release of oxygen from haemoglobin at the cellular level. Concentrations of 2,3 DPG are reduced in stored blood, particularly in blood which has been stored for more than 2 weeks, so casualties who have had massive blood transfusions may have lower levels of 2,3 DPG. Lumb (2000) suggests that levels of 2,3 DPG in transfused blood may not return to normal levels for up to 48 hours post-transfusion.

Compensatory increases in respiratory rate and cardiac output will ensure that most passengers will not experience any significant physiological effects at 8,000 feet cabin altitude, despite the reduced PAO_2, although pulse oximetry will show a fall in oxygen saturation from 98-100% to approximately 92%. Passengers with underlying medical conditions may not tolerate these compensatory mechanisms and may become symptomatic at this altitude, with the risk of hypoperfusion of tissues and end organs; this effect must be considered when emplaning casualties for aeromedical evacuation (Coker, 2006). Even casualties who are ventilated and sedated throughout their flights will be exposed

to a lower partial pressure of alveolar oxygen, despite potentially having a higher concentration of oxygen administered through the ventilator. This is because the ventilator circuit is only a closed system, not a pressurised system, so the supplied gases are subject to the same response as a result of reduced atmospheric pressure.

Pulse oximetry readings should be interpreted with care in casualties who may be acutely anaemic, as the readings may provide false reassurance. Pulse oximetry does not provide any information about the carriage of oxygen around the body; fewer haemoglobin molecules in the blood means less oxygen transport, but pulse oximetry might show 100% saturation because all of the available haemoglobin is fully saturated with oxygen, despite there not being enough haemoglobin to meet the body's oxygen requirements (Martin and Glanfield, 2006).

Regional tissue perfusion may be compromised in the critically ill casualty as the body diverts blood flow, and therefore oxygen delivery to the vital organs at the expense of other tissues. This may be exacerbated by the use of inotropes such as noradrenaline, which may be required to maintain or raise blood flow to ensure adequate perfusion of the vital organs. Even mild tissue hypoxia may have a detrimental effect on wound healing. A lack of oxygen at the tissue level affects the production of energy within the body; the combination of oxygen and glucose is required to maintain aerobic metabolism. During anaerobic metabolism, less energy is produced but lactic acid and hydrogen ions are also released, leading to acidosis within the cells. Further complex mechanisms are triggered with prolonged tissue hypoxia and worsening acidosis, including the release of potassium and sodium and hyperglycaemia; if uncorrected, these mechanisms can

result in damage to the cells or even cell death, leading to organ failure and, ultimately, even death of the casualty (Lumb, 2000; Webster, 1999).

1.2. Anaemic Hypoxia

In recent years, the Defence Medical Services have made rapid progress in the immediate management of severe trauma in the operational setting, in response to new technological innovations, equipment enhancements and improved training provision (MoD, 2006). As a result of these developments, more casualties are surviving the initial traumatic event and consequently require urgent AE for life or limb saving management. Many of the more severely injured casualties will have sustained significant haemorrhage at the time of injury and may have undergone lengthy surgical procedures. In order to correct the subsequent loss in blood volume, the casualty may have received massive transfusions of a variety of blood products. However, any significant blood loss will cause a decrease in haemoglobin levels and, subsequently, the oxygen carrying capacity within the body over the short term, as the majority of oxygen is transported as oxyhaemoglobin, with only a small proportion dissolved in plasma (Schober and Schwarte, 2012).

To reduce the risk of in-flight deterioration, current protocols (MoD, 2007) dictate that casualties undergoing aeromedical evacuation must not be emplaned with a haemoglobin level below 7.0 g/dL, although in practice, a cut-off point of 7.5 g/dL is currently employed, with supplemental oxygen available in-flight for these individuals. The origins of these AE protocols are unclear but they are likely to be based on in-hospital experience; haemoglobin results below 10 g/dL were traditionally the trigger for red cell transfusions in most western hospitals,

with little evidence base to support this practice (Ness and Rothko, 1991). Within the current AE protocols it is identified that individuals with acute anaemia as a result of recent haemorrhage may become symptomatic in-flight with haemoglobin levels up to 10g/dL. Furthermore, with the rapid evacuation of the more severely injured casualties, it is possible that haemoglobin estimates taken post transfusion / pre-flight may not be wholly accurate, as the haemoglobin level begins to fall several hours after the blood loss and will only stabilise after 2 to 5 days (de Gruchy, 1989). Massive and / or repeated transfusions of blood products will further complicate / alter the clinical picture in these casualties. In a recent study of Canadian battle-injured personnel, Hannah and Rice (2013) reviewed the surgical outcomes for casualties with extremity wounds following aeromedical evacuation. They suggested that the probability of requiring a higher level of surgical revision was 37% when the casualty was transported with a haemoglobin level of 8g/dL. This dropped to 20% when the casualty had a pre-flight haemoglobin level of 10g/dL. The findings from this study seem to suggest greater tissue damage occurs with the combination of anaemic hypoxia (from low haemoglobin levels) and hypoxic hypoxia (from aeromedical evacuation).

1.3. Near Infra-Red Spectroscopy

Near infra-red spectroscopy (NIRS) has been used to develop a non-invasive means of monitoring tissue oxygen saturation. Sensors applied to the skin illuminate the tissues beneath, using light from the near infra-red spectrum (680-1000nm). Near infra-red light readily passes through human tissue; only 3 substances within the body are known to absorb near infra-red light differently according to their concentration within the tissues and according to their

oxygenation state – haemoglobin, myoglobin and oxidised cytochrome (Creteur, 2008). In accordance with the modified Beer-Lambert law, the change in the intensity of the light as it passes through the substances indicates the changes in the concentration of these substances according to their oxygenation state (Boushel and Piantadosi, 2000). Oxyhaemoglobin and de-oxyhaemoglobin absorb near infra-red light at different wavelengths; by measuring the change in the wavelengths of the light reflected back to the receiving sensor, the relative concentrations of each compound can be calculated. A receiving sensor gathers the portion of the non-absorbed light which passes the sensor as it returns through the tissue. Using specific proprietary algorithms, the various monitors calculate the concentrations of oxy- and de-oxyhaemoglobin in the tissues, which are primarily used to indicate tissue oxygen saturation (Boushel and Piantadosi, 2000). As the technology calculates relative concentrations of each compound, tissue oxygen saturation readings should be interpreted as a trend over time rather than absolute readings.

Ward et al (2006) identify that oxyhaemoglobin and oxymyoglobin absorb light at the same wavelength, making it difficult to distinguish between the two compounds. However, the authors suggest that oxymyoglobin releases its oxygen at such a low partial pressure that it is saturated for the majority of the time, so any changes in regional tissue oxygen saturation seen can be assumed to result from changes in the oxygen state of haemoglobin. A similar situation occurs with de-oxyhaemoglobin and de-oxymyoglobin. Boushel and Piantadosi (2000) suggest that even in skeletal muscle, the majority of changes in tissue oxygen

saturation originate from haemoglobin. They also suggest that oxidised cytochrome makes only a small contribution to any observed changes in readings.

Over the past decade, interest in tissue oxygen saturation monitoring has increased. The ability to predict early changes in regional oxygenation, using a non-invasive method suitable for use in the pre-hospital or in-hospital setting is very appealing to clinicians. As a result, a number of companies are now marketing tissue oxygen saturation monitors; however, there is no standard method of measurement amongst the different commercially available devices; the calculation algorithms vary between companies and even the terminology differs according to the device used. A significant number of published studies have used the InSpectra™ Tissue Oxygenation Monitor, manufactured by Hutchinson Technology, who describes tissue oxygen saturation as StO_2. The monitoring system being used during the present study is the INVOS® 5100C Cerebral / Somatic Monitor, manufactured by Somanetics, who describe regional tissue oxygen saturation as rSO_2. Within the published studies, the terms appear to be used indiscriminately.

The INVOS system was selected for the present study as it is designed to monitor up to four body areas simultaneously[2]; the sensors can be easily applied to most areas of the body, allowing more flexibility than some other devices. It utilises "spatially resolved spectroscopy" (Ward et al, 2006), using 2 receiving sensors in the same plane (reflectance) but at different distances from the light

[2] At the start of the present study, the aim had been to monitor rSO_2 over the deltoid and quadriceps muscles, hence the requirement for multi-site monitoring; however, during the study, the introduction of topical negative pressure wound dressings prevented monitoring of the lower limbs in the majority of patients, as the dressings tended to cover the entire thigh area.

emitting source; this allows readings to be obtained from within different depths of the tissue. The closest sensor is assumed to receive light passing through superficial skin and tissue layers, while the furthest sensor is assumed to receive light which has passed through deeper tissue. The INVOS-specific proprietary algorithms account for the path lengths of the light obtained from both receiving sensors, to ensure only deeper tissue is used in the calculation of tissue oxygen saturation.

As shown in Figure 2, light is emitted from the source and passes through the tissue; some of the light will not be picked up by the receiving sensor due to its particular path through the tissue, but a portion will be detected by the 2 receiving sensors, as its particular path is elliptical.

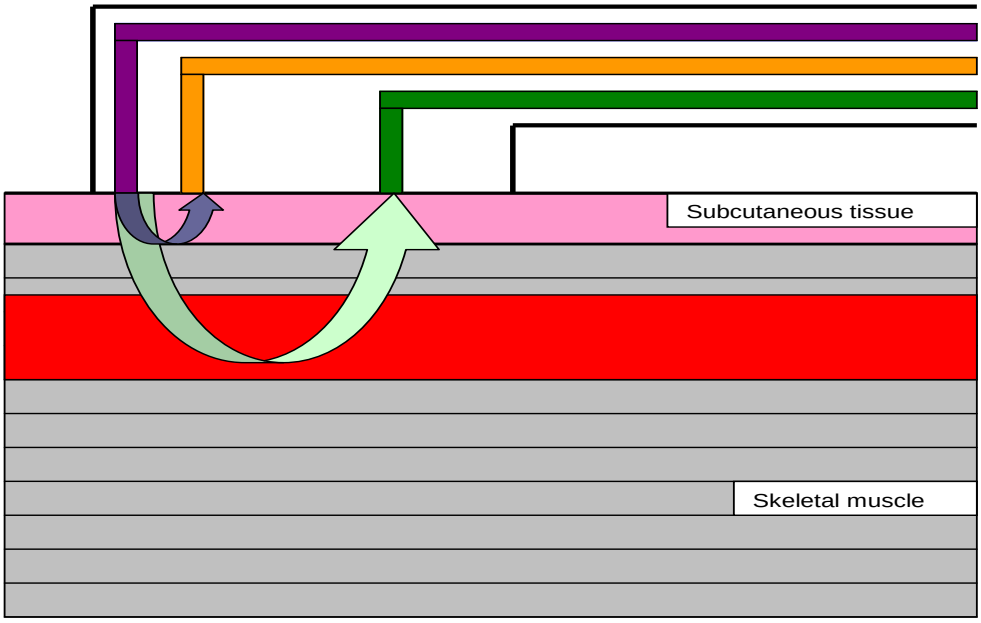

Figure 2. Tissue oxygen saturation monitoring technique

The complexity in determining the actual path length of the light detected by the receiving sensors has been discussed by some authors (Soller et al, 2008), although it is widely accepted that 70-80% of blood in the tissues is in the venous

compartment, so tissue oxygen saturation is actually a reflection of venous saturation and therefore perfusion (Keller et al, 2006; Ward et al, 2006; Schober and Schwarte, 2012).

Changes in tissue oxygen saturation readings in the critically ill casualty would indicate changes in the regional perfusion of the site being monitored. However, treatment protocols implemented to manage the casualty's condition may also affect rSO_2 readings, such as the use of inotropes (potentially increasing peripheral vasoconstriction) or the induction of anaesthesia (potentially causing peripheral vasodilation) (Sheeren et al, 2012), so readings need to be considered in context.

There is little evidence that tissue oxygen saturation monitoring has been used to evaluate the effects of altitude in aeromedical evacuation casualties. Two air evacuation studies were identified: Sagraves et al (2009) describe the use of tissue oxygen saturation monitoring in the pre-hospital setting, in both ground and air ambulances and Guyette et al (2008) describe the use of tissue oxygen saturation monitoring in conjunction with lactate monitoring during air transport of trauma patients by helicopter. Neither study considered the effect of altitude; probably because air evacuation by helicopter is generally performed over short distances at relatively low altitudes, compared with evacuation by fixed wing aircraft. The lack of related studies would suggest that this is a novel use of the monitoring system and technique.

Several recent studies have monitored tissue oxygen saturation in trauma patients to try to identify a reliable end-point for traumatic shock resuscitation. McKinley et al (2000) measured oxygen saturation in subcutaneous tissue and in

skeletal muscle in 8 severely injured casualties during and following the initiation of a standardised resuscitation protocol. Skeletal muscle oxygen saturation increased significantly during the 24 hour monitoring period, as local perfusion improved, in response to the administration of blood products and supplemental oxygen; however, subcutaneous tissue readings were higher and remained fairly constant throughout the resuscitation period. In this study, skeletal muscle tissue oxygen saturation appeared to correlate with arterial base deficit and lactate measurements, which are accepted end resuscitation points already.

Cohn et al (2007) collected tissue oxygen saturation readings from the thenar eminence of 381 torso trauma cases admitted to one of seven Level 1 trauma centres. Their aim was to determine whether tissue oxygen saturation readings could be utilised to predict those trauma patients who would go on to develop Multiple Organ Dysfunction Syndrome (MODS) or die. The results of the study suggested that tissue oxygen saturation readings could identify those patients who would develop MODS and those who would die following their trauma. Tissue oxygen saturation was as reliable as arterial base deficit and systolic blood pressure in identifying MODS and mortality amongst the study population.

In their study of 22 critically ill patients, Lima et al (2009) also demonstrated that patients with a persistently low tissue oxygen saturation reading (<70%) on admission to the intensive care unit following resuscitation had significantly worse organ failure or mortality than those with normal readings. However, the study failed to demonstrate any correlation between tissue oxygen

saturation and other haemodynamic monitoring, such as heart rate, mean arterial pressure or central venous oxygen saturation.

Putnam et al (2007) demonstrated that not only was tissue oxygen saturation as reliable as arterial base deficit and lactate in identifying hypo-perfusion, the condition could be recognised much earlier using tissue oxygen saturation readings. The results demonstrated that the lowest tissue oxygen saturation reading was recorded over 90 minutes earlier than the highest lactate value was obtained. Early identification of hypo-perfusion allows clinicians to initiate appropriate interventions early.

Convertino et al (2008) suggest that tissue oxygen saturation monitoring has multiple benefits over arterial base deficit and lactate in predicting hypo-perfusion. It is a non-invasive continuous system, which allows monitoring to be performed in a wide variety of settings with updated readings every few seconds. Blood sampling requires an invasive procedure, which may not always be possible, particularly in the pre-hospital setting and it provides intermittent data, potentially delaying the recognition of hypo-perfusion and its subsequent treatment.

The main conclusions from these studies appear to be that tissue oxygen saturation has a place in haemodynamic monitoring as a reliable non-invasive system, which shows great promise, but which requires further study.

Crookes et al (2005) recorded tissue oxygen saturation at the thenar eminence in 707 healthy volunteers to establish a normal range of readings, although the sample population consisted of more than 60% of women; over 60% of the sample group were from a Hispanic background – making the results

potentially less representative for other geographic regions. The authors also recorded thenar eminence tissue oxygen saturation in conjunction with standard haemodynamic monitoring in 145 trauma casualties admitted to a trauma centre resuscitation room. The subsequent data was presented to a panel of trauma surgeons, without the tissue oxygen saturation readings; the panel were asked to classify the severity of shock for each casualty based on the data presented. 4 categories of shock were used: no shock, mild, moderate and severe. Mean tissue oxygen saturation readings were not statistically significant between the no shock, mild and moderate categories and failed to differentiate between the 3 groups; however, tissue oxygen saturation readings did show a significant fall in the severe shock group. This study was limited by the small numbers in each group; of 145 patients, only 19 were classified as mild shock, and 14 each in the moderate and severe shock groups. The authors reported large standard deviations in each group as a result of the small numbers and concluded that a larger scale study would be required to permit the identification of any discrete patterns within the data.

Creteur, Neves and Vincent (2009) describe a study to evaluate the effects of red blood cell transfusion on tissue oxygenation. 44 patients were included in the study; haemodynamic monitoring, including tissue oxygen saturation, was recorded pre-transfusion and 1 hour post transfusion. All patients received one unit of packed red blood cells; blood gases, haemoglobin and lactate levels were also recorded pre- and 1 hour post transfusion. Although haemoglobin concentrations increased following the transfusions, tissue oxygen saturation did not consistently improve as a result; however, some individuals did demonstrate

significant changes in tissue oxygenation – interestingly, demonstrating both improvement and deterioration in readings. Again, the authors conclude that tissue oxygen saturation monitoring may have a role in the effects of transfusion in the critically ill, but more studies are required.

The majority of these studies utilised the InSpectra™ Tissue Oxygenation Monitor (Hutchinson Technology) and used the thenar eminence as the site of monitoring. Soller et al (2008a) suggest that monitoring in other sites such as the deep muscles in the forearm may be more sensitive to changes in tissue oxygenation than at the thenar eminence.

1.4. Research Aims

It is this potential combination of hypoxic hypoxia and anaemic hypoxia in military casualties undergoing aeromedical evacuation which forms the basis for this study. Anecdotal reports (Personal communication McLeod/AECC 2008) have suggested that several AE patients may have arrived at the receiving UK hospital with a haemoglobin level significantly lower than that recorded pre-flight, despite the absence of active haemorrhage or other blood loss. A review of the in-flight pulse oximetry readings for these cases failed to demonstrate a significant fall in arterial oxyhaemoglobin saturation; however, this is a systemic measurement and is not necessarily indicative of oxygenation in localised tissues (Schober and Schwarte, 2012). In severely injured casualties, who may already be experiencing anaemic hypoxia as a result of trauma, the potential addition of hypoxic hypoxia may result in inadequate peripheral tissue oxygenation and end organ damage, associated with a less favourable outcome. There is little evidence

that the effects of early aeromedical evacuation in these specific casualty groups have been empirically considered.

The aims of this research are to:

i) Review existing clinical data for outcomes of military casualties undergoing AE, with particular emphasis on pre and post flight haemoglobin levels (Phase 1).

ii) Determine the ability of tissue oxygen saturation monitoring to detect changes during a controlled model of altered perfusion (Phase 2).

iii) Undertake an observational study to identify if changes in tissue oxygenation are observed in casualties undergoing AE and whether these changes differ dependent on haemoglobin levels (Phase 3).

2. A RETROSPECTIVE REVIEW OF AEROMEDICAL EVACUATION RECORDS

2.1. Methods

Aim: The aim of phase 1 of the study was to review existing clinical data for the outcomes of military casualties undergoing aeromedical evacuation, with particular emphasis on pre- and post-flight haemoglobin levels. This was achieved through a retrospective review of the aeromedical evacuation records for casualties returned from Afghanistan to the UK, following significant traumatic injury. Specifically, the records were examined for evidence of changes in clinical condition and / or alterations in clinical management during the flight. Although it would not be possible to attribute any changes in condition or management to a specific cause, given the retrospective nature of the data, the aim was to identify the number and frequency of in-flight changes. As the primary rationale for the study focused on pre-flight haemoglobin levels, a secondary aim was to investigate whether there were more changes in those casualties with lower pre-flight haemoglobin levels. The information from this phase of the study would be used to inform the later observational phase.

Study protocol: The study protocol was submitted to and approved by the RAF Experimental Medicine Scientific Advisory Committee (RAF EMSAC) as a retrospective audit (EMSAC reference SP0933).

Subjects: An electronic search of the AE flight database held at the Aeromedical Evacuation Control Centre (AECC) at RAF Brize Norton was undertaken by AECC staff. The search parameters were all CCAST flights from Operation HERRICK (Afghanistan) between April and November 2009. During

this time frame, 97 casualties were evacuated from Afghanistan, utilising critical care escorts. Eight cases were subsequently excluded from the study, as the casualties were transferred directly to other European countries and were not admitted to UK hospitals, so there was no record of their subsequent management available for audit. Of the 89 cases remaining, a third were randomly selected for review (*n=29*), using a random number selection programme. However, during the data extraction phase, a further two cases were excluded from the audit. Although these 2 casualties had been brought back to a British airhead, on landing they had been immediately transferred to a different aircraft for onward movement to another country. A total of twenty-seven cases were included in the final audit.

In-flight records for each of the 27 casualties were retrieved from the archive held by the Aeromedical Evacuation Squadron at Tactical Medical Wing, RAF Lyneham. Anonymised photocopies of the records were made to permit off-site audit; these copies were destroyed on completion of the data analysis.

Two audit requests were made for the release of additional post-flight data from the Joint Theatre Trauma Registry (JTTR) held by the Academic Department of Military Emergency Medicine (ADMEM) at RCDM. The data request was for the post-flight haemoglobin and haematocrit levels (defined as the first results obtained on arrival at the receiving hospital) recorded during visits by the military trauma co-ordinator team and the second request was for the injury severity score (ISS) for each casualty (see Appendix A) as calculated by the trauma co-ordinator from the record of the casualty's injuries. The ISS was requested, as it allows comparison of the severity of each casualty's injuries,

irrespective of the site or modality of their injuries and is a recognised method of comparing the severity of injury between poly-trauma casualties.

***Audit Procedure**:* A standardised data collection matrix was used to extract relevant data from each set of AE records. This included:

a. Mechanism of injury
b. Injuries sustained
c. Injury Severity Score (ISS) and New Injury Severity Score (NISS)
d. Blood / blood replacement therapy post injury
e. Pre and post-flight haemoglobin and haematocrit levels
f. Documented physiological parameters including blood pressure, temperature, pulse rate, respiratory rate, pulse oximetry and arterial blood gases (where measured) throughout the aeromedical evacuation
g. Clinical in-flight management parameters, such as ventilator settings, and the rate and type of sedation agents, inotropic support or fluid replacement therapy given.

The anonymised data were stored in a Microsoft© Excel spreadsheet which permitted calculation of specific descriptive statistics.

2.2. Results

Aeromedical evacuation of the 27 casualties from Afghanistan to the UK was successfully completed with no fatalities en-route. A total of 297.75 monitoring hours were recorded by CCAST members, with a mean transfer time of 11 hours per casualty (range 7-17 hours). The difference in flight times related to the route taken by each aircraft, with some returning direct to the UK and some

making re-fuelling stops in various locations en route. All flights landed in Birmingham, where the casualties were off-loaded and transferred to RCDM.

Demographics: All twenty-seven casualties were male; the mean age was 25 years ± 6.1 (range 18-38 years). The majority of casualties (*n=26)* had received their injuries as a result of battlefield trauma, with improvised explosive devices (IED) causing the majority of traumatic injuries in this group (*n=23).* The remaining casualty had developed a non-trauma medical condition, which progressed rapidly, requiring urgent evacuation. For the 26 trauma casualties, the mean ISS (±SD) was 31.3 ± 15.46 (range 9-75) and the mean NISS (±SD) was 39.88 ± 18.23 (range 9-75), indicating that 25 of the casualties had sustained severe trauma as defined by both ISS and NISS. With an ISS of 75, termed as injuries incompatible with life, 2 of the casualties were classified as 'unexpected survivors'.

Ventilation: Twenty-six casualties had been intubated and ventilated pre-flight and were maintained in this condition throughout their transfers. One casualty was initially breathing spontaneously with supplemental oxygen via a face mask; however, his condition deteriorated during the flight and he required intubation and ventilation for stabilisation. All casualties were ventilated using the LTV 1000 patient ventilator, manufactured by Pulmonetic Systems, Inc. The majority of the casualties (*n=18*) were ventilated using the volume control mode on the LTV 1000 although one ventilator was reset to deliver pressure control mode during the transfer. The casualty intubated en route was ventilated using volume control mode. Eight casualties were ventilated using pressure control mode, although 2 were changed to volume control mode in-flight.

Details of the initial ventilator settings were extracted from the aeromedical evacuation records and every subsequent change to the original setting noted (Table 1). Excluding changes in mode of ventilation, there were 86 recorded alterations to ventilation settings in-flight, averaging 0.28 changes per hour of monitoring.

Recorded Values	Mean ± SD	Range		In-flight Changes
		Min	Max	
Set tidal volume (mL)	572.5 ± 68.36	380	690	5
Set respiratory rate (bpm)	16.1 ± 2.71	12	20	42
Set PEEP (cm H_2O)	5.9 ± 1.97	5	10	4
Set FiO_2	0.4 ± 0.16	0.3	1	35

Table 1. Initial ventilator settings and in-flight changes
PEEP = Peak End Expiratory Pressure; FiO_2 = Fraction of inspired oxygen

Changes to respiratory rates were most common, with 42 changes noted, averaging 0.14 changes per monitored hour (Table 2). Six casualties ended their flights with a higher respiratory rate setting than at the start and 11 had a lower rate setting; 8 casualties had unchanged respiratory rate settings and 2 casualties had rate changes in-flight but had returned to the original setting by the end. Three casualties did not have any documented changes to their ventilator settings throughout the transfers.

Value	Total Number of Changes	Mean Number of Changes		Range of Changes per Casualty
		Per Casualty (*n=27*)	Per Monitored Hour (*n=297.75*)	
Tidal volume	5	0.4	0.01	0-1
Respiratory rate	42	1.5	0.14	0-5
PEEP	4	0.14	0.01	0-2
FiO_2	35	1.29	0.11	0-4
Total Changes	86	3.18	0.28	0-6

Table 2. Mean number of changes per casualty and per monitored hour

The second most common alteration was to FiO_2 delivery, with 35 changes recorded. Eight casualties ended their flights with higher FiO_2 settings than at the start and 9 had lower settings; 7 were unchanged throughout the flight and 3 had been changed during the transfer but had returned to the original setting by the end of the flight.

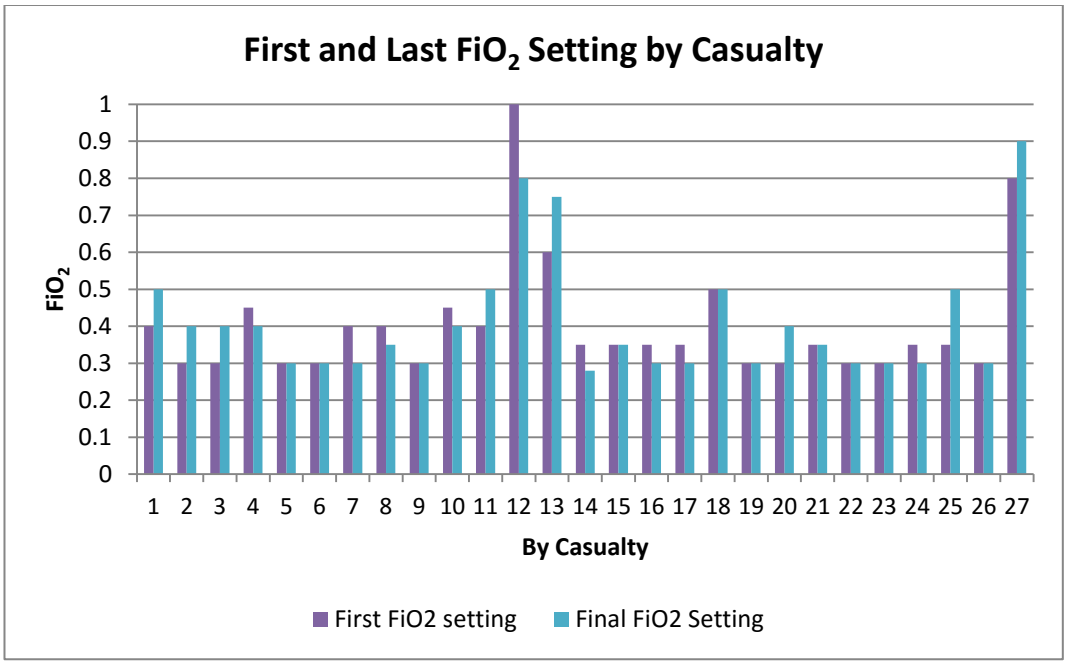

Figure 3. First and last FiO_2 setting by casualty

In the majority of cases (*n=25*), the documented peripheral arterial oxygen saturation (SpO_2) was between 95-100%. One casualty had a lower range, between 93-96%. The casualty who was initially breathing spontaneously showed a deteriorating SpO_2 level and was intubated and ventilated at saturations of 89%; with mechanical ventilation, his SpO_2 improved to 97%. Only 1 set of records recorded a de-saturation event, which had been caused by a mucus plug and was cleared with endotracheal tube suction.

Sedation: Five different medication types were used to maintain in-flight sedation, with the majority of casualties (*n=22)* receiving a combination of 2

medications and the remaining 5 casualties receiving a 3 medication combination. In total, 59 separate infusions of medication were administered between the 27 casualties. Propofol and fentanyl or a fentanyl derivative (alfentanil or remefentanil) was the most frequently used combination and was used in 17 cases to maintain sedation in-flight. A midazolam and morphine combination was used in 4 casualties, with the remaining 6 casualties receiving alternative combinations.

The rates of administration for each medication were titrated to individual need and were altered throughout the flight as required. Thirty three infusions remained unchanged throughout the administration period. In the remaining 26 infusions, there were a total of 60 changes to the rates of administration, with a mean of 2.3 changes per infusion.

By the end of the various flights, a review of the 59 infusions showed 15 cases where a higher dose was being administered compared with the start of the flight, 11 cases where the rate had decreased and 29 cases where the rate remained unchanged throughout the transfer. The breakdown of these changes is shown at Table 3. In four cases, the medication rates had been altered during the flight but had been returned to their original rate by the end of the flight.

Medication	Rate Change			Other Rate Changes[3]
	Increase	Decrease	None	
Propofol (*n=22*)	5	4	10	3
Fentanyl/Derivative (*n=20*)	3	3	13	1
Morphine (*n=7*)	4	1	2	0
Midazolam (*n=8*)	3	1	4	0
Ketamine (*n=2*)	0	2	0	0

Table 3. Comparison of pre-flight and post-flight medication administration rates

[3] Rates were changed in-flight but had been reset to the original rate by the end of the flight

Inotropic support: Sixteen of the casualties required inotropic support en route, receiving noradrenaline infusions. There were a total of 52 changes in the rates of infusion over the course of the flight, averaging 3.25 changes per casualty. At the end of their flight, the pre-flight infusion rates had been increased in 9 casualties, reduced in 5 and remained unchanged in 2 casualties.

Mean arterial pressure: Mean arterial pressure (MAP), calculated from the formula *MAP = diastolic pressure + 1/3 (systolic pressure – diastolic pressure)*, represents the average arterial pressure perfusing the body; to maintain adequate perfusion of the vital organs, fluid administration and inotrope therapy is often titrated to maintain a minimum MAP of 60mmHg. Individual MAP readings varied throughout the duration of the flights and showed wide variation between casualties. These readings were normalised, to demonstrate individual variability throughout the flight time (Figure 4).

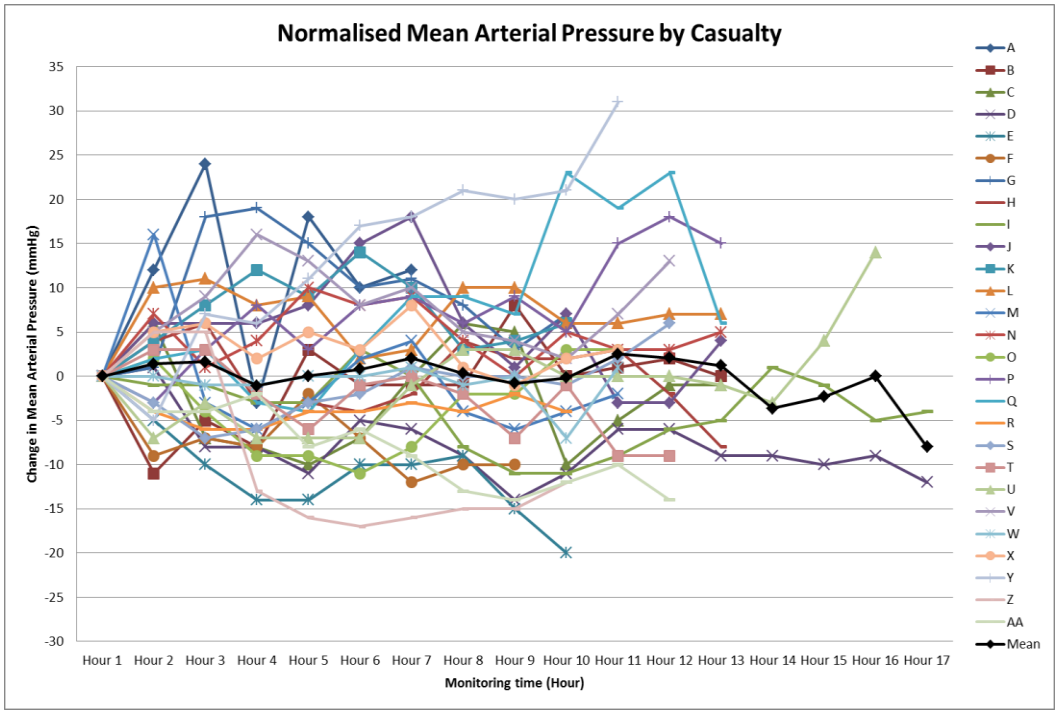

Figure 4. Normalised Mean Arterial Pressure by Casualty

The results of a paired t-test comparing the first and last MAP readings for the 27 casualties are shown at Table 4. Although mean MAP had increased slightly by the end of the flights, this was not shown to be statistically significant (*p=0.5185*).

Timing	**Mean Arterial Pressure (mmHg)**			
	Mean	***Std Err***	***Std Dev***	***95% Confidence Interval***
First Hour	69.6	1.8	9.2	65.9 73.2
Last Hour	70.9	2.1	10.7	66.7 75.1
Difference	-1.4	2.1	10.9	-5.7 2.9

Table 4. Table comparing first and last MAP readings in 27 casualties

However, the normalised MAP chart at Figure 4 demonstrated wide variations in hourly readings during the flight for some individuals. The mean MAP reading and the variance were calculated for each casualty for the duration of their flights. As a scatter plot, this appeared to show a non-linear trend in readings, so a fractional polynomial regression model was fitted to predict variance (Figure 5) in mean MAP amongst the casualties for the duration of their flights. Initially this was plotted for the entire flight duration for each casualty.

The solid blue line shows the trend for all 27 casualties with a 95% confidence interval illustrated by the grey band. As previously seen at Figure 4, there appeared to be wide variations in the hourly MAP during the early phases of the flights, so the regression analysis was repeated as previously described, using specific time subdivisions for closer examination of the variance. The total flight time was broken down into flight hour brackets of 1-5 hours, 6-10 hours and 11-17 hours. During the first 5 hours of the flight (Figure 6), the variance appeared

larger, when compared with the next 5 hours (Figure 7), when the amount of variance appeared to have reduced. Four casualties in particular demonstrated higher variance during the first 5 hours of monitoring.

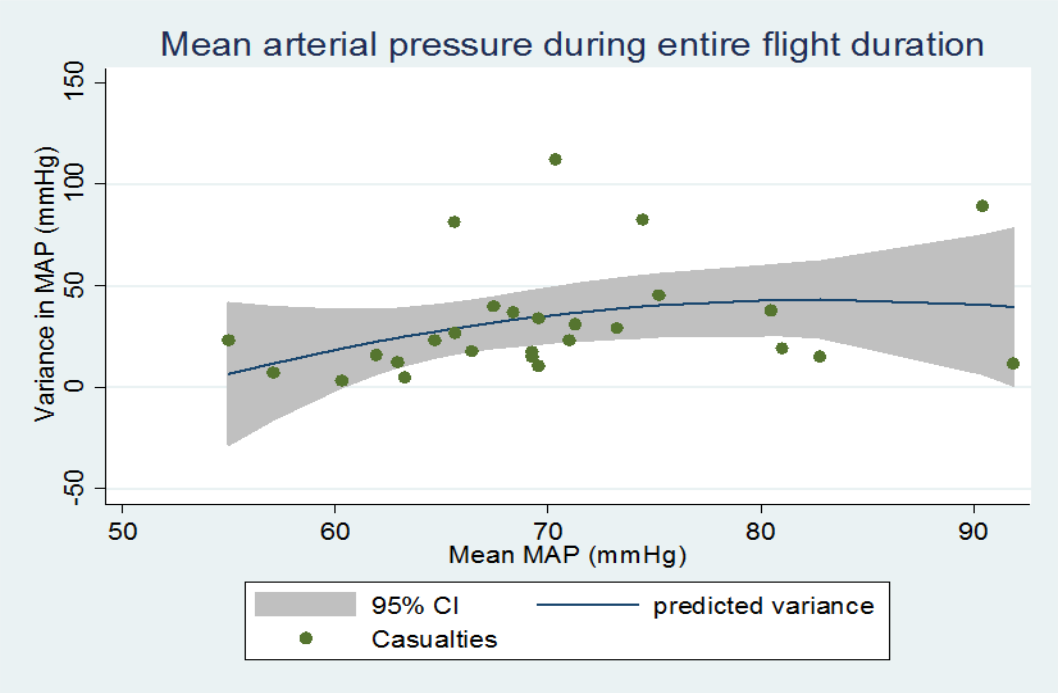

Figure 5. Mean MAP predicted variance by casualty for the total flight time

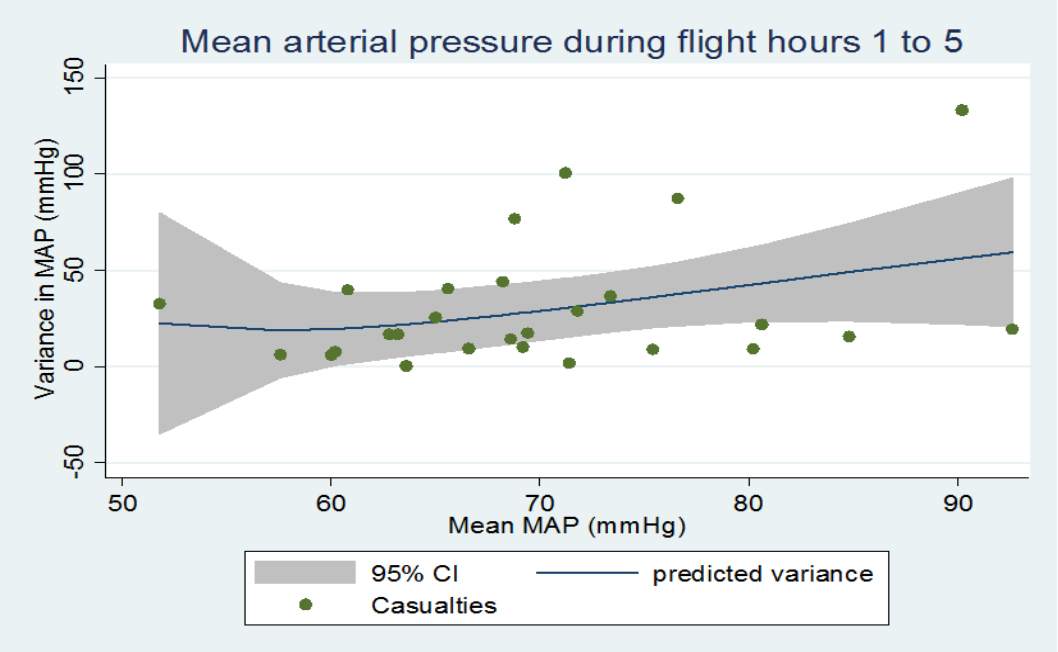

Figure 6. Mean MAP predicted variance by casualty for flight hours 1 to 5

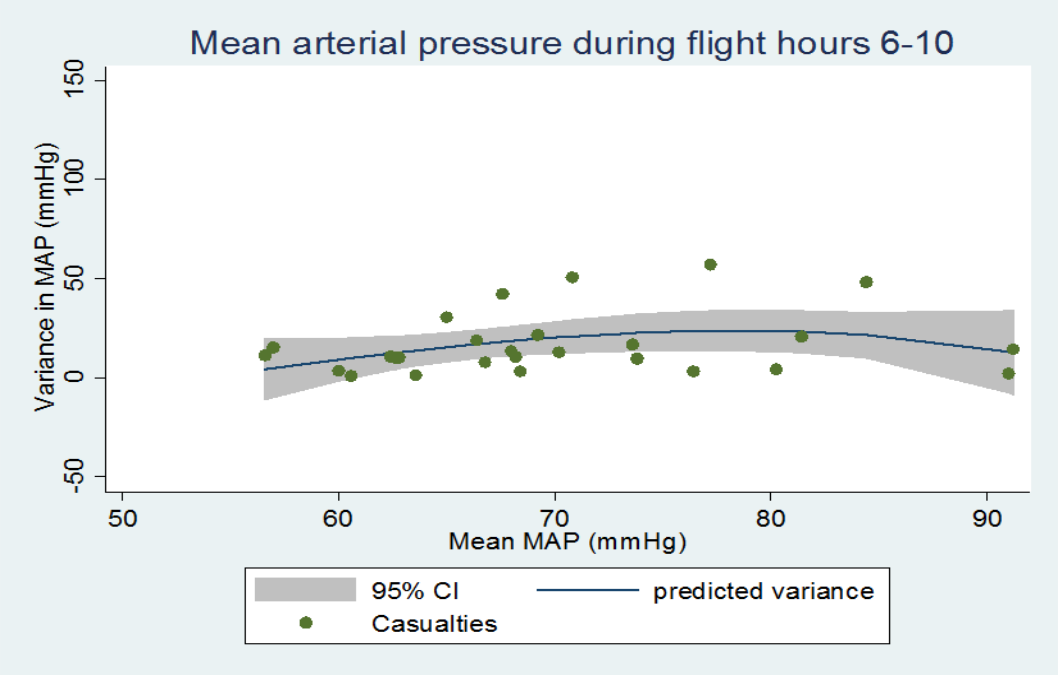

Figure 7. Mean MAP predicted variance by casualty for flight hours 6 to 10

Haemoglobin levels: A review of the pre-flight haemoglobin levels revealed that 14 casualties had a haemoglobin level below 10g/dL prior to the start of their transfers (range 6.5 – 9.9g/dL); pre-flight blood had been administered to 12 of these individuals (information for the remaining 2 casualties was not provided). A total of 208 units of blood (range 1-30; mean 17.3 units/casualty) and 206 units of fresh frozen plasma (FFP) (range 1-30; mean 17.1 units/casualty) had been transfused into this group in the time between injury and aeromedical evacuation. Nine of these casualties received further blood products in-flight: 13 units of blood (mean 0.9 units/casualty) and 5 of FFP (mean 0.3 units/casualty).

The remaining 13 casualties had haemoglobin levels above 10g/dL pre-flight (range 10.1-14.3g/dL). Eight sets of records indicated that the casualties had received blood transfusions in the time between injury and transfer, receiving

a total of 166 units of blood (range 0-31; mean 20.75 units/casualty) and 148 units of FFP (range 0-31; mean 18.5 units/casualty). Records of pre-flight administration for the remaining 5 casualties were not provided. Three of the 13 casualties received further blood products in-flight: 5 units of blood (mean 0.4 units/casualty) and 3 units of FFP (mean 0.2 units/casualty).

Of the 14 casualties with a pre-flight haemoglobin below 10g/dL, twelve had a higher post-flight haemoglobin and nine of these had a post-flight haemoglobin above 10g/dL. In the group with a pre-flight haemoglobin level above 10g/dL, seven had a higher post-flight haemoglobin level; five had a lower post-flight level (2 of which fell below 10g/dL) and 1 casualty's haemoglobin remained unchanged. Figure 8 depicts the pre and post-flight haemoglobin levels for each casualty.

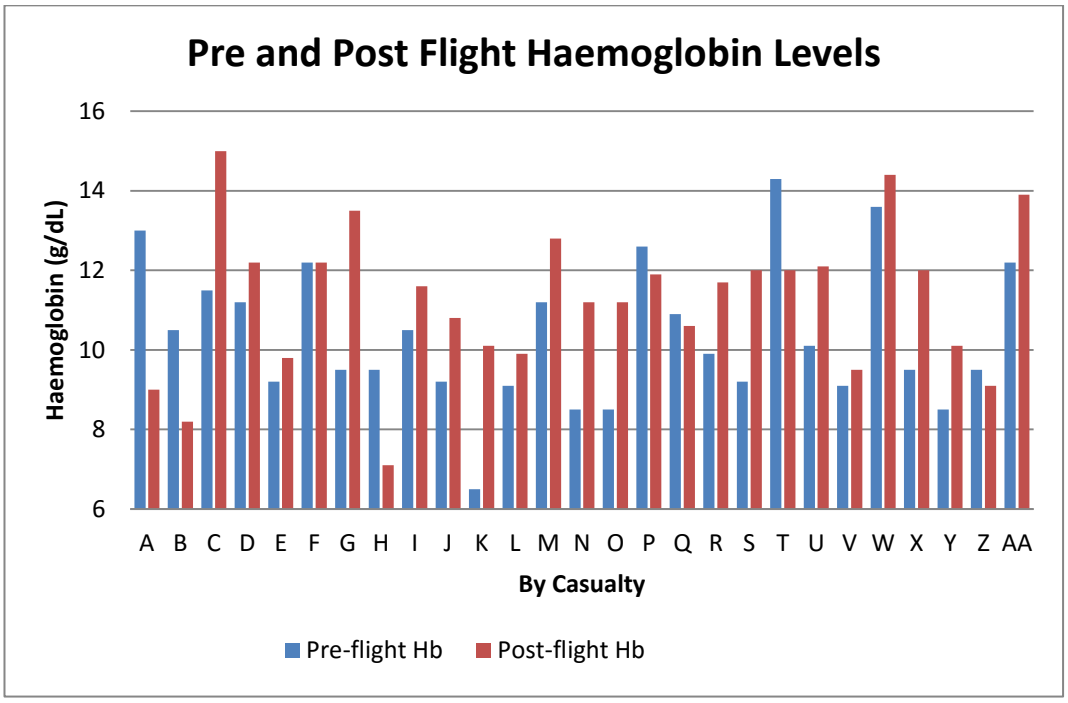

Figure 8. Pre- and post-flight haemoglobin levels by casualty

Table 5 demonstrates the results of a paired t-test comparing pre and post-flight haemoglobin levels for the 27 casualties. The mean post-flight

haemoglobin result was almost 1g/dL higher than the mean pre-flight result and this proved to be statistically significant (*p=0.0259*).

Timing	**Haemoglobin (g/dL)**				
	Mean	***Std Err***	***Std Dev***	***95% Confidence Interval***	
Pre Flight	10.4	0.3	1.8	9.7	11.1
Post Flight	11.3*	0.4	1.9	10.5	12.0
Difference	-0.9	0.4	2.0	-1.7	-0.1

Table 5. The results of a paired t-test comparing pre and post-flight haemoglobin levels in 27 casualties
* indicates $p<0.05$ compared to pre-flight value

The total number of changes in clinical management was subdivided to compare whether casualties with a lower pre-flight haemoglobin level (<10g/dL) were subject to more changes in management during aeromedical evacuation (Table 6) than were casualties with a higher pre-flight haemoglobin level (>10g/dL). The number of changes in clinical management in-flight was similar, with the exception of sedation rate changes. More changes were seen within the higher pre-flight haemoglobin group, but 19 of the 44 changes were seen in just 2 casualties, both of whom had suffered head injuries and required close control of systolic blood pressure to prevent raised intra-cranial pressure. Administration rates for sedation medication were adjusted frequently in these two casualties to assist with maintaining a stable systolic blood pressure. Excluding the changes in sedation rates for these two individuals brought the number of changes seen in the higher pre-flight haemoglobin group down to 25, which was still slightly more than in the other group.

Interventions	Haemoglobin >10g/dL (*n=13*)	Haemoglobin <10g/dL (*n=14*)
Sedation Rate Changes (*n=60*)	44	16
Inotrope Rate Changes (*n=52*)	24	28
FiO_2 Changes (*n=35*)	18	17
Respiratory Rate Changes (*n=42*)	25	17
Total Ventilation Changes (*n=86*)	47	39

Table 6. Number of clinical management changes by haemoglobin level

The earlier comparison of pre- and post-flight infusion rate settings were also subdivided by haemoglobin level, to compare whether there were more changes in the group with a lower haemoglobin level during aeromedical evacuation. The breakdown of this comparison is shown at Table 7 and demonstrates little difference between the two groups.

Interventions		Haemoglobin >10g/dL	Haemoglobin <10g/dL
Sedation Infusion (*n=59*)	Increase	9	6
	Decrease	6	5
	No Change	12 (2)[4]	17 (2)
Inotrope Infusion (*n=16*)	Increase	2	3
	Decrease	5	4
	No Change	1	1
Respiratory Rate (*n=27*)	Increase	3	3
	Decrease	7	4
	No Change	2 (1)	6 (1)

Table 7. Post-flight changes in pre-flight infusion rate settings by haemoglobin level

Table 8 demonstrates the total number of sedation infusions where the pre-flight setting had been altered by the end of the flight compared with the number of sedation infusions which were unchanged throughout the flight, further subdivided into 2 groups by haemoglobin level. Again, the numbers for each group were very similar and a Pearson's chi-squared test demonstrated no statistical significance (*p=0.244*) between the 2 groups.

[4]Bracketed figures depicts where rates were changed in-flight but had been reset to the original rate by the end of the flight

Sedation Rate	Haemoglobin >10g/dL	Haemoglobin <10g/dL
Rate Changed	15	11
Rate Unchanged	14	19

Table 8. A comparison of final sedation infusion rate changes by haemoglobin level

Eleven of the casualties had been transported with a cabin altitude restriction; in these cases, the pressurisation of the aircraft cabin was maintained at an altitude between 3,000 to 5,000ft, instead of the usual range of between 6,000 and 8,000ft. These restrictions were prompted by the casualties' injuries and clinical condition, and were made to minimise the effects of pressure change caused by ascent to altitude, which could potentially exacerbate the original injuries sustained. For example, penetrating head or eye injuries where air had entered previously closed spaces; expansion of the air with increasing altitude would potentially increase the damage caused to the brain or eye.

2.3. Discussion

Random selection of the cases included in the retrospective audit reduced the risk of any selection bias; although the 97 casualties injured during the specified time frame would be from a relatively homogenous group – as serving members of the military, the population at risk is aged between 18 and 55 years, pre-dominantly male and in good health prior to sustaining injury. In their study, Allcock et al (2011) undertook a retrospective review of the records for all UK casualties, injured in Afghanistan as a result of trauma, who received a massive blood transfusion. Some of the casualties from the current study would have been amongst the 59 cases included in Allcock's review. All casualties were male, and the authors reported the median age was 23.5 years (range 18.1 - 42.3 years),

demonstrating that serving military personnel belong to a relatively homogenous group.

This retrospective audit of aeromedical evacuation records demonstrated a number of in-flight changes in clinical condition and / or clinical management for the 27 cases reviewed. In the main, the casualties had received severe traumatic injuries which required initial damage control surgery and / or massive transfusions of blood and blood products, necessitating early aeromedical evacuation to the UK for further surgical and medical management. The hypothesis under test in this phase of the study was that casualties with lower pre-flight haemoglobin levels, defined as less than 10g/dL, would experience more in-flight changes in clinical condition and / or clinical management than casualties with higher pre-flight haemoglobin levels, above 10g/dL. However, data analysis revealed very little difference between the two groups. It was observed that most of the changes in clinical management were seen in the casualties with a higher pre-flight haemoglobin level; however, some of the in-flight management changes seen in this group were due to an improvement in the casualty's condition, leading to a reduction in their treatment requirements. A further analysis of the management changes was undertaken with the aim of dividing the changes into positive and negative changes (i.e. changes in response to an improvement in the casualty's condition (positive) compared with changes in response to any deterioration in the casualty's condition (negative)). The goal was to compare the number of positive and negative changes for both haemoglobin groups. However, it quickly became evident that this aim was too simplistic, as some seemingly positive changes could actually be negative changes. An example of this was seen

in the changes made to a casualty's sedation treatment; the charts showed the hourly rate was being reduced, which could be seen as a positive change, with the casualty requiring less sedation to maintain a stable condition. However, in the written records, it was documented that the sedation rates had been altered to maintain a narrow range of systolic blood pressure to prevent raised intra-cranial pressure in a head injured patient, so actually demonstrating a negative change in clinical management. Likewise, reductions in ventilation requirements can initially be seen as a positive change, unless the changes are made in an attempt to lower a rising end tidal carbon dioxide level, in a casualty whose condition is deteriorating.

In-flight physiological monitoring of the casualties was undertaken, capturing a variety of data including blood pressure, heart rate and temperature. The aim was to examine the hourly measurements for each casualty to identify changes in condition during the AE. However, accurate data extraction of these variables from the casualties' records was difficult to achieve, as they were documented in graphic format, more designed to show trends across time. Mean arterial pressure was recorded in numeric format, making data extraction more precise. For this reason, analysis of the physiological monitoring recorded was restricted to mean arterial pressure. A t-test comparison of the first and last MAP readings for the 27 casualties failed to demonstrate any significant changes, which was confirmed by an ANOVA comparing mean MAP readings at the first, fifth and last hour of the individual flights. However, there were obvious fluctuations in the hourly measurements for several individual casualties. During analysis of the variance in MAP between individuals, 4 casualties were identified as having a

higher variance than the remaining 23 casualties. As previously discussed, it is difficult to attribute this variation to one particular cause; although all 4 had been injured as a result of IED blasts, they had suffered different types of injuries, affecting different body regions and accordingly had received different clinical management. Interestingly, the MAP variance analysis actually demonstrated greater variance in the first five hours of in-flight monitoring, compared with later stages of the flights. During this phase, the casualties have been moved from the Intensive Care Unit at the Field Hospital via battlefield ambulance to the back of the aircraft and then exposed to pressure and environment changes as the aircraft begins the journey back to the UK. These events are likely to have an effect on the casualties' physiological condition initially. Once the casualties' conditions had stabilised and the aircraft was at a cruising altitude, fewer fluctuations in mean arterial pressure were seen in the later phases of the aeromedical evacuation, when fewer interventions were initiated. The aeromedical evacuation records end when the casualties are off-loaded at Birmingham, but it would be interesting to examine the MAP variance in the first few hours after arrival at the receiving hospital, after the casualty has been exposed to the pressure and environmental changes during the aircraft's descent followed by a road transfer by ambulance to hospital.

In their 2006 study, Barnes et al (2008) undertook continuous monitoring of 22 ventilated casualties during aeromedical evacuation between Iraq and Germany. The casualties in the 2006 study and the current study had a similar mean age (27 years compared with 25 years) and similar ISS (31.75 compared

with 31.3). The authors of the 2006 study identified that the most common change made to ventilator settings was to FiO_2 delivery, averaging 0.27 changes per monitored hour; within the current study, FiO_2 delivery was the second most common change, averaging 0.11 changes per hour. Set respiratory rate was the second most common change in the 2006 study, averaging 0.22 changes per hour which compares with 0.14 changes per hour in the current study. In total, there were fewer changes to ventilator settings in the current study compared with the 2006 study, although neither study demonstrated large numbers of changes in ventilation. However, the 2006 study recorded continuous data from the ventilators, meaning all changes were recorded; in the current study, it is possible that any changes occurring between the hourly recordings of data could be missed and so omitted from the overall analysis. Only 3 episodes of de-saturation (defined as SpO_2 less than 90%) were recorded during the continuous monitoring in the 2006 study. These events ranged from 35 seconds to 4 minutes 40 seconds in duration and all resolved without intervention. In the current study, which analysed hourly monitoring records, only one de-saturation event was described, which required clinical intervention to resolve the situation.

Limitations: The retrospective nature of the current study made analysis of the data challenging. Any changes in physiological condition which occurred between the hourly recordings were potentially lost from the analysis, unless documented in the written records. The reasons for changes in clinical management were, at times, unclear and not always documented in the aeromedical evacuation records, so although, for example, there were more

changes in sedation rates in the higher pre-flight haemoglobin group, this was not necessarily an objective comparison for the reasons discussed earlier. Likewise, the different CCAST personnel involved in each flight may have had an impact in the number or type of changes in clinical management; more experienced personnel might have been more confident in making in-flight changes in response to improvements in the casualty's condition than less experienced personnel, who might be more content to maintain pre-flight settings in the absence of any deterioration of the casualty's condition during aeromedical evacuation.

Conclusion: In this retrospective audit of aeromedical evacuation records, in-flight changes in clinical condition and medical management were seen; however, haemoglobin status did not appear to be a predictor for this, as more changes were seen in the group with higher pre-flight haemoglobin levels. This would suggest that a low haemoglobin level should not in itself delay aeromedical evacuation; however, the physiological monitoring undertaken during these flights is predominantly measuring systemic markers and provides little information on a regional level.

3. HYPOBARIC ASSESSMENT OF THE LTV1000 PATIENT VENTILATOR

3.1. Methods

The Defence Medical Services provide an aeromedical evacuation service to repatriate military personnel who become ill or are injured whilst serving abroad. Critically ill patients who require high dependency or intensive care management in-flight are escorted by a critical care air support team (CCAST) carrying appropriate support equipment.

One such item of CCAST support equipment is the LTV 1000 patient ventilator, manufactured by Pulmonetic Systems, Inc, Minneapolis, MN, USA. During the retrospective review of aeromedical evacuation records carried out during phase 1 of this study, a comment was found written in one of these sets of records suggested that the LTV ventilator did not appear to be delivering the pre-set tidal volumes whilst in use at altitude. As a result of this comment and some anecdotal reports from CCAST clinicians regarding potential physiological indications of hyperventilation at altitude, it was decided to undertake an additional experimental phase to test the LTV ventilator's performance at altitude[5].

***Aim*:** The aim of the study was to examine the performance of the LTV 1000 patient ventilator both on the ground and during an ascent in a hypobaric chamber to the maximum expected cabin altitude of 8,000 feet (2438 metres), which is equal to an environmental pressure of 565mmHg. This would allow

[5] Ventilator study undertaken in conjunction with Wg Cdr N Green, Consultant Advisor in Aviation Medicine and Gp Capt M Peterson, Consultant Anaesthetist.

comparison of operational performance at ground level and at simulated altitude to ensure consistency.

***Study Protocol*:** As the study aim was to examine the performance of the ventilator, using a lung simulator only, and did not include measurements made on human volunteers, Ministry of Defence Research Ethics Committee (MoDREC) approval was not sought.

Mechanical Ventilation: During phase 1 of the present study, it was identified that mechanical ventilation of the casualties was undertaken utilising both pressure controlled and volume controlled ventilation. In volume control mode, the tidal volume of each breath is programmed by the anaesthetist along with a respiratory rate. The inspiratory flow remains constant but airway pressure increases throughout the breath to enable volume delivery. As the volume of each breath is pre-determined, the casualty will receive a set tidal volume, but airway pressures are variable, depending on the compliance and resistance of the respiratory system. In a casualty with reduced compliance or higher resistance, there is an increased risk of ventilator induced lung injury as a result of the higher airway pressures required to deliver the set tidal volume (Campbell and Davis, 2002). In pressure control mode, the anaesthetist sets an inspiratory airway pressure and respiratory rate but the volume delivered in each breath will vary according to respiratory system compliance and resistance. Airway pressure remains constant during the breath, with a decelerating inspiratory flow pattern. (MacNaughton, 2008; Bersten, 2014). The choice of volume or pressure

controlled mode will depend on many factors, including the underlying reason for mechanical ventilation.

***Experimental Procedure*:** Three LTV 1000 patient ventilators were selected at random from the CCAST inventory held at the RAF Centre of Aviation Medicine (RAF CAM) (inventory numbers 2291, 2283 and 1458). All devices had been maintained in accordance with manufacturer's instructions. Standard pre-use checks were completed prior to any testing; all devices passed these checks. All ventilators were connected to AC mains power throughout testing and 100% oxygen was supplied to the ventilators at 50Lb.in^{-2} from a bottled source located within the hypobaric chamber. Each ventilator was fitted with a standard 'Y' patient ventilation circuit, with a positive end expiratory pressure (PEEP) valve at the end of the exhalation side and a lung simulator (IMT Medical, Switzerland) at the inhalation side – replicating the ventilator assembly used in patient care.

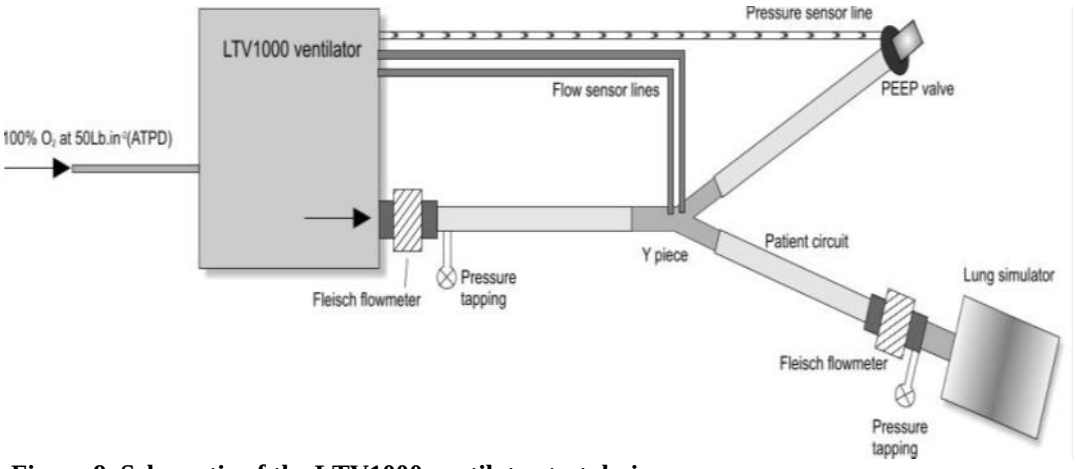

Figure 9. Schematic of the LTV1000 ventilator test design

Fleisch flow meters and piezometer pressure taps were fitted at the ventilator outlet port and at the lung simulator inlet port to measure flow and

pressure. The Fleisch flow meters were calibrated for flow using a calibrated rotameter and for pressure using a calibrated 3L syringe. Calibrations were only performed at ground level as the Fleisch flow meter is unaffected by changes in altitude, due to the laminar flow of air within the flow meter. The differential pressure transducers, connected via piezometer pressure taps, were calibrated using a calibrated manometer.

Data measured at the ventilator outlet port and at the lung simulator inlet port (Table 9) were captured by a digital data acquisition system at 400Hz (LabChart® 7, AD Instruments Ltd, Oxford) and later exported to a Microsoft© Office Excel file. All volumes were corrected to ambient temperature and pressure dry (ATPD). The lung simulator was set at a compliance of 30ml/bar with a resistance of 5 $cmH_2O/L^{-1}.s^{-1}$ to simulate a normal adult lung.

Variable	Measurement Technique
Ventilator outlet flow	Fleisch flow meter size 2 (Linton Instruments Ltd)
Ventilator outlet pressure	Differential pressure transducer model LCVR (Celesco Inc.)
Lung inlet flow	Fleisch flow meter size 2 (Linton Instruments Ltd)
Lung inlet pressure	Differential pressure transducer model LCVR (Celesco Inc.)
Hypobaric chamber differential pressure	Differential pressure transducer model LCVR (Celesco Inc.)
Chamber temperature and humidity	Digital thermometer

Table 9. Measured variables during LTV 1000 patient ventilator assessment

The ventilators were placed in the hypobaric chamber; once readings had been recorded at ground level, the pressure in the chamber was reduced to a pressure altitude of 8,000 feet. Two different ascent profiles were used during the assessment, one at 500 feet per minute (to simulate a similar climb rate to that of a standard aeromedical evacuation flight) and one at 2,000 feet per minute. During

the slower ascent profile, readings were measured continuously; at the faster ascent rate, readings were recorded on the ground and at 8,000 feet only. Once at altitude, readings were recorded for a 2 minute period before increase in hypobaric chamber pressure to ground level at 4,000 feet per minute.

Each ventilator was tested in both volume control mode and pressure control mode. In volume control mode, the ventilators were set to deliver a tidal volume of 600ml at a rate of 12 breaths per minute, both with and without PEEP (at 5cmH_2O) on air. In pressure control mode, the pressure was set to 20cmH_2O. As an additional test, 1 ventilator was set to deliver 600ml in volume control mode with and without PEEP (at 5cmH_2O) on 100% oxygen. Each ventilator was tested once for each experimental condition described. The order for the experimental conditions is shown at Table 10.

Altitude (feet)	Ascent rate (feet/min)	Ventilator number	FiO_2	PEEP (cmH_2O)	Set tidal volume (L)	Ventilator mode
0		2291	0.21	0	0.6	Volume control
8000	2000		0.21	0	0.6	Volume control
0		2283	0.21	0	0.6	Volume control
8000	2000		0.21	0	0.6	Volume control
0		1458	0.21	0	0.6	Volume control
8000	2000		0.21	0	0.6	Volume control
0		2291	0.21	5	0.6	Volume control
8000	2000		0.21	5	0.6	Volume control
0		2283	0.21	5	0.6	Volume control
8000	2000		0.21	5	0.6	Volume control
0		1458	0.21	5	0.6	Volume control
8000	2000		0.21	5	0.6	Volume control
0		2291	0.21	5	0	Pressure control (20cmH_2O)
8000	2000		0.21	5	0	Pressure control (20cmH_2O)
0		2283	0.21	5	0	Pressure control (20cmH_2O)
8000	2000		0.21	5	0	Pressure control (20cmH_2O)
0		1458	0.21	5	0	Pressure control (20cmH_2O)
8000	2000		0.21	5	0	Pressure control (20cmH_2O)
0		1458	1.0	5	0.6	Volume control
8000	500		1.0	5	0.6	Volume control
0		1458	1.0	0	0.6	Volume control
8000	500		1.0	0	0.6	Volume control

Table 10. Order of experimental conditions used during LTV ventilator assessment. Three ventilators were used, with each ventilator tested once under the conditions described
FiO_2 = Fraction of inspired oxygen

3.2. Results

Data obtained from the flow meters and pressure taps fitted at the ventilator outlet port and at the lung simulator inlet port were in good agreement.

In volume control mode on air, without PEEP, the ventilators delivered a larger tidal volume at 8,000ft compared with ground level. At the ventilator outlet port, the mean tidal volume increase was 17.5% (SD ±0.8%), as demonstrated in Figure 10. When PEEP of 5cmH_2O was added to volume control mode on air, a similar response was seen, with the mean tidal volume recorded at the ventilator outlet port 15.9% (SD ±1.8%) greater at 8,000ft than at ground level. Individual ventilator results in volume control mode are shown at Table 11, demonstrating the delivery of a larger volume at 8,000ft compared with delivery on the ground.

Ventilator number	Altitude (ft)	PEEP (cmH_2O)	Ventilator outlet TV (l) (ATPD)	Delta TV (l)
2291	0	0	0.585	
	8000	0	0.692	0.107
2283	0	0	0.613	
	8000	0	0.721	0.109
1458	0	0	0.593	
	8000	0	0.692	0.100
2291	0	5	0.585	
	8000	5	0.689	0.104
2283	0	5	0.621	
	8000	5	0.717	0.096
1458	0	5	0.593	
	8000	5	0.678	0.085

Table 11. Delivered tidal volume (TV) measured at the ventilator outlet port at both ground level and 8,000ft simulated altitude in 3 ventilators. Ventilators in volume control mode, tidal volume 0.6L with either PEEP 0 or PEEP 5cmH_20
PEEP = Positive End Expiratory Pressure

Peak inspiratory pressure (PIP) also increased at altitude in volume control mode; at the lung simulator inlet port, mean PIP increased by 17.2% (SD ±9.7%)

at 8,000ft compared with ground level. This increase in PIP was exacerbated with the addition of PEEP; with 5cmH_2O added to the ventilator settings, mean PIP at the lung simulator inlet port was 69% (SD ±48.5%) greater at altitude compared with ground level – a much greater increase than without PEEP. Individual results for each of the three ventilators are shown at Table 12, demonstrating an increased PIP at 8,000ft; each ventilator was tested once using the experimental design described.

Ventilator number	Altitude (ft)	PEEP (cmH_2O)	Peak inspiratory pressure (cmH_2O)	Delta PIP (cmH_2O)
2291	0	0	16.6	
	8000	0	17.8	1.2
2283	0	0	17.0	
	8000	0	21.5	4.6
1458	0	0	16.5	
	8000	0	19.4	2.9
2291	0	5	19.0	
	8000	5	27.6	8.6
2283	0	5	16.7	
	8000	5	37.6	20.9
1458	0	5	25.0	
	8000	5	34.2	9.2

Table 12. Peak inspiratory pressure (PIP) measured at the lung simulator inlet port at both ground level and 8,000ft simulated altitude in 3 ventilators. Ventilators in volume control mode on air, tidal volume 0.6L with either PEEP 0 or PEEP 5cmH_20
PEEP = Positive End Expiratory Pressure

As shown in Table 13 and at Figure 10, the large increases in tidal volume were not seen when the ventilators were set in pressure control mode and mean PIP was only minimally increased at altitude (3% (SD ±7.4%)) compared with ground level. Three ventilators were used and each was tested once using the described experimental design.

Ventilator number	Altitude (ft)	Pressure control (cmH_2O)	Ventilator outlet tidal volume (l) (ATPD)	Peak inspiratory pressure (cmH_2O)	Delta TV output (l)	Delta PIP (cmH_2O)
2291	0	20	0.587	23.4		
	8000	20	0.612	25.1	0.025	1.7
2283	0	20	0.636	27.8		
	8000	20	0.622	26.3	-0.014	-1.5
1458	0	20	0.614	22.8		
	8000	20	0.635	24.5	0.022	1.7

Table 13. Tidal volume (TV) measured at the ventilator outlet port and peak inspiratory pressure (PIP) measured at the lung simulator inlet port at both ground level and 8,000ft simulated altitude in 3 ventilators. Ventilators in pressure control mode (20cmH_2O) on air, with PEEP 5cmH_20

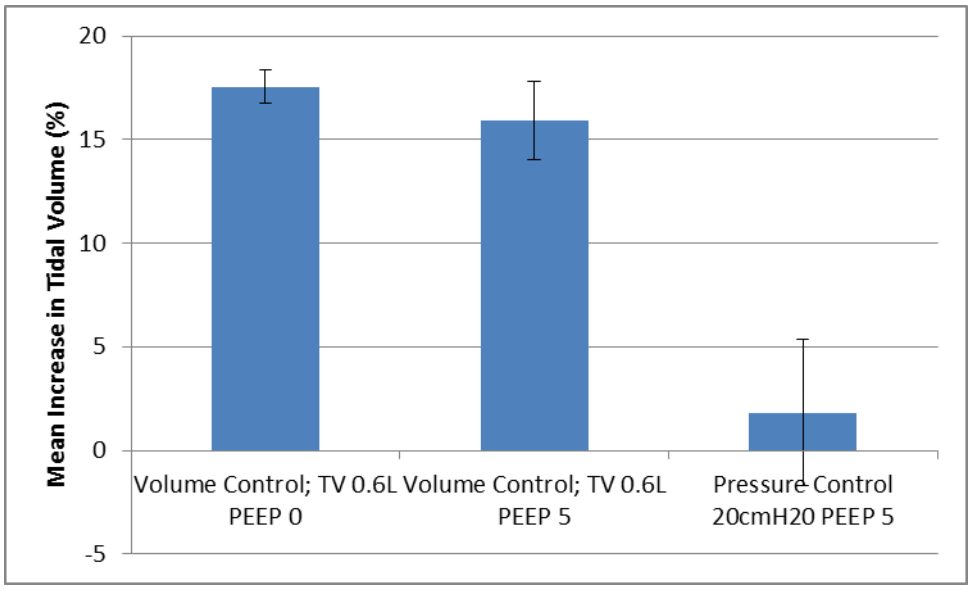

Figure 10. Mean increase in tidal volume (TV) at 8,000ft compared with ground level, measured at the ventilator outlet port in 3 ventilators
Fraction of inspired oxygen = 0.21; Error bars show ±1 standard deviation

At the slower ascent rate (500 feet per minute), readings of tidal volume and peak inspiratory pressure from 1 ventilator were monitored continuously and recorded at 1000ft intervals as the hypobaric chamber climbed from ground level to a simulated altitude of 8,000ft. Figure 11 depicts the increase in delivered tidal volume and PIP as measured at the ventilator outlet port for one ventilator (number 1458) in volume control mode, on air, without PEEP during the ascent to 8,000ft. As previously seen, the addition of PEEP caused a greater increase in

PIP, suggesting that the percentage increase in PIP shown in Figure 11 would have been greater had PEEP been added to the ventilator set up.

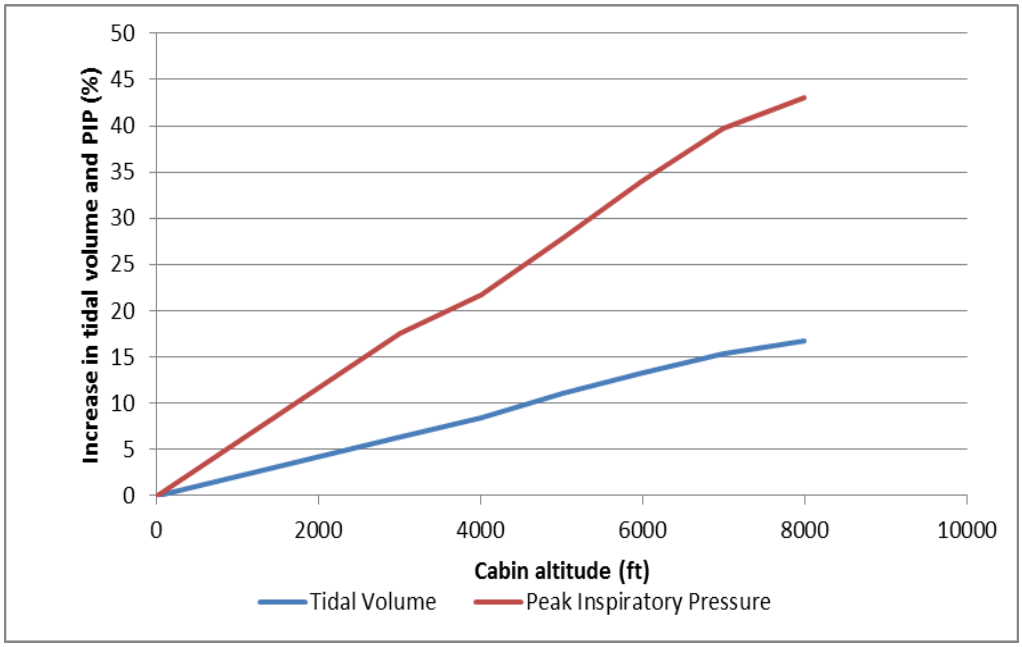

Figure 11. Increases in delivered tidal volume and peak inspiratory pressure at the ventilator outlet port during a climb to 8,000ft simulated altitude in a hypobaric chamber; data from 1 ventilator. Ventilator in volume control mode, tidal volume 0.6L, PEEP 0

Throughout the ventilator assessment, there was disparity between the set tidal volume, the tidal volume which the LTV 1000 displayed as being delivered, and the actual tidal volume recorded at the ventilator outlet port. Figure 12 depicts the mean difference in the reported tidal volume shown in the display screen on the LTV 1000 and the delivered tidal volume recorded at the ventilator outlet port. On the ground and at altitude, the actual delivered tidal volume was greater than that reported on the LTV display screen, with the difference ranging from approximately 5% to 25%, according to the ventilator mode and settings used. On the ground, the difference between delivered tidal volume and displayed tidal volume was at the maximum permitted design tolerance for the ventilator (Pulmonetic Systems 2005); at altitude, the differences were beyond these

permitted tolerances. The addition of PEEP further increased the differences in delivered tidal volume and displayed tidal volume.

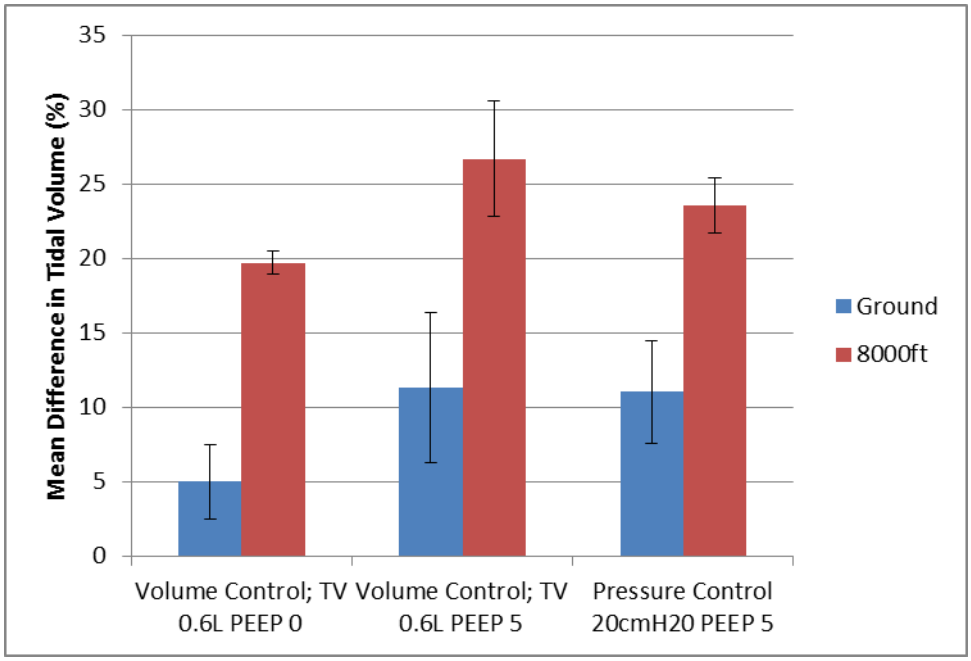

Figure 12. Mean difference in tidal volume (TV) measured at the ventilator outlet port compared with tidal volume displayed on the LTV1000 screen in 3 ventilators; each ventilator tested once.
Fraction of inspired oxygen = 0.21; Error bars show ±1 standard deviation

Data were collected from three ventilators; each ventilator was tested once under each experimental design described. Guidance from a statistician suggested that the sample size was too small to undertake any meaningful/valid statistical analysis beyond the descriptive analysis described above (Personal communication McLeod/Kiran May 2015).

3.3. Discussion

The data obtained during the experimental phases were consistent between the three ventilators tested. At simulated altitude, in volume control mode, the ventilators delivered larger tidal volumes than had been set and larger tidal volumes than were reported on the LTV 1000 screen. At 8,000ft, the mean difference in volume was approximately 20% which is a larger difference than the

5%-12% difference identified by Rodriquez et al (2009) in a similar study, examining the performance of the LTV 1000 and the Impact Eagle 754 (Impact Instrumentation Inc, West Caldwell, NJ) at various simulated altitudes. Only one LTV 1000 ventilator was tested in the Rodriquez study though, which was identified as a limitation of their study, as it only provided one set of data for analysis.

In volume control mode, peak inspiratory pressure also increased significantly at altitude, compared with ground level readings, and was further increased by the addition of positive end expiratory pressure. Measurements of PIP were not tested in the Rodriquez et al (2009) study, so no data are available for comparison with the current study. These larger tidal volumes and higher PIP were seen in all three ventilators tested and did not seem to be affected by alterations in the oxygen concentration delivered, a finding which was also reported by Rodriquez et al (2009).

The patient ventilation circuit contains a fixed orifice transducer device (Pulmonetic Systems, 2005) which measures pressure drop to gauge the flow and volume of gas delivery, which is then reported on the ventilator screen. Flow through the orifice is turbulent; therefore, as the air density falls with increased altitude, the pressure drop is reduced. This leads to the underestimation of actual tidal volume, and hence the delivery of a larger than necessary volume by the control circuit, in both volume and pressure control modes. Flynn and Singh (2008) suggest that this turbulent air flow through the ventilator's flow valve also explains the larger tidal volumes delivered in volume control mode. As altitude increases, the air density decreases, but the gas expands; to maintain the pressure

drop, this results in a larger volume being delivered at altitude. In pressure control mode, ventilation is not dependant on this flow measurement, but on differential pressure, which explains why performance at altitude is similar to that seen at ground level in this mode. The differential pressure transducer compensates for changes in ambient pressure (Pulmonetic System, 2005).

Comparing the findings of the current study with other similar studies revealed that only 1 other study examined the LTV 1000 ventilator (Rodriquez et al, 2009) at altitude; the performance of different ventilators were examined in other studies (Flynn and Singh, 2008; Roeggla et al, 1995; Thomas and Brimacombe, 1994) which demonstrated that other devices failed to operate as effectively at altitude compared with ground level, delivering larger tidal volumes and reduced respiratory rates. Each study used a different set of test parameters – different altitudes and different lung models, making direct comparison with the present study challenging. Tourtier et al (2010) recognise the problematic nature of comparing these studies and suggest that an international standard be developed to allow benchmarking of ventilator performance at altitude.

The findings from both the present study and from others may have implications for the care of critically injured ventilated casualties during aeromedical evacuation. Awareness of the potential delivery of larger than intended tidal volumes or higher PIP is essential to prevent further harm to these vulnerable personnel. Large tidal volumes and high peak inspiratory pressures in ventilated patients could be harmful (Roeggla et al, 1995), particularly in those casualties with existing lung injuries, in whom large tidal volumes will increase their risk of developing ventilator induced lung injury (VILI) (Bersten, 2014). In

phase 1 of this present study, 23 of the casualties had been exposed to blast from an improvised explosive device, potentially resulting in some degree of lung damage, which could be exacerbated in the presence of large tidal volumes or high inspiratory pressures during ventilation. High PIP could potentially cause further barotrauma to blast injured lungs; Reade and Thomas, (2014) suggest reducing PIP when managing blast injured casualties to prevent further damage and Smith (2011) suggests the use of low tidal volumes and the use of pressure controlled ventilation in this casualty group. Findings from the present study suggest that the current CCAST ventilator may deliver larger tidal volumes or higher PIP at altitude; these findings should be considered when utilising the ventilator during aeromedical evacuation, particularly when volume control mode is selected.

Barnes et al (2008) suggest that military trauma casualties are also at risk of developing Acute Respiratory Distress Syndrome (ARDS) due to the nature of the injures experienced. Lumb (2000) and Vicente et al (2015) suggest the use of smaller tidal volumes and lower airway pressures in the management of ARDS to reduce the risk of volutrauma or over-distension of the alveoli. Increased intrathoracic pressure resulting from elevated PIP may also have haemodynamic consequences for the casualty, through reduced pre-load (reduced venous return) (Cockings and Yap, 2008), ultimately reducing cardiac output. Additionally, large tidal volumes could lead to hypocapnia resulting from hyperventilation. This can lead to cerebral vasoconstriction, a left shift of the oxy-haemoglobin dissociation curve and cardiac arrhythmias (Rodriquez et al, 2009). In a casualty group who may have already experienced significant haemorrhage, blast lung,

head injury or traumatic amputations, avoidance of these additional complications is essential. The development of cerebral vasoconstriction in a head injured ventilated casualty, for example, as a result of hyperventilation from larger than intended tidal volumes during evacuation may lead to a much worse prognosis than expected.

***Limitations*:** The ventilators were only tested using a lung simulator set to represent the compliance of a normal adult lung; and altered lung compliance profiles were not assessed. Testing the ventilators at a simulated altitude in the hypobaric chamber permitted exposure to reduced barometric pressure but did not include any of the other factors potentially experienced during flight, such as noise or vibration. Only three ventilators were used during the testing, with each ventilator tested once under the experimental conditions described. As this design produced only 3 data sets, statistical analysis was not possible; however, the results obtained were borne out by results of earlier studies and have contributed to the developing body of knowledge regarding the performance of ventilators at altitude. Although the recommendations made in the next section are not based on statistical analysis, they are echoed by other researchers in this field of inquiry.

***Conclusion*:** At a simulated altitude of 8,000ft, in volume control mode, the LTV 1000 ventilator delivered higher tidal volumes than had been set, but under-reported the actual tidal volumes delivered. Peak inspiratory pressures were significantly increased at this altitude compared with ground level values and the addition of PEEP further increased the PIP at 8,000ft. In pressure control

mode, tidal volumes and PIP virtually matched ground level values, although delivered tidal volumes were under-reported on the ventilator screen. Although these findings result from a small scale study involving only 3 LTV 1000 ventilators, from which meaningful statistical analysis could not be undertaken, they still suggest that the ventilator does not compensate for the changes in barometric pressure experienced during flight and may therefore not performed as intended. As a result of these findings, CCAST personnel should consider reducing set in-flight tidal volumes if the LTV 1000 is used at altitude in volume control mode. To avoid the high PIP seen, CCAST casualties could be ventilated using pressure control mode during aeromedical evacuation where practical. In the longer term, any future replacement for the LTV 1000 ventilator currently used by CCAST should auto-compensate for the barometric changes experienced during flight.

4. HYPOBARIC ASSESSMENT OF THE ABBOTT i-STAT BLOOD GAS ANALYSER

4.1. Methods

Blood gas analysis is an essential component of critical care provision (McGuire, 2006a). During evacuation by air, clinical examination becomes more difficult due to environmental factors such as altered light levels and increased noise, which makes some techniques such as auscultation impossible. As a result, accurate blood gas analysis becomes even more critical to ensure effective ventilation is being delivered. For this reason, the critical care air support team is equipped with a portable hand held analyser, the i-Stat 1, manufactured by Abbott Laboratories Ltd. As CCAST personnel rely on the accuracy of the results from the i-Stat analyser, the performance of the i-Stat was assessed at altitude.

***Aim*:** The aim of the study was to examine the performance of the i-Stat 1 blood gas analyser both on the ground and at the maximum expected cabin altitude of 8,000 feet (2438 metres). This would allow comparison of operational performance at ground level and at simulated altitude.

***Study Protocol*:** As the study aim was to examine the performance of the blood gas analyser, using only test control solutions, and did not include measurements made on human volunteers, MoDREC approval was not sought.

***Experimental Procedure*:** Four i-Stat analysers were used during the study; one from the RAF CAM inventory and 3 provided by Abbott Laboratories (Table 14). EG7+ cartridges (Lot P10317 and N10354) were selected for the

testing to provide a wide range of commonly used biochemical and haematological investigations, including arterial oxygen and carbon dioxide, pH and electrolytes. It is also the cartridge most commonly used by CCAST personnel.

Handset Number	Serial Number
1	340202
2	309190
3	320227
4	337698

Table 14. i-Stat handset serial numbers

To confirm that the i-Stat cartridges perform within specified limits, reference assay solutions are available. Performance of the i-Stat devices was assessed using four different assay solutions, to test the high and low ranges: i-Stat Control 1 (Lot B09349), i-Stat Control 3 (Lot B09344), Haematocrit Control 1 (Lot B09322) and Haematocrit Control 3 (Lot B09323). The i-Stat Control 1 and 3 solutions are specifically prepared with known concentrations of electrolytes (sodium, potassium and chloride), arterial oxygen and carbon dioxide, glucose, lactate and creatinine, to act as quality assurance tools. i-Stat Control 1 solution has low concentrations of these assays and i-Stat Control 3 solution has high concentrations. Likewise, the Haematocrit Control solutions are designed as quality assurance tools to test the performance of the monitor and cartridges; Haematocrit Control 1 solution has a known low haematocrit (HCT) concentration and Haematocrit Control 3 solution has a known high HCT concentration. The HCT control solutions are only designed to test HCT levels detected by the cartridges and all other results obtained from the cartridge when using the HCT control solutions should be discounted (Abbott, 2015 p14-12).

The i-Stat units were tested at ground level (761mmHg) and at the pressure altitude equivalent of 8,000 feet (565mmHg) in a hypobaric chamber at RAF CAM. For each device, ground level testing was completed prior to testing at 8,000 feet; on return to ground level, the test procedure was repeated for a third time. Ascent and descent rate was 4,000 feet per minute.

Barometric pressure readings displayed by each handset were recorded prior to testing at both ground level and 8,000 feet pressure altitude (Table 15).

Handset Number	Ground Pressure Reading	Altitude Pressure Reading
1	761 mmHg	565 mmHg
2	760 mmHg	563 mmHg
3	761 mmHg	564 mmHg
4	758 mmHg	562 mmHg

Table 15. Pressure readings recorded by i-Stat device at ground level and 8,000 feet pressure altitude

All four handsets were fitted with an EG7+ cartridge; one ampoule of i-Stat Control 1 test solution was drawn into a syringe and used in each of the test cartridges, in accordance with the manufacturer's instructions. The results from each cartridge were recorded and compared to the published control range for the specific test solution. This process was repeated for the remaining 3 test solutions. Once opened, the ampoule contents were immediately drawn up and sampling rapidly performed, to reduce any equilibration of the solution.

4.2. Results

Data from the four handsets were in good agreement and, in general, fell within the control ranges for each of the test solutions (where provided by Abbott Laboratories), both on the ground and at 8,000 feet altitude. However, measurement of the partial pressure of oxygen (pO_2) taken at altitude was not in

agreement. All pO_2 values were lower than those recorded on the ground, with 5 of the 8 readings below the control range for the specific test solution. The pO_2 control range for i-Stat Control 1 solution is 9.5-13.5kPa and the pO_2 control range for i-Stat Control 3 solution is 16.7-22.7kPa. Results for the four test solutions used both on the ground and at 8,000ft altitude are shown in Tables 16-19.

	Handset 1		Handset 2		Handset 3		Handset 4	
	Ground	8,000ft	Ground	8,000ft	Ground	8,000ft	Ground	8,000ft
pH	7.192	7.187	7.188	7.183	7.188	7.184	7.195	7.178
pCO_2 (kPa)	8.25	8.59	8.2	8.51	8.17	8.42	8.23	8.33
pO_2 (kPa)	12.7	9.6	13.5	9.7	13.4	8.7	12.6	9.8
Base Excess (mmol/L)	-4	-4	-5	-4	-5	-5	-4	-5
HCO_3 (mEq/L)	23.7	24.4	23.4	24.0	23.3	23.8	23.9	23.2
TCO_2 (mmol/L)	26	26	25	26	25	26	26	25
SO_2 %	95	89	96	89	96	86	95	90

Table 16. i-Stat Control 1 test solution results for 4 i-Stat handsets on the ground and at 8,000ft simulated altitude (uncorrected for pO_2)

	Handset 1		Handset 2		Handset 3		Handset 4	
	Ground	8,000ft	Ground	8,000ft	Ground	8,000ft	Ground	8,000ft
pH	7.68	7.678	7.677	7.673	7.678	7.677	7.687	7.674
pCO_2 (kPa)	2.68	2.85	2.66	2.78	2.66	2.74	2.68	2.79
pO_2 (kPa)	19.4	14.3	19.5	14.9	19.2	15.3	19.1	14.9
Base Excess (mmol/L)	3	5	3	4	3	4	4	4
HCO_3 (mEq/L)	23.8	25.1	23.4	24.2	23.4	24.1	24.1	24.2
TCO_2 (mmol/L)	24	26	24	25	24	25	25	25
SO_2 %	100	99	100	99	100	99	100	99

Table 17. i-Stat Control 3 test solution results for 4 i-Stat handsets on the ground and at 8,000ft simulated altitude (uncorrected for pO_2)

	Handset 1		Handset 2		Handset 3		Handset 4	
	Ground	8,000ft	Ground	8,000ft	Ground	8,000ft	Ground	8,000ft
HCT	17	17	17	17	17	17	17	17

Table 18. i-Stat Haematocrit Control 1 test solution results for 4 i-Stat handsets on the ground and at 8,000ft simulated altitude

	Handset 1		Handset 2		Handset 3		Handset 4	
	Ground	8,000ft	Ground	8,000ft	Ground	8,000ft	Ground	8,000ft
HCT	54	54	53	54	53	54	53	54

Table 19. i-Stat Haematocrit Control 3 test solution results for 4 i-Stat handsets on the ground and at 8,000ft simulated altitude

The operating manual provided a correction equation to be calculated when using the test solutions at higher altitude environments (Abbott, 2011). This correction is required because the partial pressure of oxygen in the test solution changes as it equilibrates with the surrounding environment, so causing a shift in pO_2 values. The control range for each test solution is obtained at or near sea level, so the adjustments are required if the environmental partial pressure of oxygen is reduced. Once corrected, the observed pO_2 values at altitude fell within the control ranges, although the values were still considerably lower than those recorded at ground level as demonstrated at Figure 13.

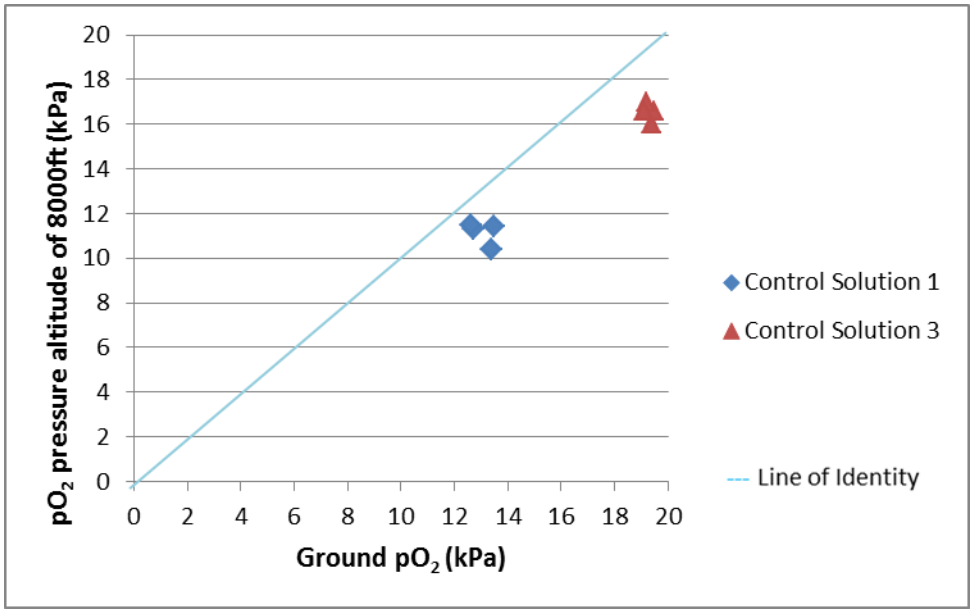

Figure 13. Comparison of pO_2 results obtained at ground level with corrected results obtained at 8,000 feet pressure altitude, using i-Stat Control Solutions 1 and 3

As there were only 4 data sets obtained for each of the four test solutions, this was considered to be insufficient to provide meaningful/valid statistical analysis, so no further analysis of these results was undertaken.

4.3. Discussion

Changes in the pO_2 results at reduced barometric pressure were considerable, even after the values were corrected for the higher altitude. This is due to the equilibration of the oxygen in the aqueous solution to the surrounding lower pressure environment. Throughout the experimental procedure, all test solutions were rapidly drawn up into a syringe once the vials were opened and applied to the test cartridges immediately, to reduce the time the solution was exposed to the atmosphere, but it is clear that a rapid rate of equilibration occurred.

In the operating manual, Abbott (2011) suggests that the rate of equilibration is faster in the aqueous solution because it does not contain any haemoglobin to hold the oxygen molecules within the solution. Whole blood taken for sampling in the i-Stat would contain haemoglobin which would bind the oxygen molecules, potentially slowing the rate of equilibration with the surrounding atmosphere. However, it is unknown how long it would take for a blood sample to equilibrate, if left for any period of time. From this experiment, it is not possible to confirm the accuracy of the i-Stat in calculating pO_2 values from a patient blood sample at altitude. Delays in analysing any drawn blood may lead to an inaccurate result, which could have clinical implications for patient management in-flight. Current practice for CCAST personnel is to perform the blood gas analysis as soon after drawing the blood sample as possible, capping the syringe prior to testing. The i-Stat is primed ready to receive the sample prior to the blood sample being drawn from the patient. It has been suggested that time

from drawing the sample to commencing the analysis is less than 1 minute (Personal communication McLeod/Rose September 2015).

***Conclusion*:** In general, values determined from samples analysed by the i-Stat were accurate at a pressure altitude of 8,000ft. However, the calculation of pO_2 values using the i-Stat control solutions is underestimated at altitude, requiring a correction equation to be used, to adjust for the reduced barometric pressure at altitude. When measurements are made using whole blood, the effect of equilibration of the test sample in the atmosphere may be less, due to the presence of haemoglobin to bind the oxygen, slowing the rate of equilibration. Although an underestimate of pO_2 is inherently safer than an overestimate, it is recommended that the operational and clinical importance of this finding is investigated further with the use of whole blood samples. It is suggested that blood samples could be drawn from healthy volunteers at ground level and analysed using the i-Stat. Using the same sample, the analysis could be repeated after 5 minutes to monitor for any changes in the results obtained. Following a simulated ascent to 8,000feet in the hypobaric chamber, a second sample could be drawn from the same volunteers and analysed, to compare with the ground result. Again, the analysis could be repeated from the same sample five minutes later to observe any effect of equilibration. As a definitive comparison, blood samples could be obtained both on the ground and at altitude directly into a blood bottle, for appropriate laboratory analysis to compare with the results obtained from the i-Stat. This would provide information on the rate of equilibration in whole blood at altitude, which might have implications for current CCAST practice, if it proved to be significant.

5. AN INVESTIGATION OF CHANGES IN TISSUE OXYGEN SATURATION DURING EXPOSURE TO SIMULATED ALTITUDE AND LOWER BODY NEGATIVE PRESSURE

5.1. Methods

The aim of this second phase of the study was to record tissue oxygen saturation in healthy volunteers, who were exposed to both simulated altitude and conditions simulating altered circulating volume (utilising lower body negative pressure), with the objective of identifying whether regional changes in tissue oxygen saturation occur in response to the experimental conditions and if the monitoring system selected is sensitive enough to detect any changes in tissue oxygen saturation that may occur. The protocol was designed to assess one tissue oxygen saturation monitoring technique in volunteers subjected to conditions resembling those experienced by AE casualties.

***Study protocol**:* The study protocol was submitted to and approved by the RAF Experimental Medicine Scientific Advisory Committee and the Ministry of Defence Research Ethics Committee (MoDREC reference 127/Gen/10).

***Subjects**:* Twelve healthy volunteers were recruited from the population of military personnel serving at Royal Air Force (RAF) Henlow. In order to make this phase of the study relevant to the later phase, only subjects between the ages of 18 and 40 years were recruited, as the majority of military AE casualties from the operational setting fall within this age range. Individuals with pre-existing health problems or those taking prescribed medication were excluded from the

study. All subjects completed a health questionnaire to ensure medical fitness to undertake the study; written consent was obtained from all subjects. The EMSAC members had requested the inclusion into the protocol of an instruction to the volunteers to refrain from products containing caffeine prior to testing, but this was removed from the protocol on the instruction of the MoDREC who stated that the volunteers should "maintain normal caffeine intake rather than change their normal behaviour" (McLeod/Linton correspondence 12 March 2010). The volunteers' smoking history was added to the pre-screening health questionnaire at the request of MoDREC although no restrictions on pre-testing smoking were set. No other exclusion criteria were applied.

***Experimental procedure**:* The 12 volunteers were subjected to 3 sets of tests over 3 separate sessions, at least 24 hours apart. The three tests were a hypoxia altitude simulation test (HAST), a lower body negative pressure test (LBNP) and one test combining HAST and LBNP. All volunteers were instructed to abstain from products containing alcohol during the 12 hours before testing.

A variety of physiological variables were recorded (Table 20) including non-invasive beat to beat systolic/diastolic blood pressure, mean arterial pressure, heart rate, SpO_2 and tissue oxygen saturation. End tidal expiratory oxygen and carbon dioxide concentrations were also recorded via the respiratory mass spectrometer as a surrogate of alveolar oxygen and carbon dioxide values. Blood pressure, heart rate and SpO_2 were measured on the right arm and tissue oxygen saturation was measured from the left arm.

Variable	Measurement Technique
Peripheral arterial oxygen saturation	Kontron pulse oximeter
Heart rate	Kontron pulse oximeter
Systolic/Diastolic blood pressure	FMS Finometer
End tidal oxygen concentration	LR-1 Respiratory mass spectrometer
End tidal carbon dioxide concentration	LR-1 Respiratory mass spectrometer
Tissue oxygen saturation	INVOS 5100C cerebral / somatic monitor

Table 20. Measured variables during hypoxia altitude simulation test and lower body negative pressure test

The volunteers were fitted with a close fitting RAF P/Q oro-nasal oxygen mask and each one was asked to lie supine on the tilt table. Arm rests were fitted to the sides of the table (at mid-axillary level) to support the volunteer's arms. A Kontron pulse oximeter (Kontron, Watford, UK) sensor clip was applied to the volunteer's right index finger to record SpO_2 and heart rate. Tissue oxygen saturation was measured from the upper third of the left upper arm, lateral aspect – over the deltoid muscle, using a self-adhesive, single use, non-invasive probe connected to the INVOS monitor (Somanetics, Troy, MI, USA). End tidal expiratory oxygen and carbon dioxide concentrations were measured by inserting the mass spectrometer capillary into a tapping in the P/Q mask cavity. The 15.1% oxygen cylinders were positioned at the head of the tilt table.

Non-invasive beat to beat systolic/diastolic blood pressure monitoring was undertaken using the Finometer monitoring system (FMS, Arnhem, The Netherlands), which was selected for use in the current study as it is able to monitor rapid changes in blood pressure, which other monitoring systems (utilising oscillatory techniques) might be slower to detect (Vos, Poterman et al, 2014). An inflatable cuff was applied to the volunteer's right middle finger between the PIP and DIP joints. The finger cuff calculates finger arterial pressure through changes in the absorption of infra-red light from an LED located within

the cuff. Changes in arterial diameter in the finger occur in response to the phases of the cardiac cycle and these can be identified from alterations in the infra-red light absorption. A pneumatic servo attached to the cuff inflates or deflates a bladder inside the cuff to apply a counter-pressure to prevent these changes in the arterial diameter in the finger, keeping it at a known diameter – the 'set point'. A Physiocal algorithm is built into the Finometer system to periodically adjust the 'set point' to account for changes in tone in the smooth muscle of the finger artery wall, which may be seen in response to alterations in temperature or haematocrit for example (FMS, 2005). Through this method, cuff pressure changes can be monitored, providing an indirect measurement of intra-arterial pressure, which is reconstructed as the brachial arterial pressure. The Finometer software calculates systolic, diastolic and mean blood pressure in this beat to beat method (Imholz et al, 1998). An additional arm cuff is used to further calibrate the reconstructed brachial pressure (Guelen et al, 2003); this cuff was applied to the right upper arm for calibration readings prior to the start of the experimental phases and was removed once the readings were obtained. The volunteer's weight, height, age and gender were entered into the Finometer Modelflow software, which permits the individual estimation of aortic flow and therefore stroke volume. The software calculates cardiac output on a beat to beat basis, using the estimated stroke volume and the measured heart rate (Jansen et al, 2001). Clinically, cardiac index is a method of normalising cardiac output to body surface area, but as the experimental phase was recording intra-subject measurements (ie repeated measures) this normalisation was not required, so cardiac output readings are reported throughout. Volunteers whose fingers/hands felt cool to the touch were

provided with commercially available hand warming packs pre-experiment to warm their upper extremities to aid data collection via the Finometer.

a) Hypoxia Altitude Simulation Test (HAST). The HAST or hypoxic challenge test was developed for use in patients with pre-existing respiratory conditions, to identify those who would require supplemental oxygen during commercial flights (British Thoracic Society, 2011). The test involves breathing a 15.1% oxygen gas mix through a tight fitting mask whilst monitoring peripheral arterial oxygen saturation (SpO_2) readings. This hypoxic gas mixture simulates the in-flight partial pressure of inspired oxygen at 8000 feet cabin altitude; supplemental in-flight oxygen can then be supplied for those patients who demonstrate a significant drop in SpO_2 during the test.

An alternative method of exposing the subjects to hypoxia would have been in the hypobaric chamber; however, the HAST is a less resource-intensive method, carries fewer potential risks for the subjects and can be more readily integrated with the LBNP test.

Baseline monitoring of the physiological parameters was undertaken for 5 minutes. After this time, the 15.1% oxygen mix was administered for a 20 minute period, via an aircraft demand oxygen regulator. At the end of the 20 minutes, volunteers reverted to breathing room air and were monitored for a further 10 minute recovery period.

b) Lower Body Negative Pressure Test (LBNP). LBNP can be used as a research tool to simulate haemorrhage or hypovolaemia; the application of negative pressure to the lower body diverts blood flow away from the upper body,

inducing a similar physiological response seen in casualties during acute haemorrhage (Soller et al, 2008a). It is estimated that the application of 40 to 60mmHg lower body negative pressure simulates blood loss of approximately 1000ml (Cooke, Ryan and Convertino, 2004). It is impossible to fully replicate in the laboratory the clinical conditions experienced by AE casualties; indeed, the LBNP test is more extreme, since most AE patients should be stabilised prior to flight, but it provides a useful analogue for research purposes.

The volunteers were fitted with the same physiological monitoring devices as previously described (Table 20). They were placed in a supine position in the LBNP device, with an airtight skirt seal fitted over the iliac crest (Figure 14). An initial five minute period of baseline monitoring was recorded. After this time, the volunteers were subjected to 5 minute (non-randomised) stepped intervals of lower body negative pressure at 20, 40 and 60mmHg. On completion of the LBNP test, the subjects were monitored for a ten minute recovery period (Figure 15).

c) HAST and LBNP Combination. During this test, the subjects were fitted with physiological monitoring as previously described (Table 20) and with the RAF P/Q oro-nasal oxygen mask. They were placed in a supine position in the LBNP device, with the skirt seal over the iliac crest. After a five minute period of baseline monitoring, the 15.1% oxygen mix was started through the mask. After 5 minutes, the volunteers were then subjected to 5 minute (non-randomised) stepped intervals of lower body negative pressure at 20, 40 and 60mmHg. On completion of the LBNP test, the oxygen mix was terminated and the subjects were monitored for a ten minute recovery period (Figure 15).

Figure 14. Study volunteer undergoing lower body negative pressure test in conjunction with the hypoxia altitude simulation test

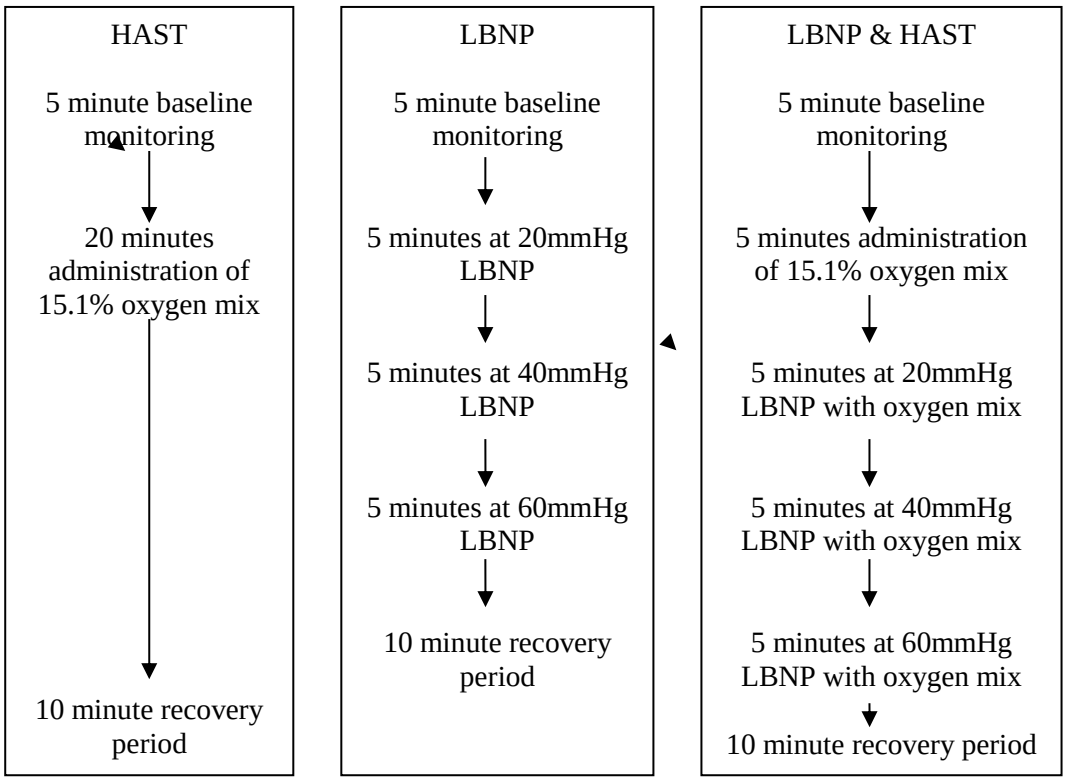

Figure 15. Flow charts demonstrating the 3 test conditions used in phase 2a of the study
HAST = hypoxia altitude simulation test; LBNP = lower body negative pressure test.

Termination of an experimental run: It was decided that an experimental run would be terminated if:

a. The volunteer exhibited signs or symptoms of impending cardiovascular collapse, defined as one or more of the following:
   (i) a sudden decrease in systolic blood pressure (greater than 15mmHg)
   (ii) a sudden decrease in heart rate (greater than 15 beats per minute)
   (iii) a reduced systolic blood pressure below 80mmHg
   (iv) a reduced conscious level
b. The volunteer self-terminated due to the onset of pre-syncope (altered vision, sweating, nausea or dizziness).

The order for the three experimental conditions is shown in Table 21. Presentation of each experimental condition was balanced over the three conditions in six casualties, according to a Latin Square design. This was repeated to include a total of twelve subjects.

Subject	Condition 1	Condition 2	Condition 3
1	HAST	LBNP	HAST & LBNP
2	LBNP	HAST & LBNP	HAST
3	HAST & LBNP	HAST	LBNP
4	HAST	HAST & LBNP	LBNP
5	LBNP	HAST	HAST& LBNP
6	HAST & LBNP	LBNP	HAST
7	HAST	LBNP	HAST & LBNP
8	LBNP	HAST & LBNP	HAST
9	HAST & LBNP	HAST	LBNP
10	HAST	HAST & LBNP	LBNP
11	LBNP	HAST	HAST& LBNP
12	HAST & LBNP	LBNP	HAST

Table 21. Order of experimental conditions for 12 subjects
HAST = hypoxia altitude simulation test; LBNP = lower body negative pressure test; HAST & LBNP = both tests in combination.

***Data collection**:* Continuous live data from the pulse oximeter, Finometer cuff and respiratory mass spectrometer were captured by a digital data acquisition system at a sample rate of 200Hz (LabChart® 7, ADInstruments Ltd). The INVOS 5100C cerebral / somatic monitor recorded measurements every six seconds to an internal file; these were later exported into a Microsoft© Office Excel file. Event markers were used to synchronise timings between the 2 sources. Data reduction was achieved by calculating the mean measurement of all variables for each minute of recording.

Data analysis was undertaken utilising Stata SE 12.1 software (StataCorps, Texas, USA). Initially box and whisker plots were calculated using the Stata software. Regression analysis was used to explain the changes in physiological variables in terms of simulated altitude (HAST) and a simulated altered circulating volume (increasing levels of LBNP). A separate model was fitted for each experiment. The mean of the final minute of readings for each variable at each experimental phase for the twelve volunteers were used in the analysis. A value of $p<0.05$ was considered to be statistically significant.

5.2. Results

Demographic and anthropometric data for the twelve volunteers are shown in Table 22.

	Variable
Age (years)	31.2 (Range 23 – 40)
Gender (*n*) (male / female)	10 / 2
Height (cm)	175.9 ±7.8
Weight (Kg)	76.6 ±10.3

Table 22. Demographic and anthropometric data for phase 2a; ***n* = 12**
Values are means ±SD.

All twelve volunteers completed the three experimental conditions; one volunteer terminated the combined HAST and LBNP test after 1 minute at 60mmHg LBNP, due to symptoms of pre-syncope. The final complete minute of readings for this individual were used in the analysis. There were no adverse effects experienced by the twelve volunteers as a result of the experimental conditions.

As an initial review of the data, separate graphs were drawn, demonstrating the effect of each experimental condition on individual physiological parameters, to observe any trends demonstrated over time. A full set of graphs can be found at Annex D, with selected findings discussed below.

Figure 16 depicts tissue oxygen saturation monitoring recorded from the left deltoid muscle in the twelve volunteers during administration of the 15.1% oxygen mix with the addition of increasing lower body negative pressure. Measurements were recorded every 6 seconds; this graph displays the mean of each minute of recording for each volunteer. In the majority of volunteers, a downward trend can be seen, which began with the start of the 15.1% oxygen mix and continued as LBNP was commenced and then increased. Once the LBNP and oxygen mix were terminated, there was an immediate response in tissue oxygen saturation, with a sharp upward turn, before the readings returned to pre-test levels. This effect was seen earlier in subject L who terminated the final test phase early. Two subjects demonstrated only small changes in tissue oxygen saturation monitoring during the combined experiment.

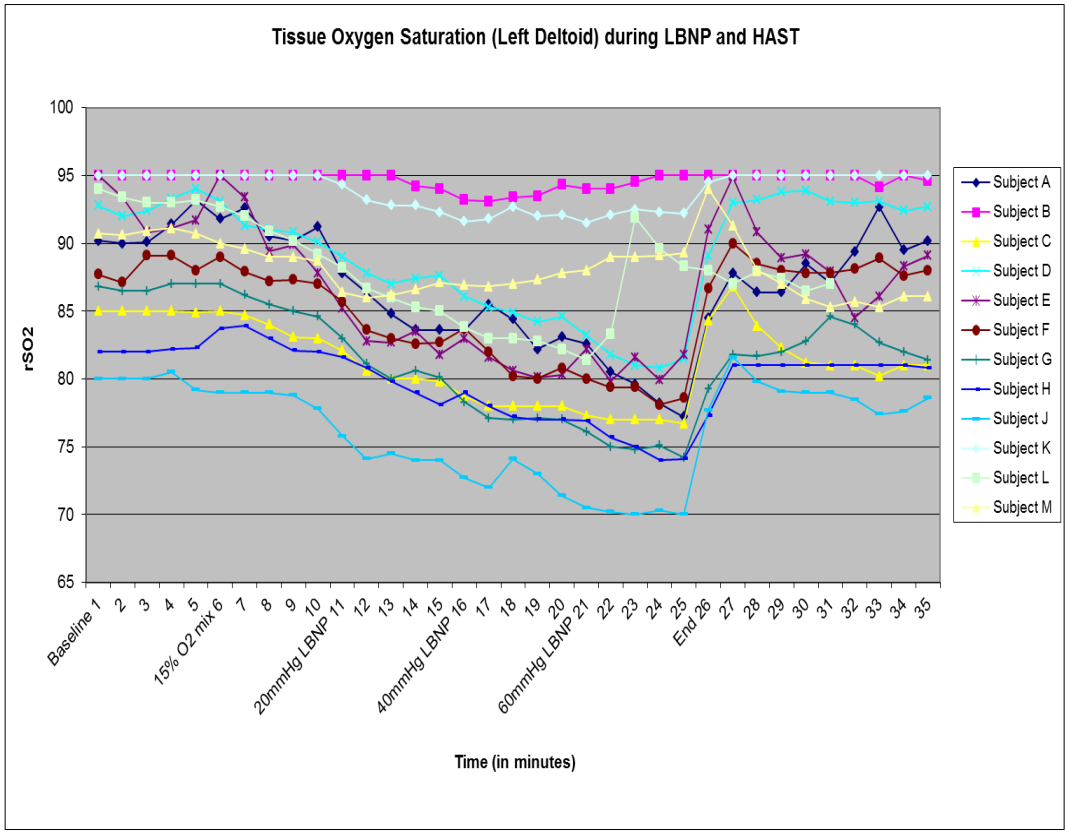

Figure 16. Mean tissue oxygen saturation recorded at the left deltoid in 12 volunteers during exposure to both HAST and LBNP
HAST = Hypoxia altitude simulation test; LBNP = Lower body negative pressure.

Figure 17 depicts the mean heart rate recorded in the twelve volunteers during exposure to 3 stepped intervals of lower body negative pressure. Continuous data was recorded; the graph depicts the mean of each minute of recording for each volunteer. A gradual increase in heart rate was seen in all volunteers in response to the increasing levels of LBNP; this effect was quickly reversed at the termination of LBNP with mean heart rates returning to pre-test levels during the recovery phase.

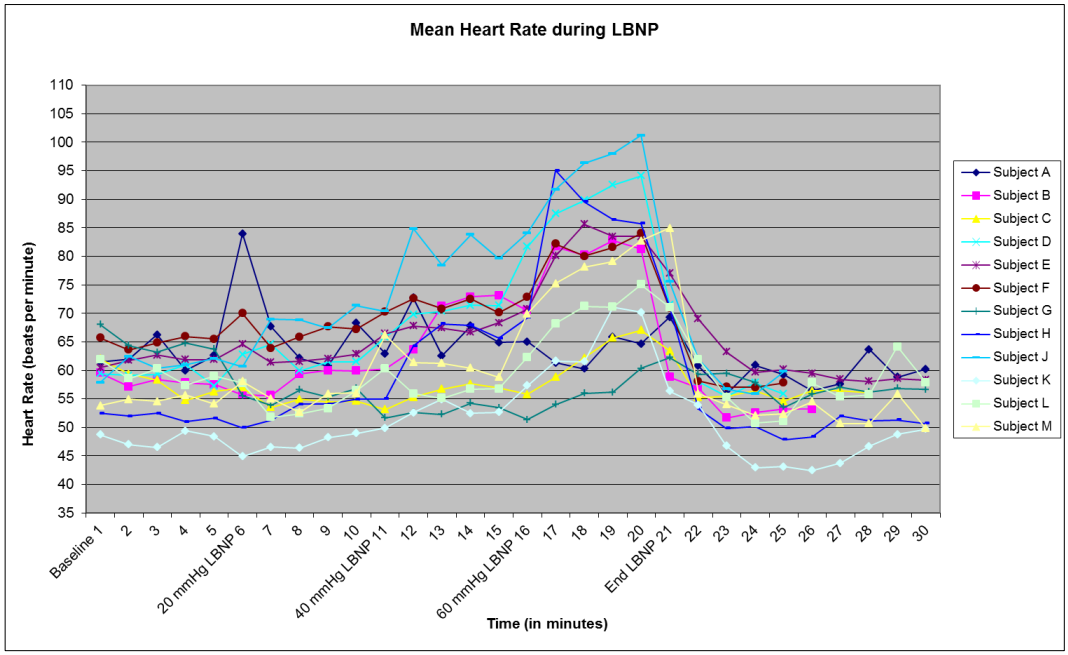

Figure 17. Mean heart rate in 12 volunteers during exposure to LBNP

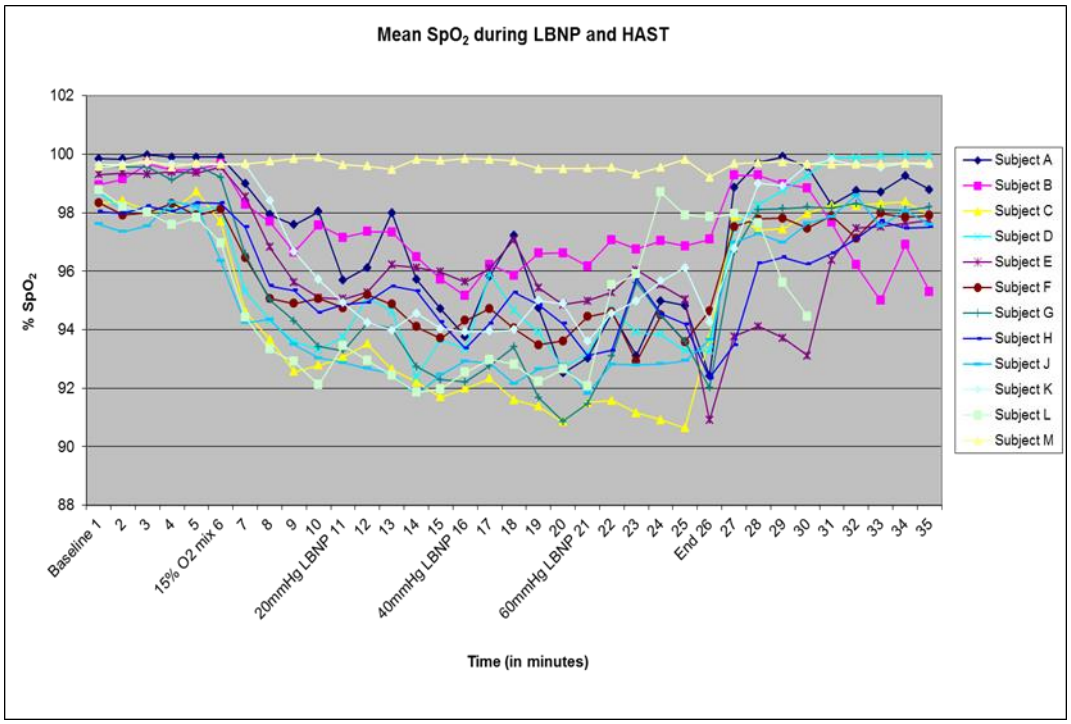

Figure 18. Mean peripheral arterial oxygen saturation in 12 volunteers during exposure to LBNP and HAST

Figure 18 above demonstrates the trend in mean peripheral arterial oxygen saturation recordings in the 12 volunteers during exposure to both LBNP and HAST. With the exception of one volunteer, there was a general downward trend in mean SpO_2 readings, primarily in response to the reduced oxygen mix administered at the start of the test. Again, an immediate improvement in readings was seen once the experimental conditions were terminated. It is suggested that Subject M may have had an ill-fitting mask, which allowed room air into the mask cavity, altering the 15.1% oxygen mix being administered, which would account for the lack of response seen.

To further investigate the effect of each experimental condition on individual physiological responses, box and whisker plots were generated, using the mean physiological readings for the final minute of each phase of the experimental condition.

Figure 19 below demonstrates the effect of the reduced oxygen mix on SpO_2 during the hypoxia altitude simulation test, with the median SpO_2 falling from 98% to 92%. Regional tissue oxygen saturation also fell during HAST. A slight increase in respiratory rate, heart rate and cardiac output were seen in response to the reduced oxygen mix.

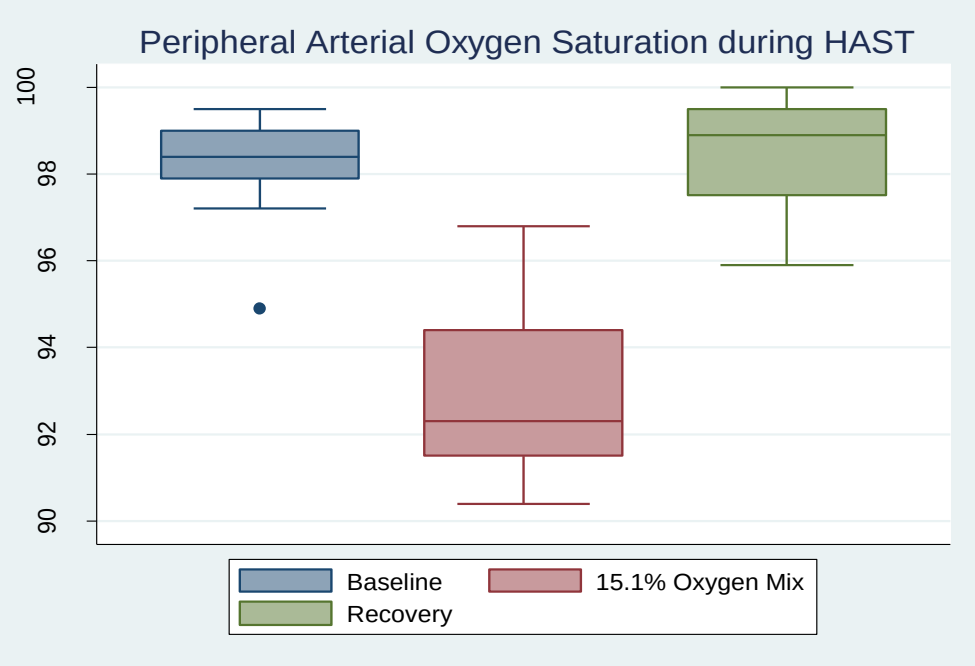

Figure 19. Mean peripheral arterial oxygen saturation recorded in 12 volunteers during hypoxia altitude simulation test
Mean readings for the final minute of each phase of the experiment; outlier shown in blue below the baseline boxplot.

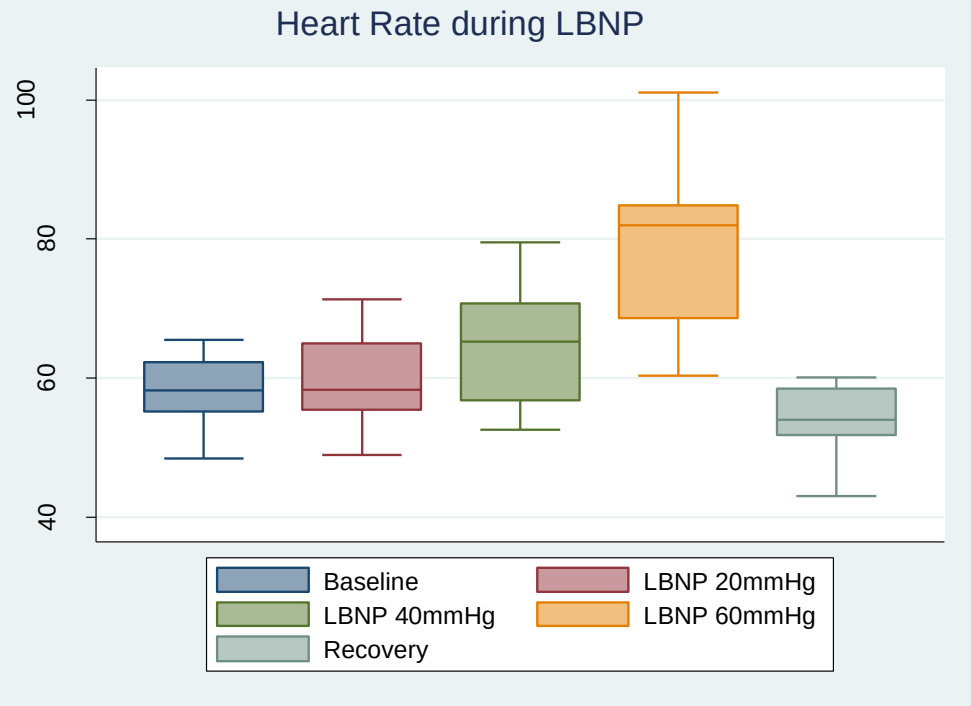

Figure 20. Mean heart rate recorded in 12 volunteers during exposure to lower body negative pressure
Mean readings for the final minute of each phase of the experiment

As shown in Figure 20 above, heart rate increased in response to stepped intervals of lower body negative pressure. This response was terminated with the cessation of LBNP, causing heart rates to return to pre-test levels. Cardiac output and rSO_2 were seen to fall in response to the LBNP test.

In response to the combined HAST and LBNP test, regional tissue oxygen saturation fell, as shown in Figure 21. Changes were seen in all physiological variables during this experimental phase, with decreases recorded in SpO_2, mean arterial pressure and cardiac output and compensatory increases in heart rate and respiratory rate.

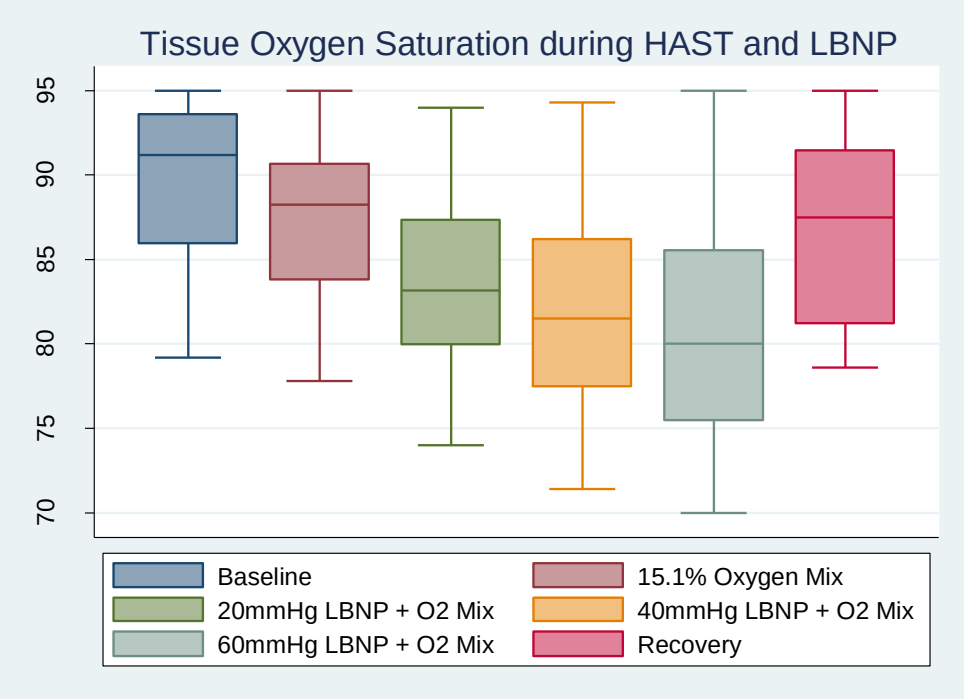

Figure 21. Mean tissue oxygen saturation recorded in 12 volunteers during exposure to HAST and LBNP in combination
Mean readings for the final minute of each phase of the experiment

Regression models were fitted to explain the changes in physiological variables in terms of simulated altitude (HAST) and a simulated altered circulating volume (LBNP). A separate model was used for each experiment.

The mean of the final minute of readings for each variable at each experimental phase for the twelve volunteers were used in the analysis.

As shown in Table 23, there were changes in all variables in response to the hypoxia altitude simulation test; however, only the decrease in rSO_2 and SpO_2 readings were shown to be statistically significant.

HAST		rSO_2	SpO_2 (%)	Resp Rate (bpm)	MAP (mmHg)	HR (bpm)	CO (L/min)
15.1% Oxygen	Change in value	-4.1	-5.2	1.1	2.4	3.3	0.43
	p-value	*0.009***	*0.000***	*0.298*	*0.665*	*0.354*	*0.533*

Table 23. Mean changes in physiological variables with associated p-values in response to hypoxia altitude simulation test
** indicates *p*-values <0.01

Larger physiological changes were seen in rSO_2, heart rate and cardiac output in response to the lower body negative pressure test (Table 24). Although the changes were only statistically significant at the highest level of LBNP (60mmHg), the coefficients suggest a dose-related response, with a falling cardiac output and rSO_2 and an increase in heart rate with the stepped intervals of LBNP.

LBNP		rSO_2	SpO_2 (%)	Resp Rate (bpm)	MAP (mmHg)	HR (bpm)	CO (L/min)
20mmHg LBNP	Change in value	-3.1	0.3	1.7	0.6	1.6	-0.4
	p-value	*0.221*	*0.620*	*0.154*	*0.903*	*0.653*	*0.430*
40mmHg LBNP	Change in value	-3.9	0.4	1.6	0.5	5.9	-0.7
	p-value	*0.121*	*0.397*	*0.175*	*0.917*	*0.095*	*0.205*
60mmHg LBNP	Change in value	-5.5	0.1	1.7	-2.5	20.8	-1.2
	p-value	*0.033**	*0.822*	*0.152*	*0.595*	*0.000***	*0.037**

Table 24. Mean changes in physiological variables with associated p-values in response to lower body negative pressure test
* indicates *p*-values <0.05; ** indicates *p*-values <0.01

When the volunteers were exposed to HAST in combination with LBNP, changes were seen in all physiological variables (Table 25). Peripheral arterial oxygen saturation decreased in response to the 15.1% oxygen mix and remained

low with the introduction of LBNP, although there did not appear to be any evidence of an interaction between HAST and LBNP on SpO_2 readings.

A reduction was seen in regional tissue oxygen saturation readings with the start of the 15.1% oxygen mix, although this was not demonstrated to be statistically significant. The rSO_2 readings continued to decrease with the addition of LBNP, again demonstrating a statistically significant dose-related response. There was some evidence of an interaction between HAST and LBNP on rSO_2, with larger changes in rSO_2 readings seen in the combination test, when compared with the individual test conditions.

The dose-related response of LBNP was also seen in heart rate readings, with increases in heart rate as a result of the introduction of the reduced oxygen mix and then stepped intervals of LBNP, although only LBNP at 40 and 60mmHg proved to be statistically significant.

Changes in respiratory rate in response to HAST and 60mmHg LBNP in combination were shown to be marginally statistically significant and appeared to demonstrate some interaction between the two test conditions; however, this effect was not clear due to the presence of collinearity.

LBNP AND HAST		**rSO_2**	**SpO_2 (%)**	**Resp Rate (bpm)**	**MAP (mmHg)**	**HR (bpm)**	**CO (L/min)**
15.1% Oxygen	Change in value	-1.9	-3.9	1.3	1.2	4.7	0.5
	p-value	*0.452*	*0.000***	*0.238*	*0.783*	*0.467*	*0.431*
20mmHg LBNP/O_2	Change in value	-5.7	-4.7	1.6	1.6	3.4	-0.3
	p-value	*0.028**	*0.000***	*0.162*	*0.707*	*0.592*	*0.621*
40mmHg LBNP/O_2	Change in value	-7.1	-5.1	1.6	-0.5	10.3	-0.7
	p-value	*0.006***	*0.000***	*0.162*	*0.913*	*0.111*	*0.264*
60mmHg LBNP/O_2	Change in value	-8.5	-4.5	2.3	-6.9	33.5	-1.2
	p-value	*0.001***	*0.000***	*0.049**	*0.113*	*0.000***	*0.062*

Table 25. Mean changes in physiological variables with associated p-values in response to hypoxia altitude simulation test in combination with lower body negative pressure
* indicates *p*-values <0.05; ** indicates *p*-values <0.01

5.3. Discussion

Overall, changes in physiological readings in response to the hypoxia altitude simulation test were primarily seen in rSO_2 and SpO_2 values. There was evidence of a dose-related effect on heart rate, rSO_2 and cardiac output seen in response to increasing intervals of lower body negative pressure. This was also evident in the combined HAST and LBNP experiment, where changes were seen in all variables, although not all were statistically significant. Regional tissue oxygen saturation was the only monitoring technique to demonstrate an effect in response to all 3 test conditions, suggesting that it may be more sensitive to changes than standard physiological monitoring.

Analysis of the data showed that peripheral arterial oxygen saturation (SpO_2) decreased amongst the volunteers during the hypoxia altitude simulation test (Figure 19). In the majority of volunteers, mean individual SpO_2 fell from a range of 97-100% to 90-94%. This response was similar to that observed by Smith (2007), who monitored SpO_2 in six healthy volunteers exposed to an altitude of 7,100ft (2743m) in a hypobaric chamber; over a five minute period, mean SpO_2 fell from over 97% to 92%. In an earlier study, Cottrell et al (1995) recorded SpO_2 in 38 airline crew members during scheduled short haul flights and identified a fall in SpO_2 from a range of 99-95% at ground level, to a range of 92-87% at 6,000-7,000ft.

Clumper (2011) describes four stages of hypoxia in relation to altitude, the first of which is defined as ‘indifferent hypoxia’, due to the minor physiological effects experienced up to an altitude of 10,000 feet. Healthy individuals compensate for the fall in the partial pressure of alveolar air at this altitude by

increasing respiratory rate and depth (Dine and Kreider, 2008; Lyznicki et al, 2000), through the hypoxic stimulation of arterial chemoreceptors (Levick, 2010); mild tachycardia is also commonly reported (Clumper, 2011). There were small increases in respiratory rate, heart rate and cardiac output recorded amongst the volunteers during the hypoxia altitude simulation test, although the responses were not statistically significant.

The results shown in Table 23 suggest that the majority of volunteers demonstrated a significant fall in tissue oxygen saturation recorded in the left deltoid in response to the hypoxia altitude simulation test. The paucity of previous studies utilising tissue oxygen saturation monitoring at altitude means there are few data available to permit comparison of the results obtained. However, the majority of volunteers demonstrated similar trends in response to the reduced oxygen mix, suggesting a common physiological response to simulated altitude. The results suggest that a fall in systemic oxygenation at simulated altitude (measured using SpO_2) is associated with a reduction in regional tissue oxygen saturation.

In the present study, lower body negative pressure did not have an effect on SpO_2. This lack of response was also reported by Soller et al (2008a).

The body's immediate response in recognising hypovolaemia involves the chemoreceptors and baroreceptors. A fall in the circulating volume of blood causes a decrease in the ventricular end diastolic volume, which reduces cardiac contractility, causing a fall in stroke volume (in accordance with Starling's Law)

and pulse pressure. If uncorrected, this would lead to a fall in cardiac output and arterial blood pressure, subsequently affecting cerebral and myocardial perfusion with potentially catastrophic consequences. This is identified by a reduction in baroreceptor activity, which effects a decrease in vagal nerve activity and an increase in sympathetic activity, causing vaso- and veno-constriction in the cutaneous, skeletal muscle, splanchnic and renal circulation to redistribute blood into the central circulation to improve venous return and cardiac filling, which increases peripheral vascular resistance (Levick, 2010). A reflex tachycardia in combination with this vaso-constriction helps to maintain mean arterial pressure, to preserve cerebral and cardiac perfusion (Ernsting et al, 2006; Lott et al, 2009). Sympathetic stimulation also triggers the release of adrenaline and noradrenaline which act to increase heart rate and cardiac contractility, contributing to the maintenance of mean arterial pressure. Decreased blood flow to the tissues during hypovolaemia results in the development of metabolic acidosis. The chemoreceptor response to this metabolic acidosis (and reduced oxygenation of the chemoreceptors themselves) is to increase the rate and depth of respiration to improve gas exchange and restore a normal blood pH. Chemoreceptor response also supports peripheral vasoconstriction to maintain MAP. Later responses to hypovolaemia, such as renal fluid retention, are not considered in the context of the present study.

LBNP is acknowledged as an appropriate means to simulate the body's immediate response to hypovolaemia (Soller et al, 2008a; Cooke et al, 2004). However, the circulating volume is not lost from the body with LBNP as would occur with hypovolaemia; blood is redistributed from the thorax into the pelvis

and legs (Cooke et al, 2004), with blood vessels, predominantly in the muscles, 'stretching' to accommodate the extra volume (Hachiya et al, 2012). This reduces cardiac filling which then induces the body's response as described above.

Cardiovascular responses to lower body negative pressure were not seen, with one exception – heart rate increased significantly in response to the highest level of LBNP. The trend effect of LBNP on mean arterial pressure, heart rate and cardiac output appeared to be dose-related and may have become significant with an additional level of LBNP. Soller et al (2008b) identified a similar response in MAP to LBNP – changes in MAP became statistically significant once the LBNP level reached 90mmHg; changes in heart rate became significant at 60mmHg as was seen in the present study. This was also reported in a study by Ryan et al (2008), who demonstrated that significant changes in heart rate, systolic and diastolic blood pressure were seen at 60mmHg LBNP, but changes in mean arterial pressure were not observed until LBNP was increased to 80mmHg. This preservation of MAP and CO through the body's immediate response to simulated hypovolaemia can be observed within the present study, with only small changes in CO and MAP recorded.

The graph at Figure 21 showed a downward trend in tissue oxygen saturation in response to the hypoxia altitude simulation test in combination with increasing lower body negative pressure. Constriction of the peripheral blood vessels occurs to maintain core perfusion and oxygenation, which reduces oxygenation of the peripheral tissues – as shown by the falling rSO_2 readings. Once LBNP and HAST were terminated, there was a sharp upward trend in readings, above the pre-test levels, as blood flow and perfusion improved in the

upper body. Tissue oxygen saturation returned to values similar to those seen pre-test as the blood vessels then constricted to maintain blood pressure and cardiac output. Analysis of the data seemed to suggest that combined LBNP and HAST had a greater effect on tissue oxygen saturation, than either test in isolation, with the combined test demonstrating a greater reduction in mean rSO_2 values than HAST or LBNP alone. Again, a lack of prior published studies examining rSO_2 at altitude prevents any comparison of the results obtained. This greater combined effect could have significance for the casualty with an altered circulating volume following traumatic injury who is then exposed to altitude; a larger fall in rSO_2 suggests a greater reduction in peripheral perfusion, potentially leading to tissue damage and a less favourable outcome – perhaps resulting in an increased requirement for debridement of devitalised tissue, a higher amputation, or organ failure.

Correct positioning of the volunteers in the LBNP device was essential, to ensure that the airtight skirt seal was positioned over the iliac crest rather than the upper abdominal area, to reduce any measurement error as a result of the incorrect application of LBNP. Goswami et al (2009) reported increased haemodynamic responses in volunteers exposed to LBNP where the skirt seal had been positioned over the abdomen when compared with responses from volunteers exposed to LBNP with a seal over the iliac crest.

Limitations: A limitation of the present study was the inability to reproduce the exact conditions experienced by AE casualties; although the application of LBNP produces a hypovolaemic response within the body (Soller et

al 2008b), it doesn't take account of other factors such as pain or inflammatory responses or replicate tissue damage seen in traumatic injuries or the ensuing biochemical effects on the body (Cooke et al, 2004). For the purposes of this study, however, the use of LBNP to produce an altered circulating volume in the volunteers was sufficient to introduce a physiological response which was identified and reported by the tissue oxygen saturation monitor being tested.

Conclusion: The aim of this second phase of the study was to record tissue oxygen saturation in healthy volunteers, who were exposed to both simulated altitude and conditions simulating altered circulating volume, with the objective of identifying whether regional changes in tissue oxygen saturation occur in response to the experimental conditions and if the monitoring system selected is sensitive enough to detect any changes in tissue oxygen saturation that may occur. The data obtained suggests that regional changes in tissue oxygenation do occur in response to the test conditions and that the rSO_2 monitoring technique is sensitive enough to detect those changes, and would therefore be suitable for use in the observational study planned for phase 3.

6. AN INVESTIGATION OF CHANGES IN TISSUE OXYGEN SATURATION DURING EXPOSURE TO SIMULATED ALTITUDE AND LOWER BODY NEGATIVE PRESSURE AND TILT

6.1. Methods

Background: In phase 2a, lower body negative pressure and / or a hypoxia altitude simulation test were used to assess the effectiveness of the INVOS 5100C cerebral / somatic oximeter in identifying changes in tissue oxygen saturation in volunteers exposed to these test conditions. The monitoring system proved to be effective in identifying changes in tissue oxygen saturation seen in response to the test conditions and could therefore be used in the observational study proposed for phase 3 of this research. As an extension of this earlier study, an additional experimental phase was proposed. Critical care casualties escorted by a CCAST are generally transported head first in-flight (i.e. with their heads pointing towards the cockpit), in contrast to non-critical aeromed patients who travel feet first. It was hypothesised that, in casualties already experiencing an altered circulating volume as a result of their injuries, this head first position, which exposes the casualties to a head up tilt during take-off, and other phases of flight, may lead to a reduction in upper body regional tissue oxygen saturation. During a study in which 16 casualties underwent transthoracic bioreactance monitoring throughout their aeromedical evacuation with the French Air Force, Dubost et al (2013) identified a decrease in median cardiac index during and immediately after take-off. They suggested that the supine casualty, travelling head first, may be subjected to a greater physiological challenge as a result of acceleration loads

during take-off, particularly when departing from operational locations where the rate of ascent increases more rapidly than would otherwise be experienced.

Non-ventilated patients travel feet first on the C-17 aircraft, as the Patient Service Module (PSM), which contains the emergency decompression oxygen system, is located on the aft stretcher stanchion. As ventilated patients do not require access to the PSM in the event of a rapid decompression, as they are already receiving supplemental oxygen, they are permitted to travel head first on the C-17 aircraft to minimise the otherwise slight head-down position during flight[6].

Aim: The aim of this additional experimental phase was to record tissue oxygen saturation in healthy volunteers, exposed to lower body negative pressure, HAST and a head up tilt, with the objective of identifying whether regional changes in tissue oxygen saturation occur in response to the experimental conditions and if the monitoring system selected is sensitive enough to detect any changes in tissue oxygen saturation that may occur.

Study protocol*:* The study protocol was submitted to and approved by the RAF Experimental Medicine Scientific Advisory Committee and the Ministry of Defence Research Ethics Committee (MoDREC reference 127/Gen/10).

Subjects*:* Twelve healthy volunteers were recruited from the population of military personnel between the ages of 18 and 40 years, who are currently serving

[6] C-17 Release to Service C17A/08/31 Issue 4 Released 12 Mar 10; Section C22 (Role Equipment) para C22.2.4-C22.2.5

at RAF Henlow. Individuals with pre-existing health problems or those taking prescribed medication were excluded from the study. All subjects completed a health questionnaire to ensure medical fitness to undertake the study; written consent was obtained from all subjects. As a result of the information provided in the health questionnaire, one volunteer was withdrawn from the study.

***Experimental procedure**:* The 11 volunteers were subjected to 2 tests on 2 separate days, at least 24 hours apart. One test combined HAST and LBNP as described in phase 2a of the study, with the same physiological monitoring as previously defined (Table 26), although the Kontron pulse oximeter probe was fitted to the left index finger and the Finometer cuff to the left middle finger, as the right arm was being used to simultaneously collect data for a separate research project. The second test was HAST and LBNP in combination, with the addition of a 70° head up tilt after 5 minutes at 20mmHg LBNP (Figure 22). Manual tilting of the table took approximately 5 seconds to achieve. Once the table was tilted, the volunteers spent a further 5 minutes at 20mmHg LBNP, followed by 5 minute stepped intervals of LBNP at 40 and 60mmHg, with the tilt maintained. At the end of the testing, the table was lowered to a supine position, with the termination of LBNP; the volunteers reverted to breathing room air and were monitored during a 10 minute recovery period.

Variable	Measurement Technique
Peripheral arterial oxygen saturation	Kontron pulse oximeter
Heart rate	Kontron pulse oximeter
Systolic/Diastolic blood pressure	FMS Finometer
End tidal oxygen concentration	LR-1 Respiratory mass spectrometer
End tidal carbon dioxide concentration	LR-1 Respiratory mass spectrometer
Tissue oxygen saturation	INVOS 5100C cerebral/somatic monitor

Table 26. Measured variables during hypoxia altitude simulation test and lower body negative pressure test

Termination of an experimental run: It was decided that an experimental run would be terminated if:

a. The volunteer exhibited signs or symptoms of impending cardiovascular collapse, defined as one or more of the following:

(i) a sudden decrease in systolic blood pressure (greater than 15mmHg)

(ii) a sudden decrease in heart rate (greater than 15 beats per minute)

(iii) a reduced systolic blood pressure below 80mmHg

(iv) a reduced conscious level

b. The volunteer self-terminated due to the onset of pre-syncope (altered vision, sweating, nausea or dizziness).

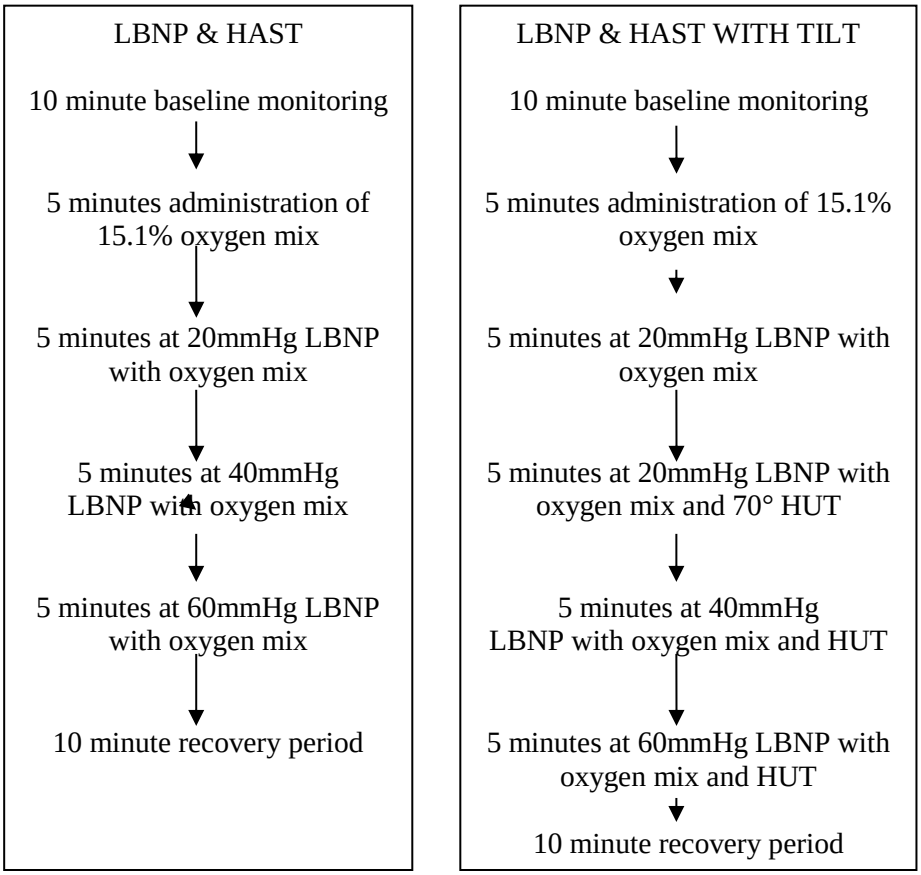

Figure 22. Flow chart demonstrating the 2 test conditions used in phase 2b of the study
HAST = hypoxia altitude simulation test; LBNP = lower body negative pressure test; HUT = head up tilt.

The order for the two experimental conditions is shown in Table 27 below.

Subject	Condition 1	Condition 2
1	HAST & LBNP	HAST & LBNP with HUT
2	HAST & LBNP with HUT	HAST & LBNP
3	HAST & LBNP	HAST & LBNP with HUT
4	Withdrawn from study	Withdrawn from study
5	HAST & LBNP	HAST & LBNP with HUT
6	HAST & LBNP with HUT	HAST & LBNP
7	HAST & LBNP	HAST & LBNP with HUT
8	HAST & LBNP with HUT	HAST & LBNP
9	HAST & LBNP	HAST & LBNP with HUT
10	HAST & LBNP with HUT	HAST & LBNP
11	HAST & LBNP	HAST & LBNP with HUT
12	HAST & LBNP with HUT	HAST & LBNP

Table 27. Order of experimental conditions for 12 subjects
HAST = hypoxia altitude simulation test; LBNP = lower body negative pressure test; HUT = 70° head up tilt.

Data collection*:* Data collection, reduction and analysis were undertaken using the processes previously described in Chapter 5.

6.2. Results

Demographic and anthropometric data for the eleven volunteers are shown in Table 28. Three of the volunteers had already participated in phase 2a of the study.

	Variable
Age (years)	29.7 (Range 23 – 37)
Gender (*n*) (male / female)	9 / 2
Height (cm)	172.9 ±6.46
Weight (Kg)	76.2 ±10.94

Table 28. Demographic and anthropometric data for phase 2b; ***n* = 11**
Values are means ±SD**.**

All eleven volunteers completed both experimental conditions; one volunteer terminated the combined HAST and LBNP test before completing a full 5 minutes at 60mmHg LBNP, due to symptoms of pre-syncope. Four volunteers terminated the combined HAST, LBNP and tilt test before completing a full 5

minutes at 60mmHg LBNP, also due to symptoms of pre-syncope. In these cases, the final complete minute of readings were used in the data analysis. There were no adverse effects experienced by the eleven volunteers as a result of the experimental conditions.

Tissue oxygen saturation readings in 1 volunteer were very low compared with other volunteers and with the previous study; taken in combination with a low signal strength indicator on the INVOS oximeter, these low readings were interpreted as erroneous due to a poor connection. Despite replacing the sensor, the rSO_2 signal strength indication for this volunteer did not improve, so the rSO_2 results were excluded from the final analysis.

A full set of graphs can be found at Annex E, with selected findings discussed below.

When the volunteers were exposed to HAST in combination with LBNP and tilt, changes were seen in all physiological variables (Table 29). Peripheral arterial oxygen saturation decreased in response to the 15.1% oxygen mix and remained low with the introduction of LBNP and then tilt, although there did not appear to be any evidence of an interaction between the test conditions on SpO_2 readings.

Regional tissue oxygen saturation readings showed a decreasing trend with the administration of the 15.1% oxygen mix, although this was not shown to be statistically significant. Further decreases in rSO_2 readings were noted with the introduction of LBNP and tilt, with a greater response seen with higher levels of LBNP, as previously noted in phase 2a.

The dose-related effect of LBNP and tilt were also seen in heart rate readings, with increases in heart rate seen at all phases of the experiment, although these increases only became statistically significant at 40 and 60mmHg LBNP with tilt. Dose-related changes in cardiac output and mean arterial pressure were also seen at the higher levels of LBNP and tilt.

Individual increases in heart rate combined with a fall in MAP and CO were extreme enough for a number of the volunteers to terminate the test phase before completing the full 5 minutes at 60mmHg LBNP with tilt.

LBNP AND HAST WITH TILT		**rSO_2**	**SpO_2 (%)**	**Resp Rate (bpm)**	**MAP (mmHg)**	**HR (bpm)**	**CO (L/min)**
15.1% Oxygen	Change in value	-1.6	-3.1	-2.4	1.7	4.8	0.6
	p-value	*0.669*	*0.003***	*0.104*	*0.750*	*0.367*	*0.227*
20mmHg LBNP/O_2	Change in value	-5.2	-3.6	-2.1	1.9	5.9	-0.7
	p-value	*0.159*	*0.001***	*0.149*	*0.714*	*0.265*	*0.873*
20mmHg LBNP/O_2/ Tilt	Change in value	-6.3	-4.4	-2.2	3.2	8.8	-0.2
	p-value	*0.094*	*0.000***	*0.133*	*0.540*	*0.097*	*0.661*
40mmHg LBNP/O_2/ Tilt	Change in value	-6.9	-3.8	-1.5	-0.7	19.2	-0.6
	p-value	*0.065*	*0.000***	*0.285*	*0.899*	*0.001***	*0.205*
60mmHg LBNP/O_2/ Tilt	Change in value	-8.0	-3.9	-1.0	-15.3	34.6	-1.9
	p-value	*0.035**	*0.000***	*0.487*	*0.005***	*0.000***	*0.000***

Table 29. Mean changes in physiological variables with associated p-values in response to hypoxia altitude simulation test in conjunction with lower body negative pressure and head up tilt
* indicates *p*-values <0.05; ** indicates *p*-values <0.01

6.3. Discussion

In summary, adding a 70° head up tilt to the combined HAST and LBNP experimental procedure used in phase 2a of the study did elicit some physiological changes, primarily seen in the cardiovascular variables - heart rate, cardiac output and mean arterial pressure. An increase in heart rate and a corresponding fall in cardiac output and mean arterial pressure were recorded, which proved to be

statistically significant at the highest level of LBNP when combined with HAST and tilt. Changes in the coefficients for rSO_2, SpO_2 and respiratory rate were consistent with the results seen with the HAST and LBNP only combination, suggesting that adding a head up tilt did not greatly effect these variables.

Cooke and Convertino (2002) suggest that the physiological sympathetic response is withdrawn (in healthy volunteers) at the point when the body cannot further increase peripheral vascular resistance in response to a continued stimulus such as LBNP. They postulate that the withdrawal of sympathetic activity, which results in peripheral vasodilation, leading to syncope, is the body's way of restoring cerebral perfusion when increasing peripheral vascular resistance has failed to do so.

It is suggested that the fall in mean CO and MAP observed during this phase of the study result from the body's inability to further compensate for LBNP and tilt and would likely have resulted in syncope had the experimental conditions not been terminated. This suggestion is supported by the fact that 4 volunteers terminated the final experimental phase before completion of the full 5 minutes due to symptoms of impending syncope. Hachiya et al (2004) suggest that a head up tilt between 60-70° is equal to LBNP of 40mmHg, indicating that the volunteers in the present study were exposed to a considerable physiological assault.

In the present study, rSO_2 was recorded in the upper arm only; for future work, it would be interesting to repeat the study using a second, more distal site to compare the effect of peripheral vaso-constriction on rSO_2 readings taken further from the central circulation and over a different anatomical area. Monitoring

blood flow simultaneously would also add greater understanding of the value of rSO_2 measurements as an indicator of poor perfusion.

The low rSO_2 readings combined with poor signal strength indication obtained for 1 of the volunteers suggested a poor connection at some point between the volunteer and the oximeter. Replacing the NIRS sensor did not improve the readings obtained – although both discarded sensors subsequently appeared to function appropriately when applied to the upper arm of the principal investigator. A review of the literature led to the suggestion that the darker skin pigmentation seen in the volunteer may have contributed to the loss of signal, as melanin absorbs more of the near infra-red light emitted (Shuler et al, 2009). During their study, Wassenaar and Van den Brand (2005) attempted to record tissue oxygen saturation in the lower leg anterior compartment muscles of 17 volunteers with dark skin pigmentation. In the 28 sets of data obtained from the 17 volunteers, the NIRS signal was lost in 2 sets where the tissue oxygen saturation was >50% and 12 sets where the tissue oxygen saturation was <50%. The mean melanin level of the volunteers in whom the NIRS signal was lost was greater than the melanin levels for the volunteers in whom the NIRS signal was not lost (p=0.012). The authors suggested that higher melanin levels may affect the reliability and veracity of tissue oxygen saturation readings obtained. Certainly, within the current study, rSO_2 levels were significantly lower and were excluded from the analysis as a result.

A similar issue was identified with tattooed skin; several of the volunteers had large tattoos to the upper arm, covering the proposed monitoring site. In these individuals, it was more difficult to obtain a reliable signal strength indication

when monitoring through the tattoo. As a solution, monitoring was undertaken in the opposite arm, or, in one case, the position of the monitoring sensor had to be slightly adjusted as the volunteer had tattoos to both upper arms. The tattoos which incorporated coloured ink did not seem to cause an issue, but the black ink used in monochromatic designs such as illustrated in Figure 23 proved problematic. Barker (2011) identified a comparable issue and concluded that the tattoo ink absorbed the near infra-red light in a manner similar to that described in dark pigmented skin.

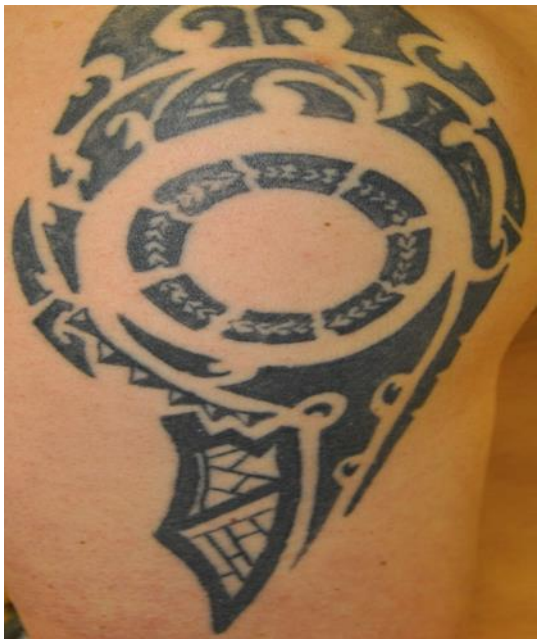

Figure 23. An example of a monochromatic tattoo to the upper arm

Conclusions: The aims of this additional experimental phase were met; changes in tissue oxygen saturation in response to LBNP, HAST and tilt were observed, but they demonstrated similar trends to those seen in response to the LBNP and HAST only combination, leading to the conclusion that the 70° head up tilt did not exacerbate the fall in rSO_2 seen in the earlier experimental phase, as was anticipated. Further investigation is recommended as this may have implications for the use of the monitoring system in trauma casualties. The fact

that peripheral oxygen saturation was maintained during these experimental conditions despite the significant changes seen in other physiological markers may be considered a positive when considering the safety of early aeromedical evacuation– although it must be remembered that this is not indicative of cerebral oxygenation which might display different trends under the same conditions.

7. AN INVESTIGATION OF CHANGES IN TISSUE OXYGEN SATURATION IN MILITARY CASUALTIES UNDERGOING AEROMEDICAL EVACUATION

7.1. Methods

Aim: During the second phase of this study, regional tissue oxygen saturation monitoring was demonstrated to be sensitive to changes occurring as a result of simulated alterations to altitude and circulating volume in healthy volunteers. The main aim of this third phase of research was to undertake a prospective observational study to identify if changes in tissue oxygen saturation occur in military casualties during aeromedical evacuation from Afghanistan to the UK. A secondary aim was to investigate whether there were more changes in tissue oxygen saturation in those casualties with lower pre-flight haemoglobin levels.

Study protocol: The study protocol was submitted to and approved by the RAF Experimental Medicine Scientific Advisory Committee and the Ministry of Defence Research Ethics Committee (MoDREC reference 285/Gen/11). CCAST personnel were briefed on the nature and format of the proposed study at their quarterly meeting.

Subjects: Military casualties who sustained a significant traumatic injury whilst serving in Afghanistan, who required aeromedical evacuation back to RCDM for in-patient management were included in the study. For the purpose of this study, a significant traumatic injury was defined as an ISS or NISS of 9 or

greater (Appendix A). A request for aeromedical evacuation for each casualty was raised by the in-theatre Aeromedical Evacuation Liaison Officer (AELO), as usual. This request was sent to AECC personnel, who authorised the AE and arranged a suitable flight. On receipt of an AE request for a critical care casualty, AECC personnel contacted the principal investigator to discuss whether the casualty met the study criteria. Once a suitable casualty had been identified, the principal investigator travelled to RAF Brize Norton to join the CCAST members for the AE flight. As all casualties included in the study were ventilated and sedated at the time of AE, informed consent was not obtained; however, agreement for inclusion in the study was obtained from the consultant anaesthetist responsible for the casualty in-flight. As the tissue oxygen saturation monitoring did not impact on the casualty's continuing care, nor alter his existing condition, retrospective consent was not sought from the casualties or their relatives. The issue of not seeking retrospective consent was articulated in paragraph 14a of the study protocol submitted to, and approved by, MoDREC (MoDREC reference 285/Gen/11).

Monitoring technique: Continuous in-flight physiological monitoring of the casualties was undertaken by the CCAST escorts, using the MRL PIC 50 monitor (WelchAllyn, New York), in accordance with existing CCAST protocols. Table 30 lists the standard monitoring which was recorded during each aeromedical evacuation.

Variable	Measurement Technique
Peripheral arterial oxygen saturation	MRL PIC 50
Heart rate	MRL PIC 50
Respiratory rate	MRL PIC 50
Invasive systolic/diastolic blood pressure	MRL PIC 50
End tidal carbon dioxide concentration	MRL PIC 50
Temperature	MRL PIC 50
Central venous pressure	MRL PIC 50
Tissue oxygen saturation	INVOS 5100C Oximeter

Table 30. Measured variables recorded during aeromedical evacuation

All medical monitoring equipment undergoes a rigorous testing procedure before being approved for use in military aircraft. Each item of equipment is tested to ensure that it is capable of operating in-flight as the manufacturer intended, despite being potentially exposed to altitude, vibration, sudden decompression, acceleration/deceleration forces and changes in temperature and humidity (Lamb, 2003). Items are also tested to ensure that they do not have an adverse effect on the aircraft, such as electromagnetic interference (EMI); this is particularly important on-board a military aircraft which may have defensive aids fitted – any EMI may inadvertently activate these defensive aids, or affect other electrical systems, such as navigation or flight controls. Nish et al (1989) previously reported a high incidence of neonatal monitoring equipment failing to meet United States Air Force EMI regulations. Electromagnetic compatibility testing is also undertaken, to ensure that the aircraft and its systems do not affect the correct functioning of the medical monitoring devices (McGuire, 2006b).

As tissue oxygen saturation monitoring was not a standard monitoring technique, there were no approved devices available for use in-flight. The INVOS 5100C cerebral/somatic oximeter underwent limited airworthiness testing to ensure that the device did not endanger the aircraft; as a result of the testing,

temporary air clearance was issued permitting use of the monitor on board the C-17 aircraft only, for a 6 month period. A further request for a 3 month extension to the temporary air clearance was submitted to the C-17 Release to Service authority to permit an additional data collection period, which was approved. The full airworthiness test schedule was not performed due to the trial nature of the study. Likewise, the limited airworthiness testing was only undertaken for the C-17 aircraft, as the majority of CCAST casualties are evacuated on this airframe; adding other aircraft to the test schedule would have prolonged the clearance process and increased the financial cost.

Data Collection: All monitoring devices were tested and used in accordance with the manufacturer's instructions. Prior to use on each casualty, the data log on the MRL PIC 50 was cleared, to ensure that only data pertaining to the current casualty was recorded. The CCAST escorts connected the casualty to the MRL PIC monitor using the appropriate leads or transducers during retrieval from the Intensive Care Unit in the Field Hospital. Although live continuous data was shown on the monitor's screen, the MRL PIC was set to record readings of the physiological parameters to the internal data log every 5 minutes for the duration of the flight. The readings were printed from the log at the end of the flight; the data was later exported into a Microsoft© Office Excel file.

To ensure standardisation in monitoring technique, the same methods were used for setting up the INVOS Oximeter and recording data as were described in chapters 5 and 6. Due to the limited space around the casualty's stretcher on-board the aircraft, the INVOS monitor and cables were placed directly onto the

aircraft floor and secured in place utilising strops and the 'D' ring securing points which are built into the floor.

Once the casualty had been transferred to the aircraft, the INVOS Oximeter was switched on and the 'new patient' option selected from the start up screen, which reset the default parameters and started a new data log. The INVOS Oximeter was then attached to the casualty, with the sensor placed on the lateral aspect of the upper third of the upper arm over the deltoid muscle. The left upper arm was the preferred site, but this was dependent on the injuries sustained by the casualty and on direction from the consultant anaesthetist responsible for the casualty's in-flight care. Where required, the right upper arm was the alternative site used for monitoring. Tissue oxygen saturation readings were recorded to an internal file every 6 seconds for the duration of the flight; these were later exported into a Microsoft© Office Excel file. Event markers were used to synchronise timings between the 2 sources. Data reduction was achieved by calculating the mean rSO_2 measurements for each 5 minute period of recording to permit comparison with the 5 minute readings of the other physiological variables obtained from the MRL PIC.

CCAST personnel were blinded to the readings obtained from the INVOS to ensure that there were no in-flight changes in clinical management instigated in response to tissue oxygen saturation readings. Data collection ended when the aircraft came to a stop on the designated stand at Birmingham International Airport. Data from the MRL PIC was printed prior to the casualty being off-loaded from the aircraft. The casualty was disconnected from the INVOS monitor

at this time, but the CCAST continued to use the MRL PIC to monitor the casualty's condition during the road transfer to RCDM.

A standardised data collection matrix was used to extract relevant data from the casualty's hospital records. This included:

a. Mechanism of injury
b. Injuries sustained
c. Blood / blood replacement therapy post injury
d. Pre-flight haemoglobin and haematocrit levels
e. Clinical in-flight management parameters, such as ventilator settings, and the rate and type of sedation agents, inotropic support or fluid replacement therapy given.

The anonymised data were stored in a Microsoft© Excel spreadsheet which permitted calculation of specific descriptive statistics.

Two audit requests were made for the release of additional post-flight data from the JTTR held by ADMEM at RCDM. The first data request was for the post-flight haemoglobin and haematocrit levels (defined as the first results obtained on arrival at the receiving hospital) which were recorded during visits by the military trauma co-ordinator team and the second request was for the injury severity score for each casualty (see Appendix A) as calculated by the trauma co-ordinator from the record of the casualty's injuries.

7.2. Results

Tissue oxygen saturation monitoring was recorded in 15 casualties undergoing aeromedical evacuation from Afghanistan to the UK during the period

January – August 2012. All flights were successfully completed with no fatalities en-route. A total of 147 monitoring hours were recorded, with a mean transfer time of 9.8 hours per casualty (range 8 to 13 hours). The difference in flight times related to the route taken by each aircraft, with some returning direct to the UK and some making re-fuelling stops en-route. All flights landed in Birmingham, where the casualties were off-loaded and transferred to RCDM.

Demographics: All 15 casualties were male; the mean age was 25.2 years ± 4.2 (range 21-38 years). The majority of the casualties (*n=10)* had received traumatic injuries as a result of IED activation. The mean ISS (±SD) was 37.1 ± 22.5 (range 8-75) and the mean NISS (±SD) was 48.9 ± 19.1 (range 12-75). Three casualties had ISS and NISS scores of 75. Mean cabin altitude was 5933.3ft (range 3000-8000ft).

Ventilation: All casualties had been ventilated and sedated during the initial management of their injuries and this was maintained during their aeromedical evacuation. Seven of the casualties were ventilated using pressure control mode and 3 on volume control mode. Five casualties began their flights on volume control mode but were changed to pressure control mode in-flight to reduce factors such as high airways pressure or a rising PCO_2 level.

The initial ventilator settings are shown in Table 31, with any in-flight changes made. Excluding changes in mode of ventilation, there were 42 recorded alterations to the ventilator settings in-flight, averaging 0.28 changes per monitoring hour.

Recorded Values	Mean ± SD	Range		In-flight Changes
		Min	Max	
Set tidal volume (mL)	557.3 ± 50.9	450	660	5
Set respiratory rate (bpm)	16.8 ± 1.88	14	20	19
Set PEEP (cm H_2O)	5.6 ± 1.4	5	10	2
Set FiO_2	0.4 ± 0.06	0.3	0.5	16

Table 31. Initial ventilator settings and in-flight changes
PEEP = Peak end expiratory pressure; FiO2 = Fraction of inspired oxygen

As seen in phase 1, respiratory rate was the most commonly adjusted variable in-flight, with 19 changes seen in the current study, averaging 0.12 changes per monitored hour (Table 32). Six casualties ended the flight with a lower set respiratory rate, 1 with a higher set rate and 5 did not have any rate changes initiated. Three casualties had rate changes in-flight but had returned to the original setting by the end of the evacuation.

Fraction of inspired oxygen was the second most common change with a total of 16 changes in-flight; 10 casualties ended the flight with a lower FiO_2, 3 with a higher FiO_2 and 2 with an unchanged FiO_2. The mean number of changes by monitored hour and per casualty was similar to those seen in the first phase of the study.

Value	Total Number of Changes	Mean Number of Changes		Range of Changes per Casualty
		Per Casualty (*n=15*)	Per Monitored Hour (*n=147*)	
Tidal volume	5	0.3	0.03	0-3
Respiratory rate	19	1.26	0.12	0-4
PEEP	2	0.13	0.01	0-1
FiO_2	16	1.06	0.11	0-2
Total Changes	42	2.8	0.28	1-5

Table 32. Mean number of changes per casualty and per monitored hour

Sedation: Three different medications were used to maintain sedation in-flight. Eight casualties received a midazolam, propofol and fentanyl (or fentanyl derivative – alfentanil) combination, six casualties received a propofol and fentanyl combination and 1 casualty received midazolam with fentanyl. In total, 38 separate infusions were administered between the 15 casualties; the breakdown of changes in the medication administration rates is shown in Table 33. In 9 infusions, no rate changes were seen; in the remaining 29 infusions, there were a total of 53 changes in administration rate, with a mean of 1.8 changes per infusion.

Medication	Rate Change			Other Rate Changes[7]
	Increase	Decrease	None	
Propofol (*n=14*)	3	8	2	1
Fentanyl/Derivative (*n=15*)	4	6	3	2
Midazolam (*n=9*)	2	0	4	3

Table 33. Comparison of pre-flight and post-flight medication administration rates

Inotropic Support: Six casualties received noradrenaline infusions in-flight. There were a total of 14 changes in administration rates during the flight, averaging 2.3 changes per casualty. By the end of the flight, 3 casualties were receiving higher doses than during the immediate pre-flight period and 3 casualties were receiving lower doses.

Haemoglobin: Eleven casualties had a recorded pre-flight haemoglobin level below 10g/dL (range 7.5 – 9.9g/dL); pre-flight blood transfusions had been

[7] Rates were changed in-flight but had been reset to the original rate by the end of the flight

administered to all of the casualties, although detailed information regarding transfusion amount was missing from 1 set of records. A total of 113 units of blood (range 2-42 units; mean 11.3 units/casualty) and 101 units of FFP (range 2-35 units; mean 10.1 units/casualty) had been transfused into 10 of these casualties in the time between injury and AE. Five of these casualties received further blood products in-flight, with 10 units of blood (range 1-3; mean 2 units/casualty) and 3 units of FFP (range 0-1; mean 0.6 units/casualty) transfused during the flight.

The remaining 4 casualties had pre-flight haemoglobins levels above 10g/dL (range 10.2 - 12.1g/dL). Fifty four units of blood (range 0-34; mean 13.5 units/casualty) and 58 units of FFP (range 0-36; mean 14.5 units/casualty) were transfused in the time between injury and transfer. Only 1 of these casualties was transfused in-flight – receiving 2 units each of blood and FFP.

Of the 11 casualties with a pre-flight haemoglobin level below 10g/dL, 6 had a higher post-flight level (all of which were above 10g/dL). In the higher haemoglobin group, only one of the casualties had a lower haemoglobin level post-flight, but this was still above 10g/dL. Figure 24 demonstrates the pre- and post-flight haemoglobin levels for each casualty.

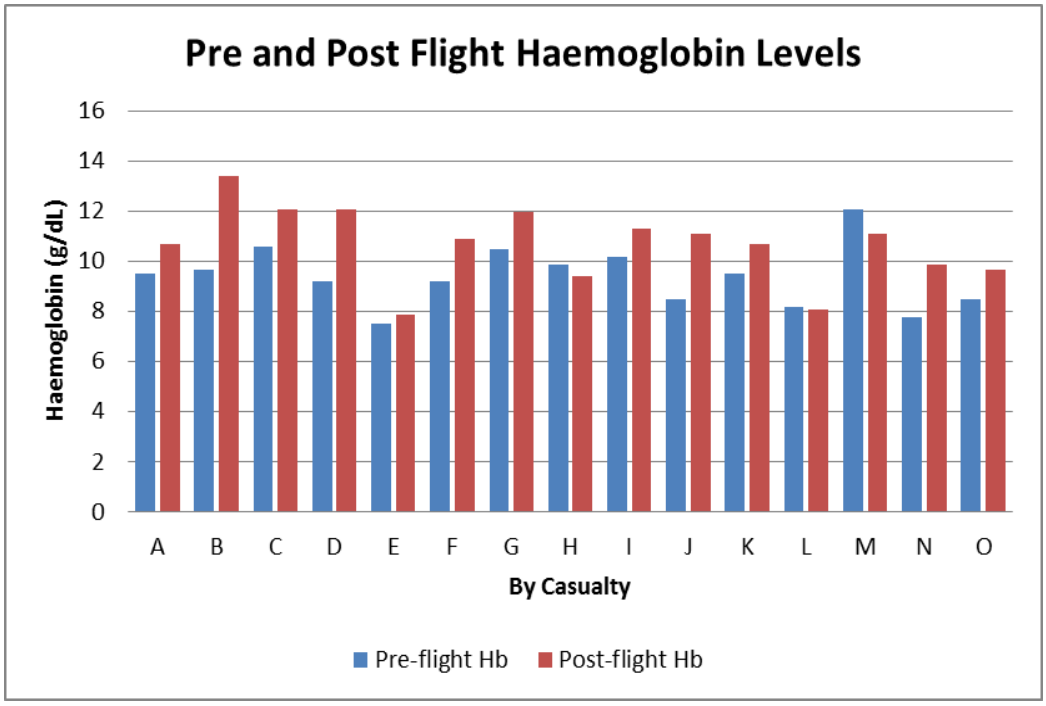

Figure 24. Pre- and post-flight haemoglobin levels by casualty

The results of a paired t-test comparing the pre and post-flight haemoglobin levels for the 15 casualties are shown below. The mean post-flight haemoglobin level was over 1g/dL higher than the pre-flight level and, as in phase 1, this was shown to be statistically significant (*p=0.0013*).

Haemoglobin	Mean	Std Err	Std Dev	95% Confidence Interval	
Pre Flight	9.4	0.3	1.2	8.7	10.0
Post Flight	10.7**	0.4	1.5	9.9	11.5
Difference	-1.3	0.3	1.3	-2.0	-0.6

Table 34. The results of a paired t-test comparing pre- and post-flight haemoglobin levels in 15 casualties
** indicates p<0.01 compared to pre-flight value

Tissue oxygen saturation monitoring was undertaken in all 15 casualties; however, 1 set of results was not included in the final analysis as prolonged periods of the data collection was compromised due to poor adherence of the monitoring sensor on the casualty's arm. In the remaining 14 casualties, rSO_2

monitoring was performed in the deltoid muscle of the left or right upper arm, depending upon injury sites, with readings recorded every 6 seconds. Several of the casualties had tattoos to the upper arm, and, following the lessons learned in phase 2, care was taken to ensure that data collection was not compromised from placing the monitoring sensor directly over the tattooed area – where possible, the other arm was used for monitoring.

The data were reduced to the mean reading for each 5 minute period, with the first 5 minute period used as a baseline for comparison with later readings. Data from 4 of the 14 casualties (28.6%) demonstrated that the in-flight rSO_2 readings fell by more than 10% of the initial baseline reading recorded pre-flight, during at least 1 five minute period in the flight.

Figure 25 demonstrates the mean rSO_2 readings for the 14 casualties for each 5 minute period of monitoring throughout the duration of their flights. To aid interpretation, the readings are shown across three graphs (0-245 minutes, 250-495 minutes and 500 to 835 minutes). Flight duration varied for each casualty depending on the route taken by each aircraft, with some returning direct to the UK and some making re-fuelling stops en route.

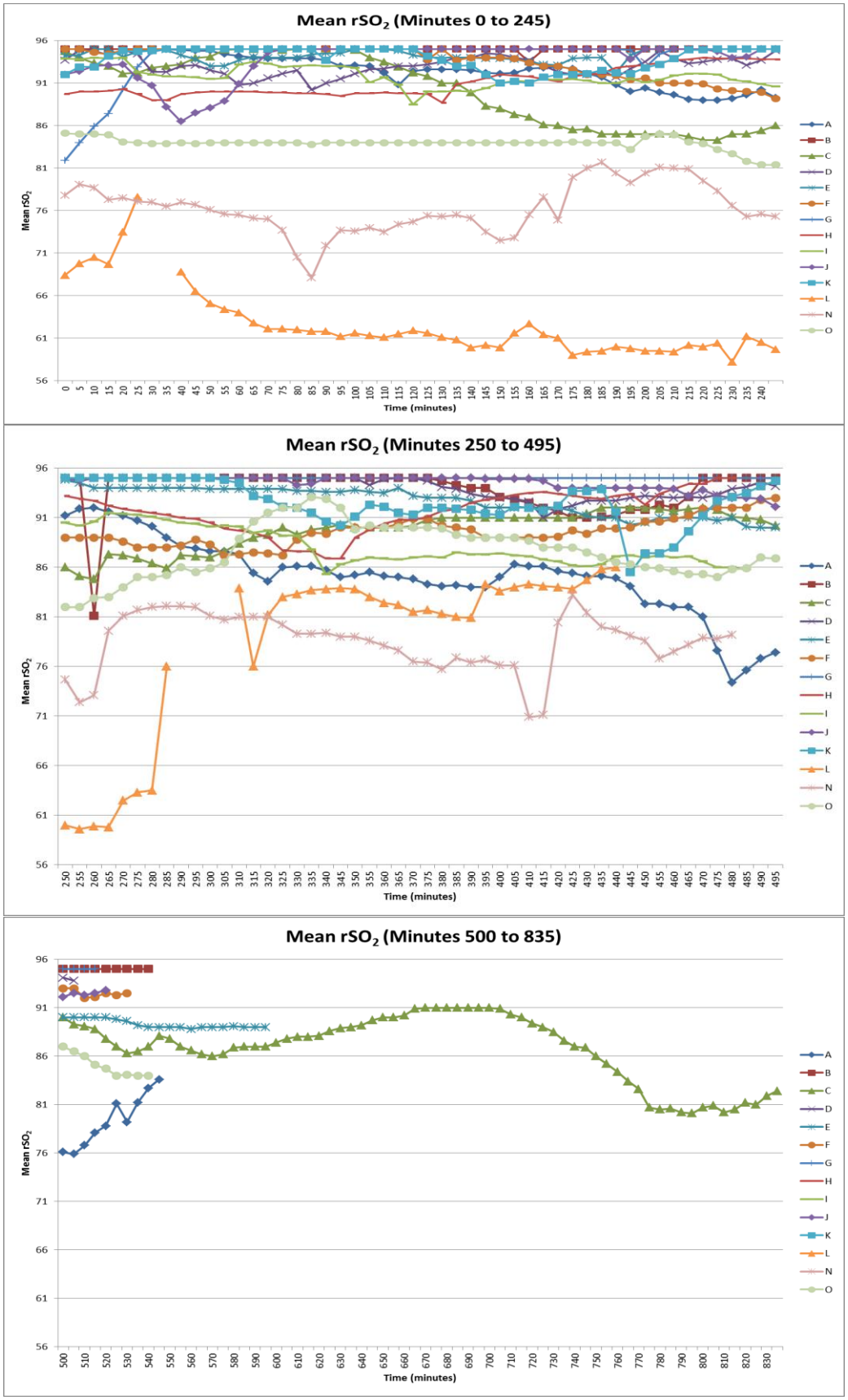

Figure 25. Mean rSO2 readings in 14 casualties for each 5 minute period of monitoring for the duration of each flight.

Amongst the four identified casualties, the readings fell by 11%, 12%, 15% and 22% of the initial baseline reading respectively. In all four cases, the rSO_2 readings showed a gradual decline, over a period of time, rather than a steep or abrupt drop. There appeared to be no pattern to the decline, with some of the casualties demonstrating a later recovery towards the baseline reading. Analysis of the time to event data demonstrated that the start of all four reductions took place at different time points during the flight (Figure 26), ranging from 90 minutes to 320 minutes. The remaining ten casualties (71.4%) maintained rSO_2 readings within 10% of their individual baseline, until monitoring was completed at the end of each flight (range 485-600 minutes).

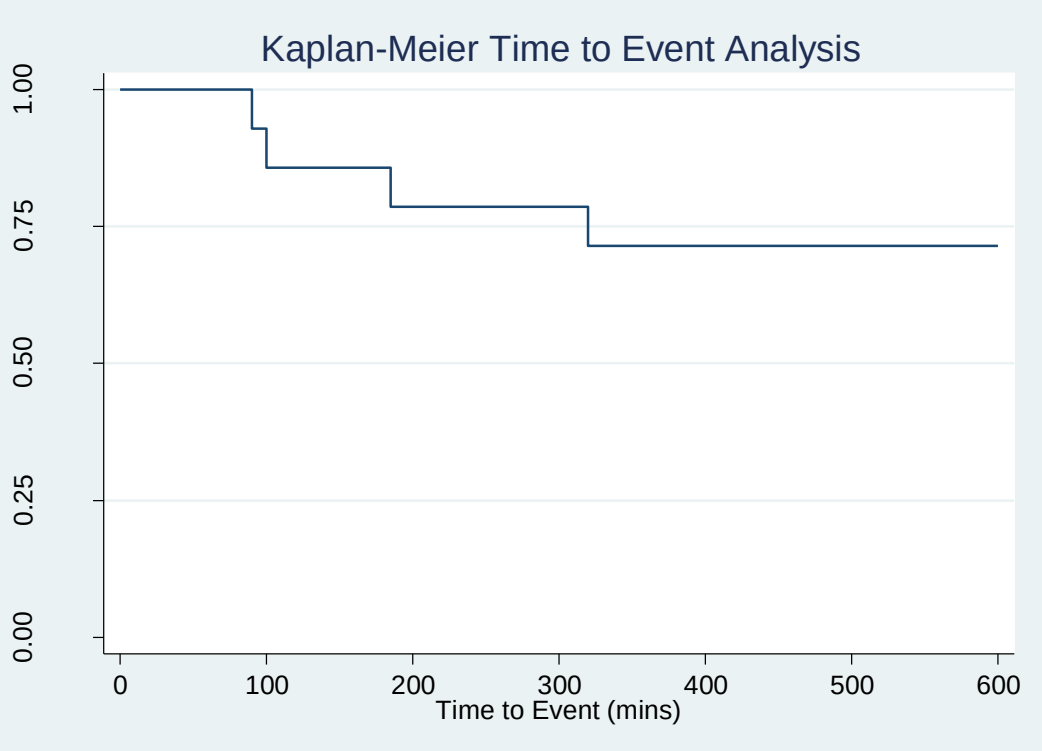

Figure 26. Kaplan-Meier chart showing in-flight time to loss of ≥10% baseline rSO_2 readings (4 from 14 casualties)

A review of all four casualties was undertaken in an attempt to identify the potential cause of the reduced tissue oxygen saturation observed. All four had

sustained their injuries as a result of IED blast, although their actual injuries were different, both in location and severity. Compared with the group who did not demonstrate any fall in rSO_2, the ISS/NISS in this group was lower, as shown in Table 35. However, there were 3 casualties who had sustained penetrating head injuries, which were subsequently awarded an ISS/NISS of 75, which skewed comparison of the trauma scores, as the rSO2 fall group did not contain any head injured casualties. If the 3 head injured casualties were excluded, the results for the no rSO_2 fall group reduced to ISS 30.1 (±13.4) and NISS 43.1 (±11.1). A one-way Kruskal-Wallis test was performed using the ISS/NISS by rSO_2 fall or no fall group. With a p-value >0.5, the results were not significant, demonstrating there was no evidence of a difference between the two groups. The result was also not significant when the test was repeated with the ISS/NISS of the 3 head injured cases excluded.

	No rSO_2 fall observed (n=10)	**rSO_2 fall observed (n=4)**
Mean ISS (±SD) (Range)	43.6 (±23.4) (16-75)	28.25 (±3.1) (25-33)
NISS (±SD) (Range)	52.7 (±17.3) (24-75)	48.5 (±12.6) (33-66)

Table 35. Comparison of ISS/NISS scores between casualties with and without a fall in rSO_2 results

Three of the four casualties had received massive transfusions of blood products in the time between injury and aeromedical evacuation. Transfusion data was not available for the fourth casualty, but it is likely that he would have received a sizeable transfusion, given the type and extent of the injuries suffered. As shown in Table 36, the mean transfusion volume per casualty was higher for those in whom an rSO_2 fall was observed. Again, the head injured patients

slightly skewed this result as they tended to receive smaller transfusions than other casualty groups, as the actual blood loss they experienced as a result of their injury was generally less.

	No rSO_2 fall observed (n=10)	**rSO_2 fall observed (n=3)**
Pre-flight blood transfused (Range) Mean units/casualty	114 units (2-42 units) 11.4 units/casualty	53 units (11-28 units) 17.6 units/casualty
Pre-flight FFP transfused (Range) Mean units/casualty	102 units (2-36) 10.2 units/casualty	57 units (11-28 units) 19 units/casualty
In-flight blood transfused (Range) Mean units/casualty	9 (0-3 units) 0.9 units/casualty	3 (1-2 units) 1 unit/casualty
In-flight FFP transfused (Range) Mean units/casualty	7 (0-2 units) 0.7 units/casualty	2 (0-1 units) 0.66 units/casualty

Table 36. Comparison of blood and fresh frozen plasma administration in casualties with and without a fall in rSO_2 readings

In-flight clinical management changes were very similar amongst the 4 casualties, with only minor adjustments to ventilation settings and sedation rates. Sedation rate changes are shown in Table 37 below.

Medication	Rate Change			Other Rate Changes[8]
	Increase	Decrease	None	
Propofol (*n=3*)	2	1	0	0
Fentanyl/Derivative (*n=4*)	2	1	1	0
Midazolam (*n=2*)	0	0	1	1
Noradrenaline (*n=1*)	0	1	0	0

Table 37. Comparison of pre- and post-flight medication administration rates in 4 casualties

Respiratory rate was changed in 2 casualties, with one rate being reduced and one rate being altered but returning to pre-flight settings by the end of the flight. In 3 cases, the initial FiO_2 setting was reduced during the flight.

[8] Rates were changed in-flight but had been reset to the original rate by the end of the flight

A review of the physiological variables in the two groups was then undertaken. The rSO_2 trends for the four casualties demonstrating an in-flight fall were plotted against their heart rate, arterial oxygen saturation and systolic blood pressure readings to see if there were similar changes seen in these variables at the time the rSO_2 readings were decreasing (Figures 27 to 30).

By inspection, there appeared to be little correlation between the changes in rSO_2 readings and the other physiological variables. In the main, SpO_2 readings barely changed for the duration of the four flights. In cases 1 and 4, there is evidence of falling heart rate in response to rising blood pressure, which is possibly mediated by the baroreceptor reflex. In cases 2 and 3, there is no clear relationship between heart rate and blood pressure, but other factors could be influencing heart rate response, including metabolic factors or therapeutic interventions. In case 4, there appears to be an inverse relationship between rSO_2 and heart rate, although this is not as clear in cases 1 to 3. The changes in case 4 may reflect local vasoconstriction promoting a fall in rSO_2.

The timings of changes in ventilation or sedation management or other clinical care did not appear to directly correlate with the changes seen in rSO_2. There were some brief downward trends in all four variables seen in case 4, particularly at 265 minutes and 425 minutes; these correspond to the timings of pressure area care provision, during which time the casualty was being rolled from side to side, affecting all variables. When the monitored arm was uppermost, a fall in rSO_2 was clearly seen, which resolved once the casualty was supine.

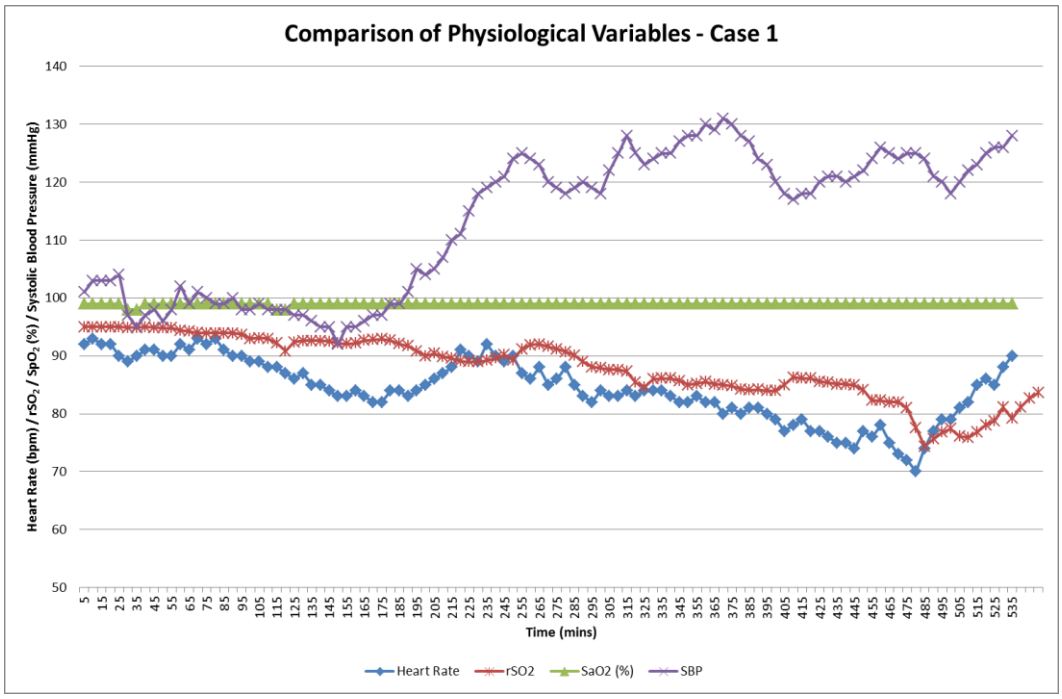

Figure 27. Comparison of mean 5 minute intervals of heart rate, blood pressure, rSO_2 and SpO_2 for Case 1

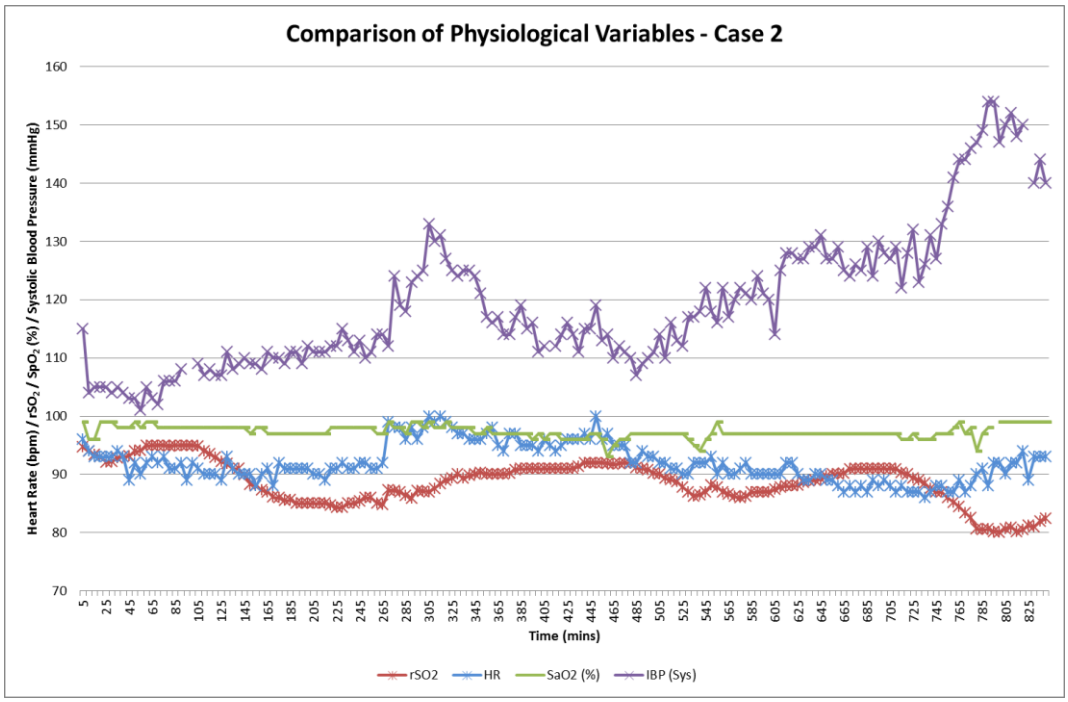

Figure 28. Comparison of mean 5 minute intervals of heart rate, blood pressure, rSO_2 and SpO_2 for Case 2

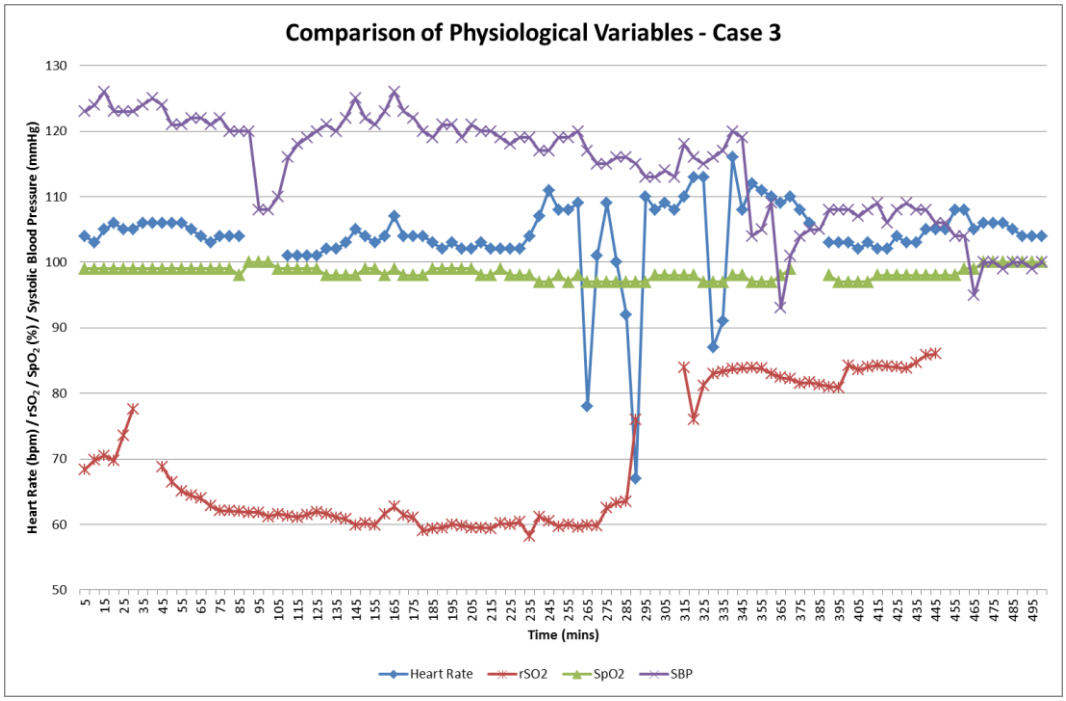

Figure 29. Comparison of mean 5 minute intervals of heart rate, blood pressure, rSO_2 and SpO_2 for Case 3

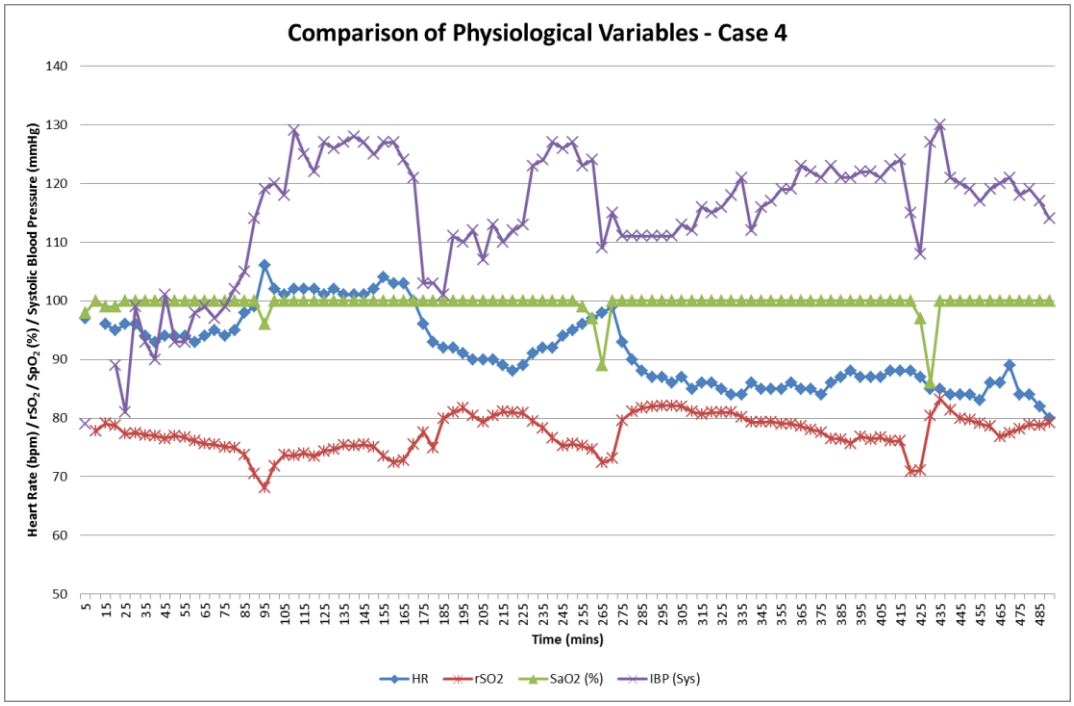

Figure 30. Comparison of mean 5 minute intervals of heart rate, blood pressure, rSO_2 and SpO_2 for Case 4

The results from in-flight arterial blood gas samples were also reviewed, to investigate whether any trends in changes to lactate, pH and base excess could be observed to compare with the trends seen in rSO_2 monitoring. However, in the 4 cases in question, arterial blood gases were sampled infrequently throughout the flight, so it was difficult to match any trends in the two results with any certainty.

7.3. Review

Summary: Tissue oxygen saturation monitoring was undertaken in all 15 casualties, without significant incident. The inability of the monitoring sensor to adhere to the upper arm of one casualty is thought to be linked to the condition of the casualty's skin – most likely that the casualty's skin was moist as a result of the mild pyrexia observed during the flight. The monitoring system performed well at altitude and no interactions between the aircraft and the monitor were seen.

The different flight profiles utilised during the various flights added further complexity to the data analysis as some casualties were exposed to additional changes in the partial pressure of alveolar air during the en-route descents and ascents pre- and post-refuelling. Likewise, the wide range of cabin altitudes experienced during the different flights meant that some casualties were exposed to higher altitudes than others, providing an additional confounder when comparing the results obtained.

In 10 cases, there was little change in tissue oxygen saturation readings throughout the flights. In the 4 cases where > 10% fall in readings was observed, the changes happened at different points in the flight and at a time when the aircraft was in the cruise – not specifically during the ascent or descent elements

as had been anticipated pre-study. In explaining these decreases in tissue oxygen saturation, a number of confounders must be considered. These casualties had been exposed to significant trauma and blood loss for which they required fluid resuscitation and damage control surgery. They had received large transfusions of blood and blood products prior to flight and continued to receive some products in-flight. Other clinical management protocols were in progress, including mechanical ventilation, and the use of sedation and inotropes to maintain and improve the casualty's condition throughout the flight. The body's immediate response to traumatic injury is to initiate vasoconstriction of the vessels, to prevent further blood loss and to maintain central perfusion. Once fluid resuscitation is achieved, the body undergoes a period of vasodilatation to restore blood flow and oxygen supply to all areas of the body (Brøchner and Toft, 2009). In addition to this reaction, the body also initiates an immunological response to the traumatic injury and to the blood transfusions used to counter the initial hypovolaemia, which may have an effect on peripheral perfusion. Added to all of these factors, the casualties have then been exposed to the effects of changing altitude. With so much activity at the cellular level, the mechanism behind the reductions in tissue oxygen saturation is not clear, particularly when other casualties, with potentially more severe injuries, who were also exposed to these same factors, did not experience the same reductions.

Discussion: The changes observed in tissue oxygen saturation did not seem to occur in conjunction with changes in other physiological variables. However, Scheeren et al (2012) identify that vasoconstriction in response to

hypovolaemia or other physiological assault may lead to reduced peripheral perfusion, (which could potentially be seen in lower rSO_2 readings) even though systemic indicators, such as systolic blood pressure or heart rate, remain within normal limits. Once the compensatory response to the physiological assault was exhausted, then the systemic indicators would begin to demonstrate compromise. Within the current study, it is hypothesised that the on-going clinical management (such as fluid / blood / inotrope administration, and mechanical ventilation) of the casualties prior to, and during their flights may have reversed the deterioration in their physical condition before systemic responses were identified. As peripheral perfusion improved, so the rSO_2 readings also improved. Oedema in damaged tissues as a result of traumatic injury could also lead to reduced peripheral perfusion due to higher tissue pressures (Schober and Schwarte, 2012), which could potentially be observed in a trend of falling rSO_2 readings, although direct readings over traumatised tissue were not undertaken in this study. Alternatively, given that the casualties were all repatriated within 12-24 hours of the injury, the low rSO_2 readings could have been the 'tail-end' of the initial response to the trauma, with the systemic responses having been managed and the peripheral tissues now returning to normal perfusion and therefore restoring oxygenation. As rSO_2 monitoring was only instigated when the casualty arrived at the aircraft, a comparison with earlier readings was not possible.

Interestingly, in their 2013 paper, Dubost et al monitored minute-by-minute heart rate and stroke volume to calculate cardiac index in military casualties undergoing aeromedical evacuation. During the ten minute period from take-off, cardiac index fell significantly, particularly during the 4^{th} to 10^{th} minute,

despite the fact that heart rate did not change throughout the entire period. A reduction in cardiac index may lead to a loss of peripheral perfusion even though there were no overt signs in systemic readings (heart rate). A similar response was seen in the current study, in that changes in tissue oxygen saturation were observed but other systemic physiological variables such as SpO_2 or heart rate did not change. This suggests that monitoring of systemic variables may not provide the whole picture regarding the casualty's clinical condition.

The remaining 10 casualties did not demonstrate any meaningful decreases in tissue oxygen saturation throughout their flights, suggesting that adequate peripheral oxygenation was maintained throughout the aeromedical evacuation. The phase 2 volunteers experienced greater changes in tissue oxygen saturation during exposure to LBNP and HAST; however the experimental conditions simulated hypovolaemia, which should have been corrected in the casualties by the time they were emplaned, perhaps explaining why smaller changes in readings were observed. The earlier work identified that rSO_2 was sensitive to changes in clinical condition, so it could be suggested that clinically stable casualties might not demonstrate any in-flight decreases in rSO_2 readings.

The clinical significance of the decreases in rSO_2 readings seen in 4 casualties is not fully understood. As the end point for the current study was the conclusion of the aeromedical evacuation flight, clinical outcomes for the casualties were not captured, so it is unknown whether these individuals experienced negative sequelae. However, as previously discussed, other studies have identified tissue oxygen saturation monitoring as a potential early indicator for the development of multiple organ dysfunction syndrome (Cohn et al, 2007)

and as an indicator for effective traumatic shock resuscitation (McKinley et al, 2000), so further work is required to understand the clinical significance of any decreases in in-flight tissue oxygen saturation.

Limitations: The original aim was to recruit 30 casualties to the study to provide sufficient data from which to draw some conclusions; however, the casualty numbers seen at the beginning of 2012 fell significantly compared with the same time period in earlier years. The actual data collection period was extended by 3 months in an attempt to meet the sample size; however, casualty rates remained low and this was not achieved.

Additional data sources were also sought from other NATO allies; and, in principle, agreement was obtained. However, the complexities of a UK researcher collecting data on non-UK casualties, combined with the extended period required to obtain host nation ethics approval and flight clearance for the monitoring system made this an unworkable solution.

Conclusion: The aim of this third phase of the study was to undertake a prospective observational study to identify if changes in tissue oxygen saturation occur in military casualties during aeromedical evacuation from Afghanistan to the UK. The study did identify changes in tissue oxygen saturation in some of the trauma casualties during repatriation to RCDM, Birmingham. The changes observed ranged from 11-22% decrease in saturation during in-flight monitoring, although it is not clear that these changes were a direct result of the aeromedical evacuation. However, with only four sets of data to analyse, any meaningful

conclusions become difficult to justify. Having identified that changes do occur though, further work is required to investigate the cause and severity of these changes and to develop some potential management/treatment techniques. Additionally, no casualties experienced serious clinical deterioration in flight, so it was not possible to determine how rSO_2 might have responded or been useful in identifying this scenario.

A secondary aim was to investigate whether there were more changes in tissue oxygen saturation in those casualties with lower pre-flight haemoglobin levels. As seen in phase 1, the haemoglobin status of the casualties was obscured by the additional confounders encountered during data analysis. Since the majority of casualties demonstrated a higher post-flight haemoglobin level, this might suggest that the risk of anaemic hypoxia had been addressed pre-flight through appropriate transfusion of blood and blood products.

8. DISCUSSION / RECOMMENDATIONS

The overall aim of this study was to investigate changes in tissue oxygen saturation in military casualties during aeromedical evacuation. Military casualties injured during recent operations in both Iraq and Afghanistan have often sustained extensive traumatic injuries, the degree of which is rarely seen in civilian practice. As a result of these emerging injury patterns, new treatment protocols for the immediate management and resuscitation of the casualties have been developed. The success of these protocols has meant there are larger numbers of severely injured personnel surviving the initial injury, who require aeromedical evacuation to the UK for on-going medical management. As these casualties are often flown home within hours of their primary injury, they are generally still in the early stages of treatment, having received immediate resuscitation care, followed by damage control surgery. This rapid evacuation system means that casualties are still receiving medical treatment to correct issues such as acidosis or fluid loss whilst being exposed to the additional hazards of flight, including altitude and pressure changes. There is little evidence within the literature that the combined effects of these factors have been considered.

Findings: Phase 1 of the study was a retrospective review of the in-flight records for 27 military casualties undergoing aeromedical evacuation following significant traumatic injury. The review identified a number of in-flight changes in clinical condition and management, although, as a retrospective review, it was not possible to attribute the changes to a specific cause. However, the severity of the casualties' injuries and the complex medical management required in-flight to

maintain a stable condition were evident from the review. Systemic physiological monitoring did not demonstrate any gross changes in clinical condition as a result of early aeromedical evacuation.

Phase 2 of the study sought to validate the technique of tissue oxygen saturation monitoring, using near infra-red spectroscopy, at simulated altitude. Healthy volunteers were exposed to a hypoxia altitude simulation test and/or a lower body negative pressure test to investigate whether the monitoring system could identify changes in tissue oxygen saturation induced by a simulated altered circulating volume and/or altitude up to 8,000 feet. The results showed that regional tissue oxygen saturation was the only monitoring technique to demonstrate an effect in response to all 3 test conditions, suggesting that it may be more sensitive to changes than standard physiological monitoring and proving that it would be a suitable technique for use in phase 3 of the study.

The aim of the third phase of the study was to investigate whether changes in tissue oxygen saturation occurred in military casualties during aeromedical evacuation. The timing of the study coincided with the draw-down of combat operations in Afghanistan, leading to a reduction in the numbers of casualties compared with previous years, so data collection was limited to fifteen casualties. In four of those casualties, a fall in rSO_2 readings of between 11% and 22% was observed during the flights, compared with a pre-flight baseline. Due to the small sample size and the number of confounding variables, it was unclear whether these changes occurred as a result of the increased altitude or as a result of the casualty's clinical condition and/or medical treatment received – or even as a combination of these factors. However, decreases in tissue oxygen saturation

were apparent, in some casualties, during the flight. The longer term consequences of these decreases were not examined in the current study, so further work is required to determine the significance of these observed changes.

Future work: Having identified that some casualties do experience periods of lower regional tissue oxygen saturation in-flight, there exists a requirement for follow-on studies, to investigate these findings further. Even with the end of combat operations in Afghanistan imminent, the Royal Air Force Medical Service, like its international counterparts, continues to repatriate severely ill and injured military personnel from around the world. Even if only a small percentage of the casualties experience reduced tissue oxygenation, this may have implications for their future management or even outcome. As outlined in the preceding chapters, lower tissue oxygen saturation has been shown to be an early indicator of increasing hypovolaemia (Soller et al, 2008b), a marker for those patients likely to develop multiple organ dysfunction syndrome or die following trauma (Cohn et al, 2007) and a guide to identify those trauma patients who require early blood transfusions (Smith et al, 2008). If, in future work, tissue oxygen saturation can be used to identify poor perfusion in local tissues after trauma (as a result of exposure to altitude or as a result of low haemoglobin levels, for example), it may be possible to treat the poor perfusion earlier and reduce the number of casualties who later require repeated wound debridement or amputation (as suggested by Hannah and Rice, 2013), or go on to develop organ failure. A comparison of tissue oxygen saturation readings with blood flow monitoring

(using plethysmography, for example), would confirm whether rSO_2 readings are actually a predictor of poor perfusion.

An end-to-end study would be required, to record tissue oxygen saturation from point of injury (or as close as possible) through the aeromedical evacuation to the point of discharge from intensive care, to observe outcomes in this casualty group. This will also provide more in-depth understanding of rSO_2, its applications and its sensitivity compared with the standard physiological monitoring currently in use. A control group of casualties who did not undergo aeromedical evacuation would provide further information about the effects of altitude on tissue oxygen saturation. Even as operations in Afghanistan come to a close, this information may be relevant for future conflicts, or even to civilian settings. Tissue oxygen saturation data obtained in a fixed wing aircraft with a cabin altitude restriction of 2,000 feet, for example, may provide lessons for the management of civilian trauma casualties transported in an unpressurised helicopter at similar altitudes. Likewise, information obtained in civilian practice would help to develop military practice appropriately.

One final recommendation as a result of the lessons identified during this study is the requirement for greater visibility of aeromedical evacuation research. Notwithstanding military sensitivities or commercial restrictions, sharing research data helps to improve casualty care for all. It was identified that several abstracts from oral presentations discussed the use of tissue oxygen saturation monitoring during air medical (helicopter) transport (Guyette et al, 2008; Brywczynski et al, 2009), but follow-on articles to develop the abstracts and support the presentations could not be located, suggesting that either they were not written or not published.

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10. APPENDICES

APPENDIX A

INJURY SEVERITY SCORE

1. Records for all UK military trauma casualties are returned to ADMEM where the listed injuries are coded using the Abbreviated Injury Scale (AIS) – a method of ranking and comparing injuries which was originally developed by the Association for the Advancement of Automotive Medicine during the 1960s. AIS is defined as "an anatomically-based, consensus derived, global severity scoring system that classifies each injury by body region according to its relative importance on a 6-point ordinal scale" (p.8) (Gennarelli and Wodzin, 2007).

2. Each injury is assigned to a specific code from the AIS dictionary, which relates to a defined body region, anatomical structure and type of injury. A severity number is also assigned to each code, according to the severity of that specific injury in an 'average' patient. The level of severity ranges from 1 (minor) to 6 (maximum).

   a. As an example, a fracture of the head of femur is assigned the code 853171.3

   b. This code is constructed from the following points:
      8 – Body region (lower extremity)
      5 – Structure type (skeletal)
      31 – Specific structure (proximal femur)
      71 – Level of injury (femoral head)
      3 – Severity number (serious)

3. Baker et al (1974) later used the AIS coding system to develop the Injury Severity Score (ISS), which allowed an assessment of the severity of the injuries suffered by a poly trauma casualty. To calculate the ISS, the body is divided into 6 regions:

a. Head or neck
b. Face
c. Chest
d. Abdominal or pelvic contents
e. Extremities or pelvic girdle
f. External (body surface)

4. The ISS is the sum of the squares of the highest AIS severity codes in each of the three most severely injured ISS body regions. Only 3 codes are used to calculate ISS, even if the casualty has suffered 10 different injuries. The ISS ranges from 1 to 75; a score of 75 is considered to be incompatible with life. Any casualty suffering an injury which is coded with a severity number of 6 (maximum) is automatically assigned an ISS of 75. A casualty with an ISS of 16 or greater is considered to have suffered major trauma, as a result of the 10% mortality rate seen in casualties who score an ISS of 16 (Russell et al, 2011).

5. The New Injury Severity Score (NISS) was developed by Turner et al (1997) in an attempt to improve the existing system. All injuries are coded using the AIS dictionary as before, but the NISS is calculated from the 3 highest severity codes, irrespective of the body region; this system attempts to account for the casualty who sustains multiple injuries in one body region, whose injury severity is potentially underscored by ISS.

6. ISS and NISS are calculated for all casualty records returned to ADMEM; for the purpose of this study, a significant injury is defined as an ISS or NISS of 9 or more, which allows the inclusion of isolated limb trauma, such as a single lower leg amputation, which can cause considerable blood loss and require transfusion therapy, making these casualties relevant to the study.

APPENDIX B

McLeod J. (2013) An investigation of changes in tissue oxygen saturation during exposure to altitude and lower body negative pressure. *Aviat Space Environ Med*, 84 (4): 366 [Abstract 299]

Presented at the Aerospace Medical Association 84th Annual Scientific Meeting, 12-16 May 2013, Sheraton Hotel & Towers, Chicago, IL

Introduction: UK military personnel injured in an operational setting will often have sustained significant haemorrhage at the time of injury and may have undergone lengthy surgical procedures, receiving massive transfusions of blood/blood products. The potential effects of early aeromedical evacuation combined with a reduced / altered haemoglobin status on tissue oxygenation and viability are not fully understood. Near infra-red spectroscopy has been used to develop methods of monitoring regional tissue oxygen saturation (rSO_2) although its potential use has not been evaluated in the aeromedical evacuation context. This study was undertaken as a pre-cursor to an in-flight observational study in military casualty populations. ***Methods:*** Twelve healthy volunteers were subjected to 3 separate tests: 1) Hypoxia altitude simulation test (HAST) using 15.1% oxygen mix to simulate a cabin altitude of 8,000ft, 2) Lower body negative pressure (LBNP) at 3 increments to simulate an altered circulating volume, and 3) HAST and LBNP combined. A device utilising near infra-red spectroscopy (NIRS) was used to record deltoid muscle rSO_2 in conjunction with standard physiological monitoring in these volunteers. ***Results:*** Multivariate regression models were fitted to explain changes in pulse oximetry, heart rate, cardiac output, mean arterial pressure and regional tissue oxygen saturation in terms of simulated altitude and simulated altered circulating volume. Deltoid rSO_2 proved to be the physiological measure most responsive to each experimental condition. ***Discussion:*** The NIRS monitoring technique proved sensitive in identifying changes in rSO_2 in response to the environmental and physiological conditions anticipated during aeromedical evacuation.

Learning Objective:

1. To understand the effects of simulated altitude and simulated altered circulating volume on regional tissue oxygen saturation in healthy volunteers.

APPENDIX C

McLeod J. and Green NDC. (2015) An investigation of changes in tissue oxygen saturation in military casualties during aeromedical evacuation [Abstract 86]

Presented at the 63rd International Congress of Aviation and Space Medicine, 20-24 September 2015, Oxford, UK

Introduction: UK military personnel injured in an operational setting will often have sustained significant haemorrhage at the time of injury and may have undergone lengthy surgical procedures, receiving massive transfusions of blood/blood products. The potential effects of early aeromedical evacuation combined with a reduced haemoglobin (Hb) status on tissue oxygenation and viability are not fully understood. A near infra-red spectroscopy (NIRS) technique has been developed to monitor regional tissue oxygen saturation (rSO_2) in the aeromedical evacuation setting. ***Methods:*** rSO_2 was recorded in the deltoid muscle of 15 ventilated military casualties during aeromedical evacuation from Afghanistan, together with standard critical care physiological variables. The casualties had all experienced significant traumatic injuries, requiring damage control surgery and/or massive transfusions of blood/blood products. ***Results:*** Deltoid rSO_2 fell by $\geq$ 10% in 28% of the casualties, despite the absence of a significant corresponding change in systemic physiological variables, such as pulse oximetry or heart rate, or overt clinical deterioration. There was no relationship between transfusion status and rSO_2 response. ***Discussion:*** This study suggests that patients with reduced Hb do not experience a greater degree of tissue hypoxia in flight. A definitive role for rSO_2 monitoring to identify clinically significant physiological changes in flight has not yet been established.

APPENDIX D

The following stacked graphs demonstrate the mean physiological readings recorded in the 12 volunteers during the final minute of each phase of the experimental condition shown. Figures 31 and 32 display the results from the hypoxia altitude simulation test; Figures 33 and 34 show the results from the lower body negative pressure, and Figures 35 and 36 demonstrate the results of the hypoxia altitude simulation test in conjunction with the lower body negative pressure test.

Cardiac output was not recorded in subjects A and C during the hypoxia altitude simulation test as it was a late inclusion in the data collection protocol. Cardiac output was not recorded in subject A during the lower body negative pressure test, for the same reason. Data recording failed during the hypoxia altitude simulation test for subject B, so data were not included in Figures 31 and 32.

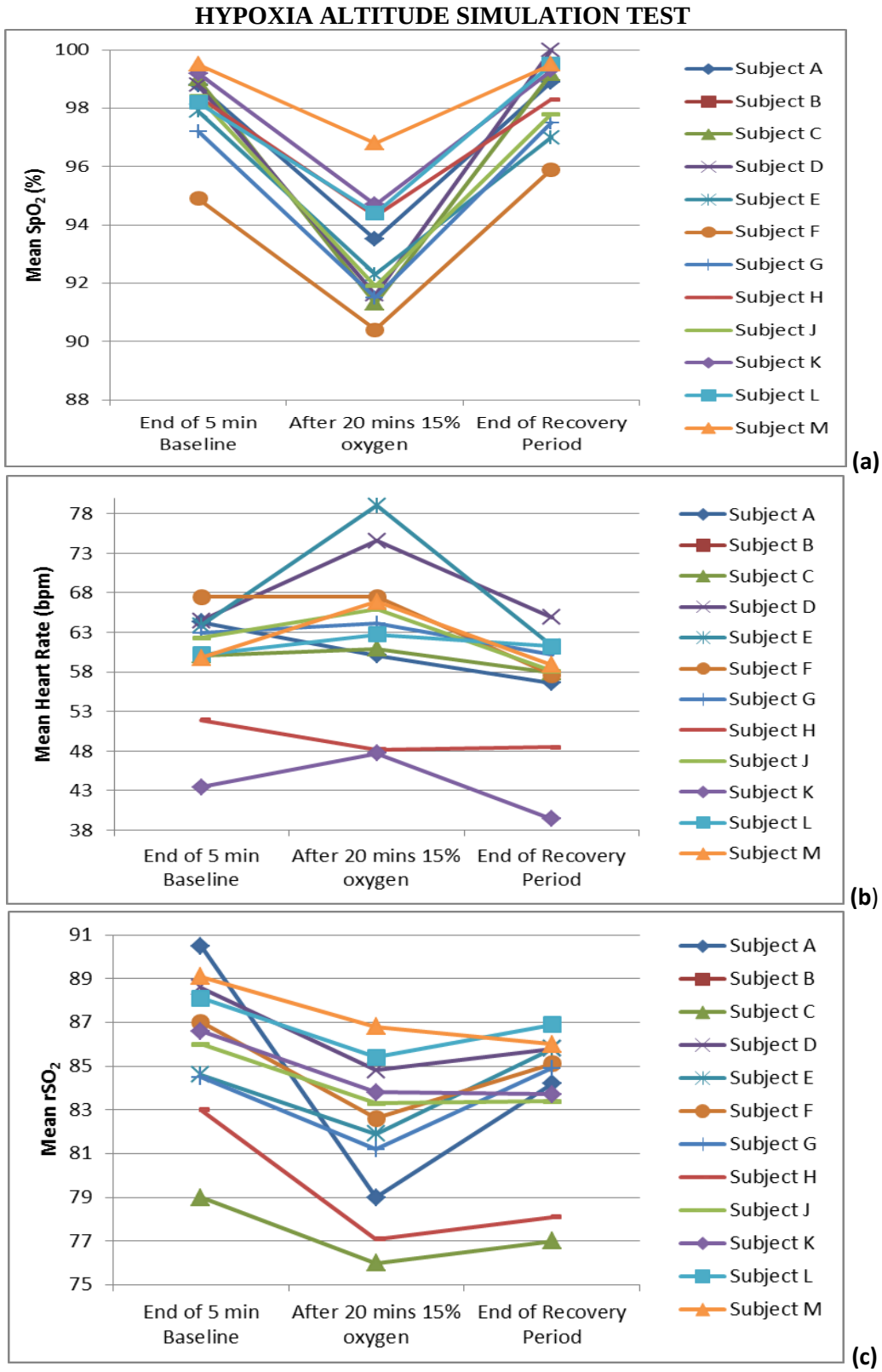
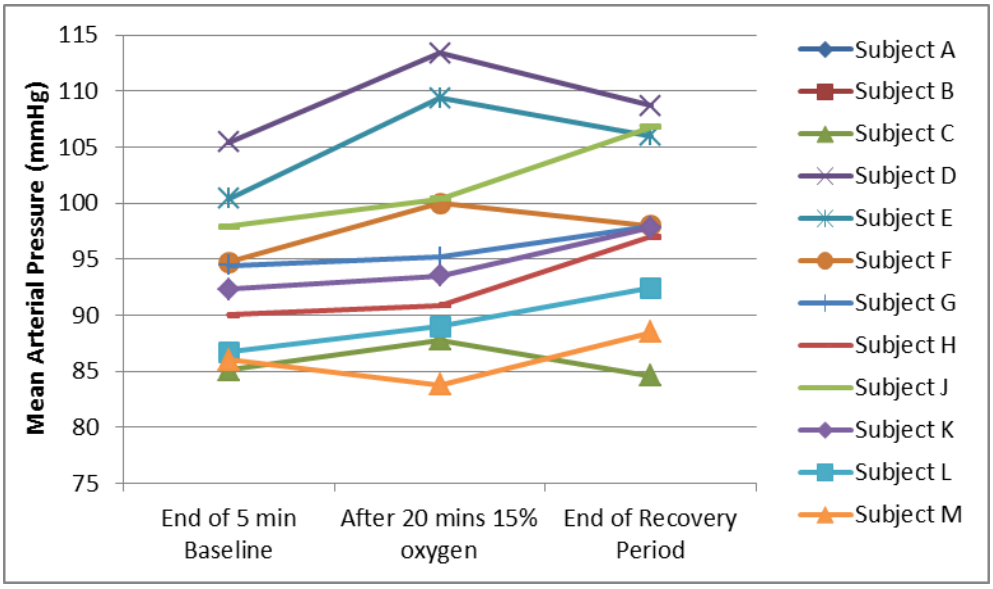


Figure 31. Mean physiological readings for the final minute of each phase of the experimental condition recorded in 12 volunteers during hypoxia altitude simulation test a) Peripheral arterial oxygen saturation, b) heart rate, and c) tissue oxygen saturation.



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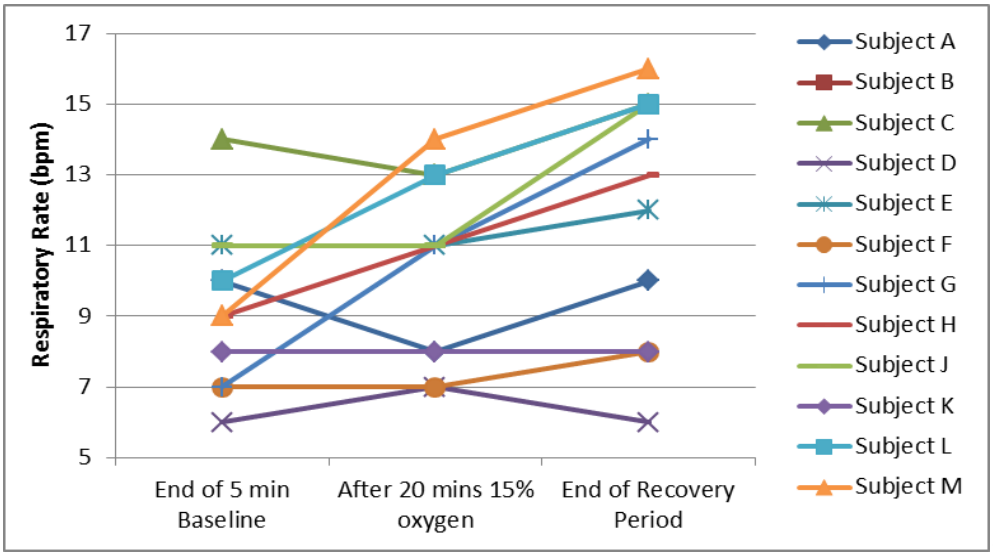

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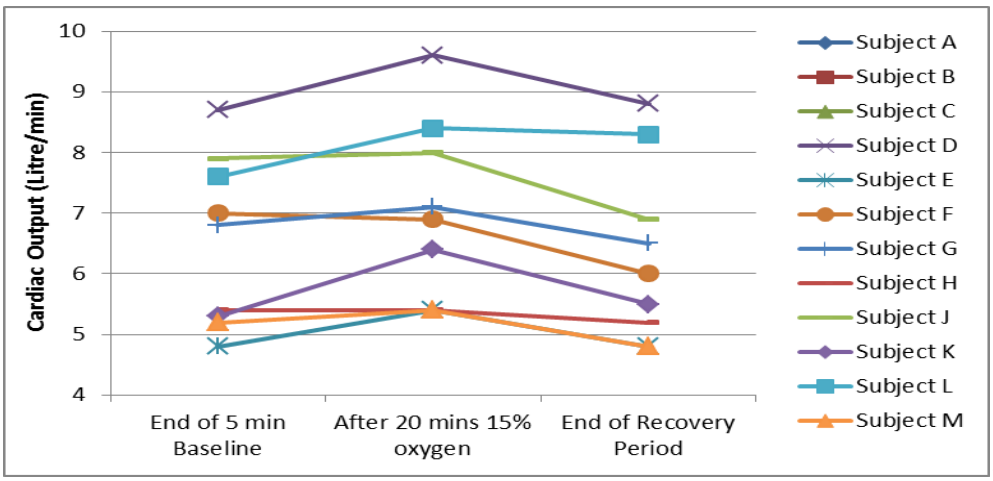


(f)

Figure 32. Mean physiological readings for the final minute of each phase of the experimental condition recorded in 12 volunteers during hypoxia altitude simulation test d) Mean arterial pressure, e) respiration rate, and f) cardiac output

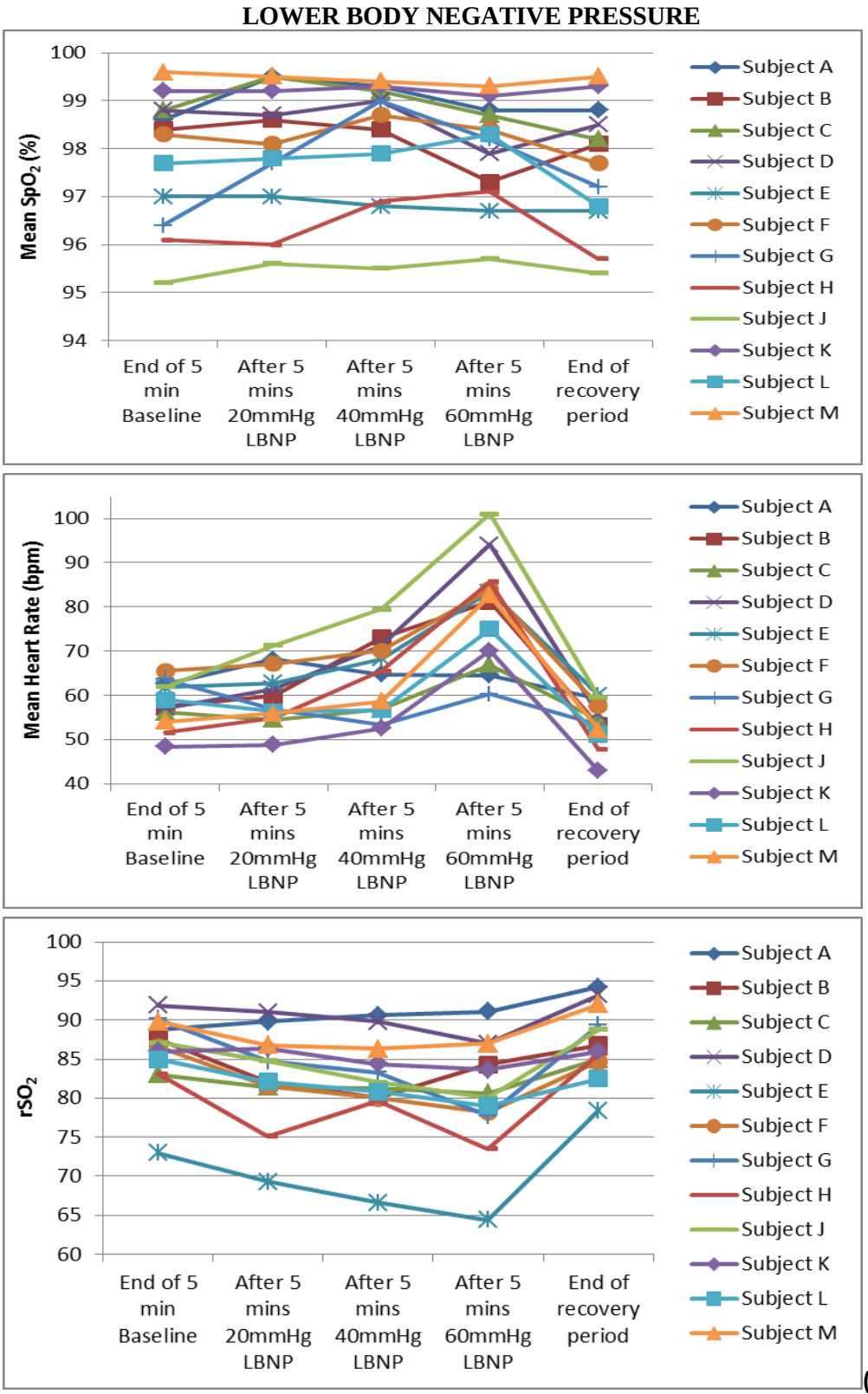


Figure 33. Mean physiological readings for the final minute of each phase of the experimental condition recorded in 12 volunteers during lower body negative pressure test a)Peripheral arterial oxygen saturation, b) heart rate, and c) tissue oxygen saturation

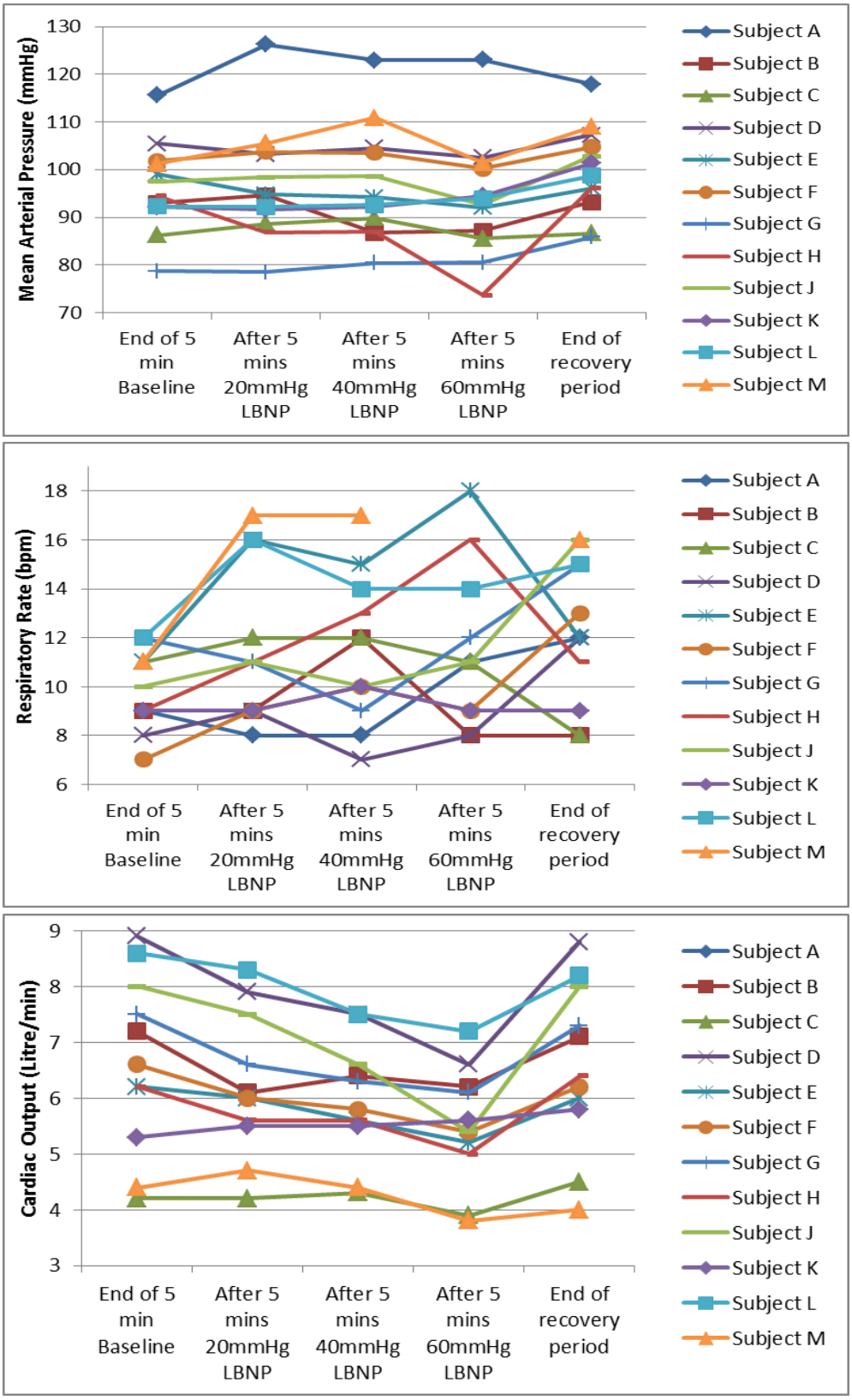
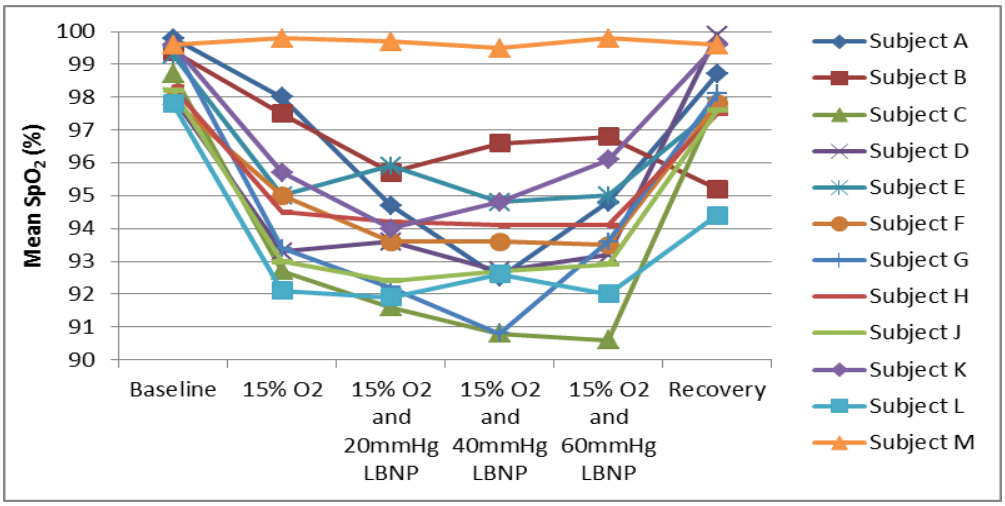


Figure 34. Mean physiological readings for the final minute of each phase of the experimental condition recorded in 12 volunteers during lower body negative pressure test d) Mean arterial pressure, e) respiration rate, and f) cardiac output

HYPOXIA ALTITUDE SIMULATION TEST WITH LOWER BODY NEGATIVE PRESSURE TEST



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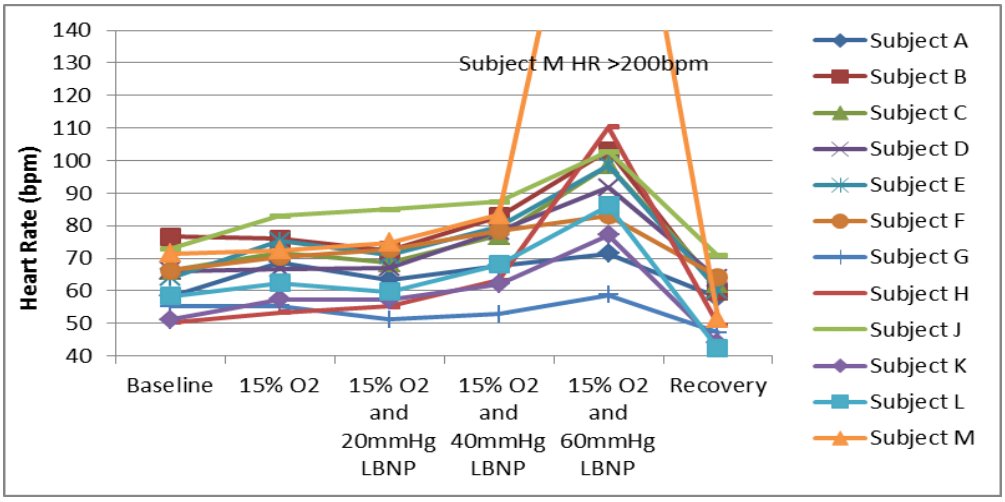

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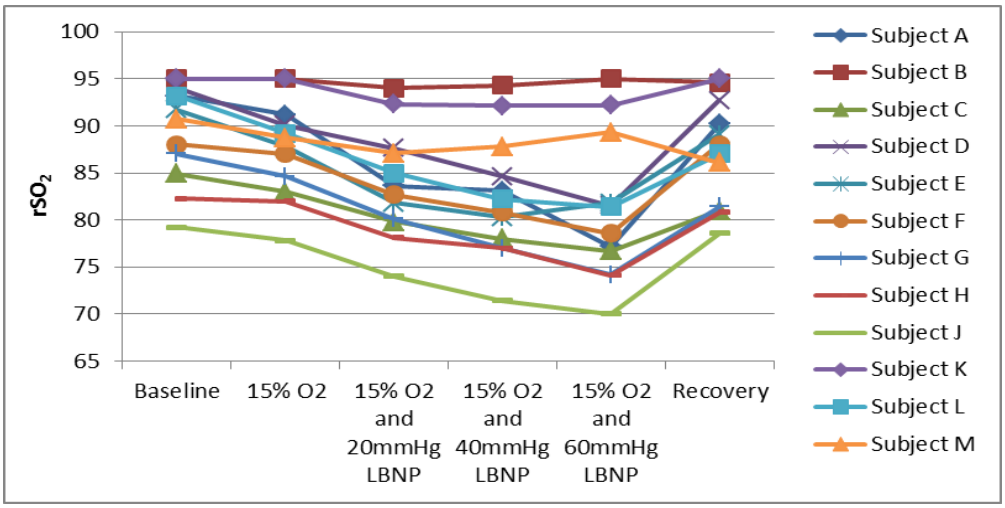
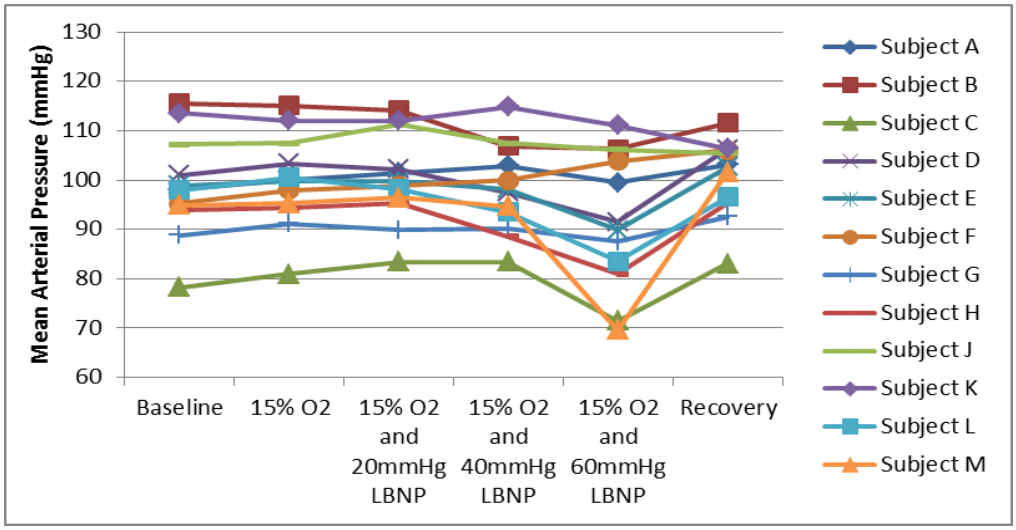


(c)

Figure 35. Mean physiological readings for the final minute of each phase of the experimental condition recorded in 12 volunteers during hypoxia altitude simulation test with lower body negative pressure test
a) Peripheral arterial oxygen saturation, b) heart rate, and c) tissue oxygen saturation



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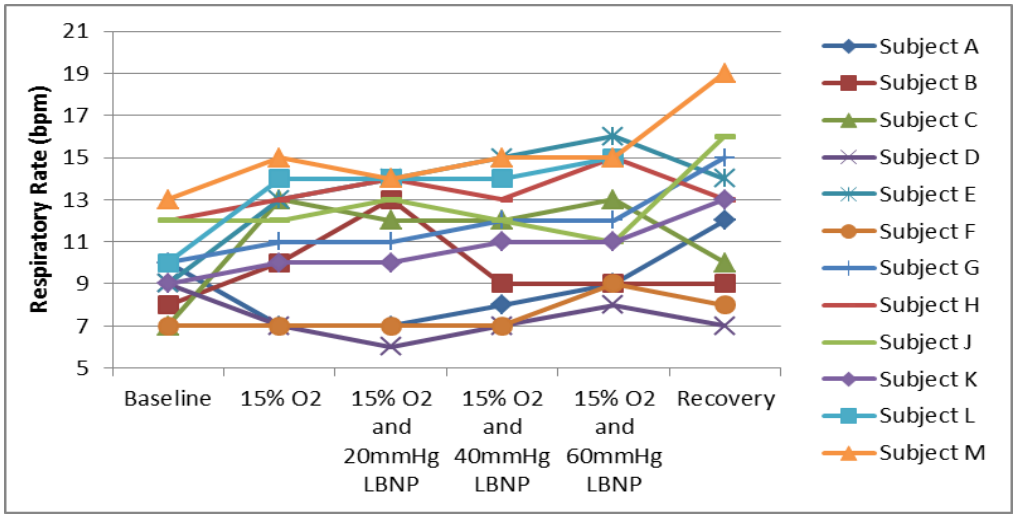

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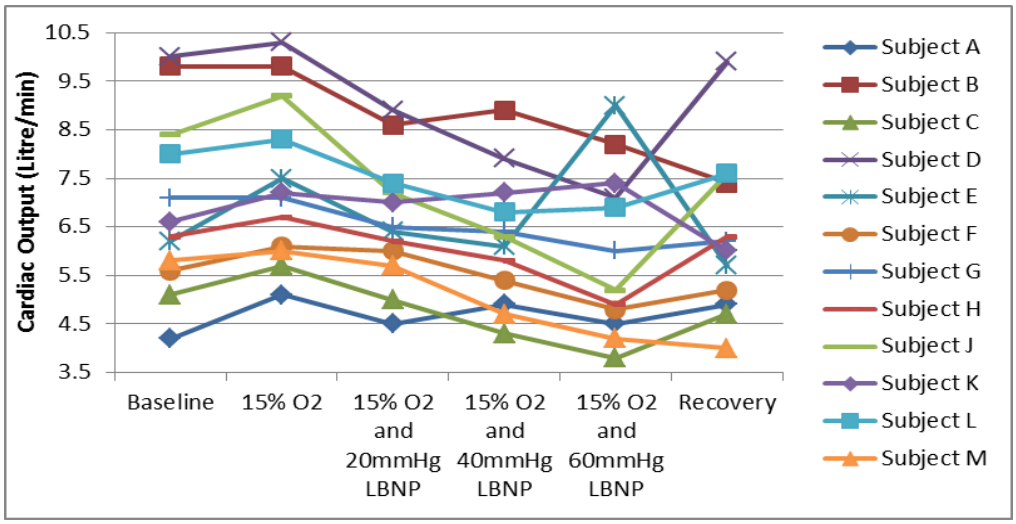


(f)

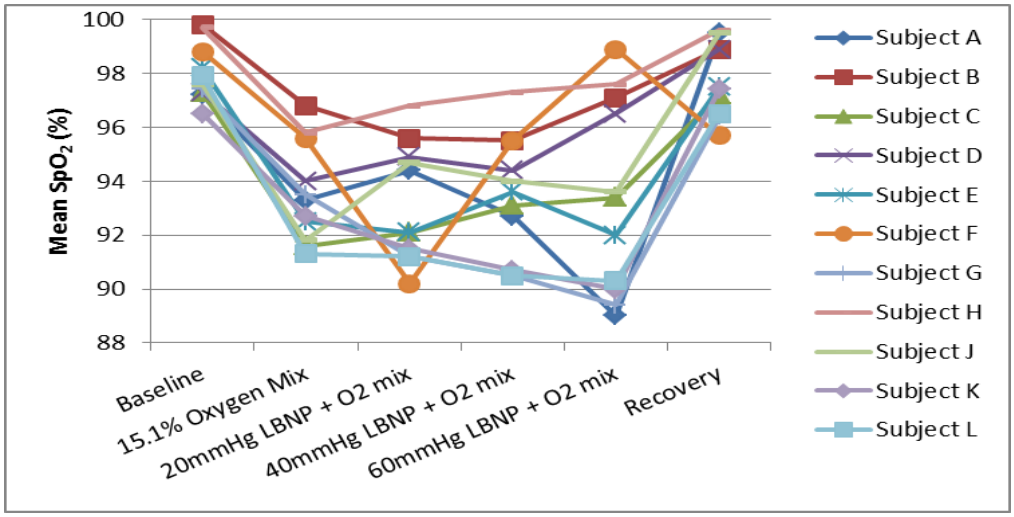
Figure 36. Mean physiological readings for the final minute of each phase of the experimental condition recorded in 12 volunteers during hypoxia altitude simulation test with lower body negative pressure test
d) Mean arterial pressure, e) respiration rate, and f) cardiac output

APPENDIX E

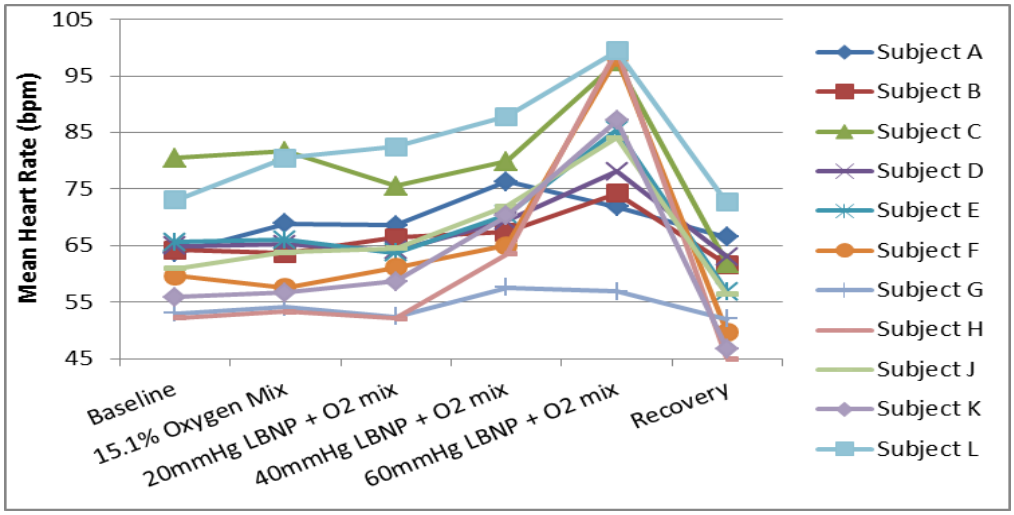
The following stacked graphs demonstrate the mean physiological readings recorded in the 11 volunteers during the final minute of each phase of the experimental condition shown. Figures 37 and 38 show the results from the lower body negative pressure, and Figures 39 and 40 demonstrate the results of the hypoxia altitude simulation test in conjunction with the lower body negative pressure test and a 70 degree head up tilt.

Two values for cardiac output are missing for subject C in Figure 38(e) due to equipment failure during recording. Respiratory rates were not recorded during the recovery phase of either experimental condition, as the majority of the volunteers couldn't tolerate the mask. Tissue oxygen saturation readings for subject D were excluded from both Figures 38(f) and 40(f) due to low rSO_2 readings combined with poor signal strength indication thought to be related to skin pigmentation issues, as discussed in Chapter 6.

HYPOXIA ALTITUDE SIMULATION TEST COMBINED WITH LOWER BODY NEGATIVE PRESSURE



(a)



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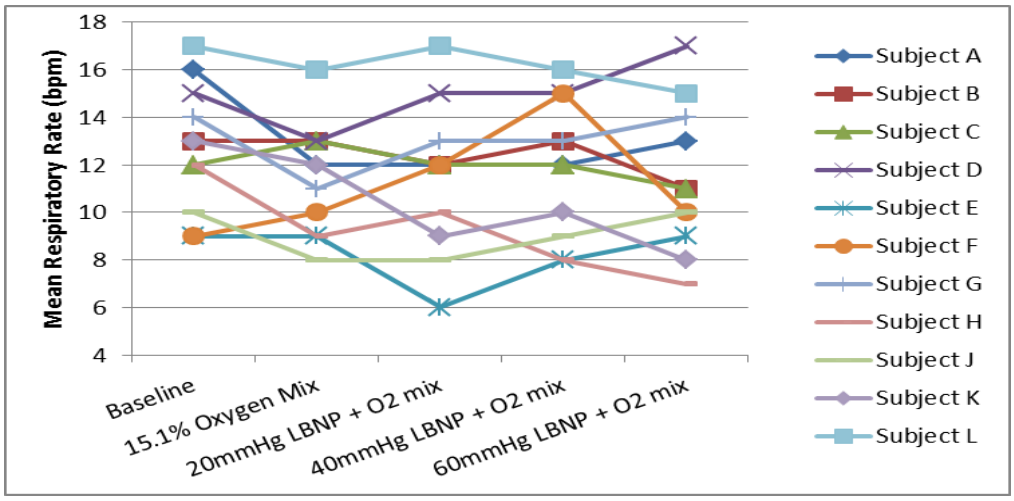
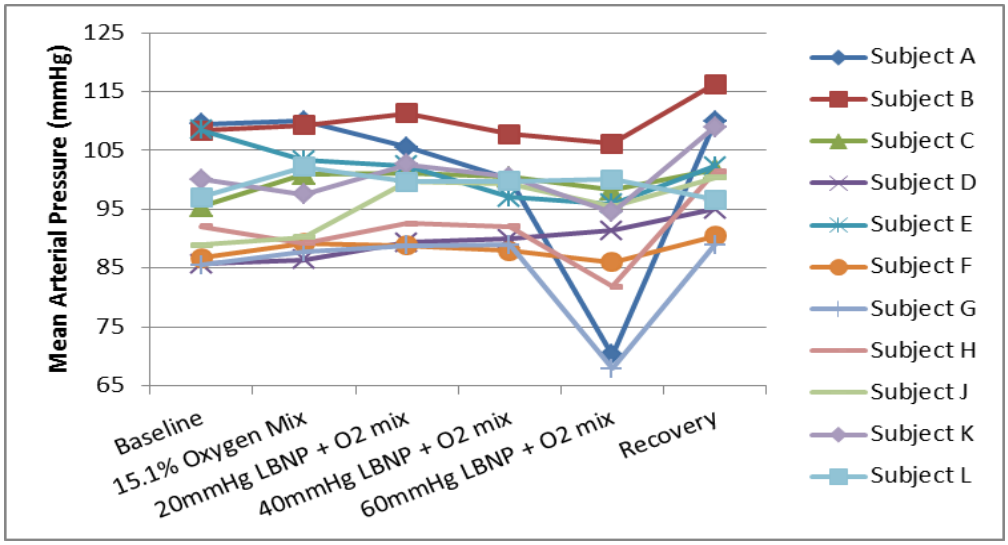


(c)

Figure 37. Mean physiological readings for the final minute of each phase of the experimental condition recorded in 11 volunteers during hypoxia altitude simulation test with lower body negative pressure test
a) Peripheral arterial oxygen saturation, b) heart rate, and c) respiratory rate



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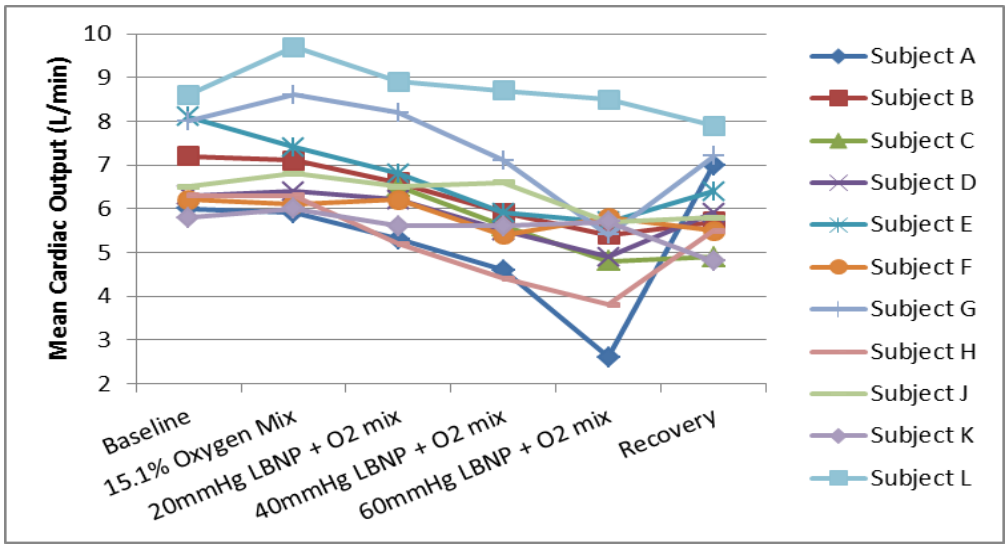

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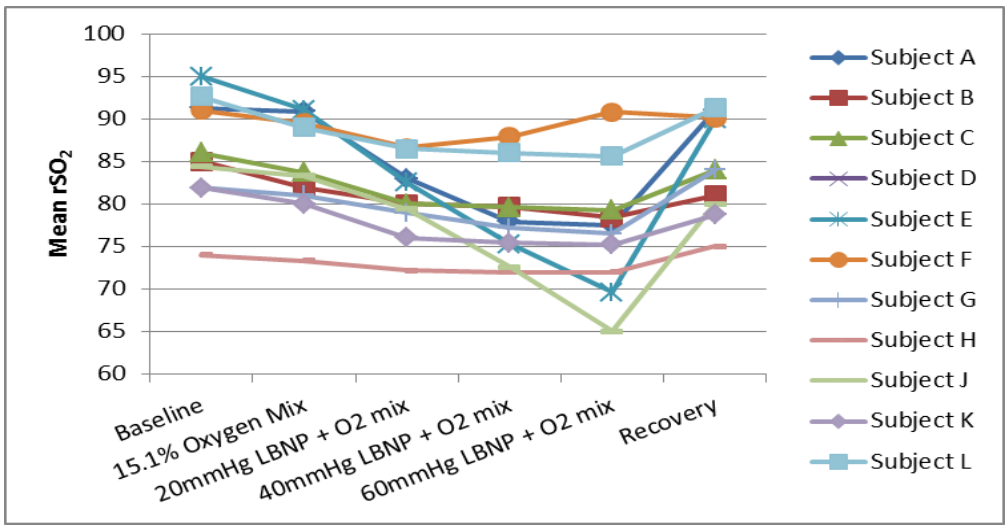
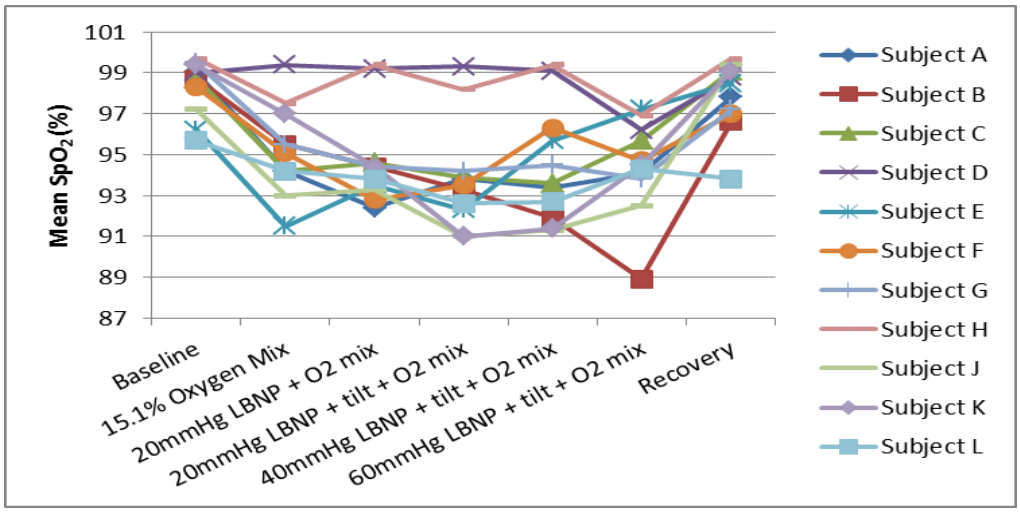


(f)

Figure 38. Mean physiological readings for the final minute of each phase of the experimental condition recorded in 11 volunteers during hypoxia altitude simulation test with lower body negative pressure test
d) Mean arterial pressure, e) cardiac output, and f) tissue oxygen saturation

HYPOXIA ALTITUDE SIMULATION TEST COMBINED WITH LOWER BODY NEGATIVE PRESSURE AND 70 DEGREE HEAD UP TILT



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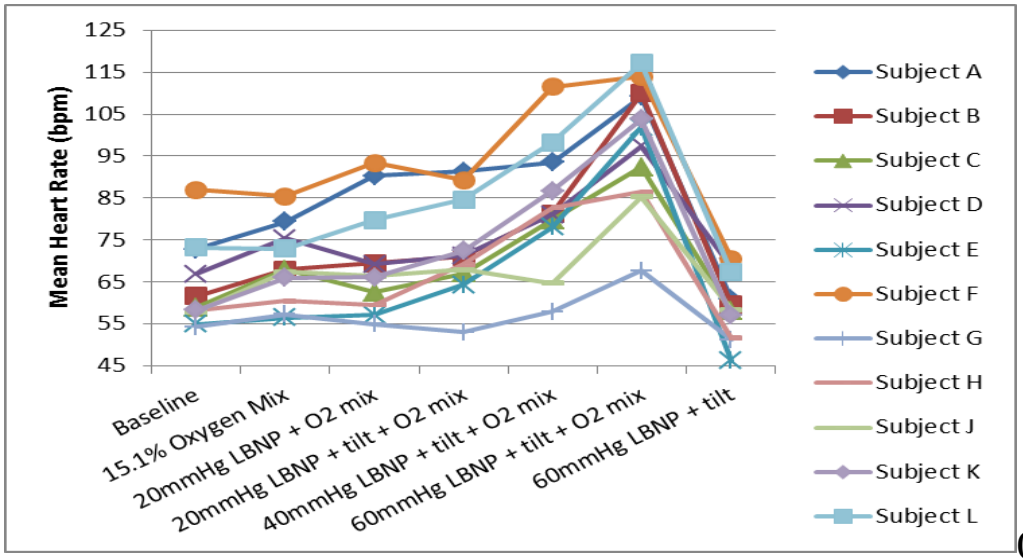

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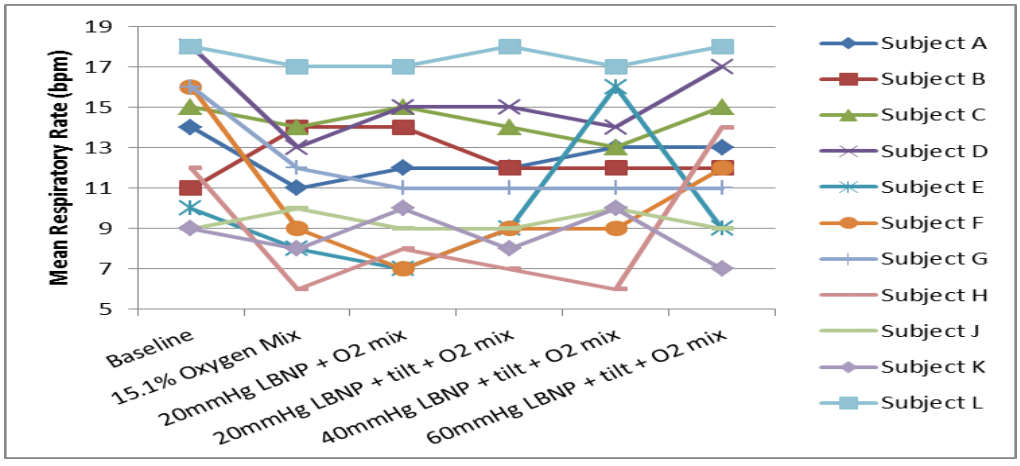
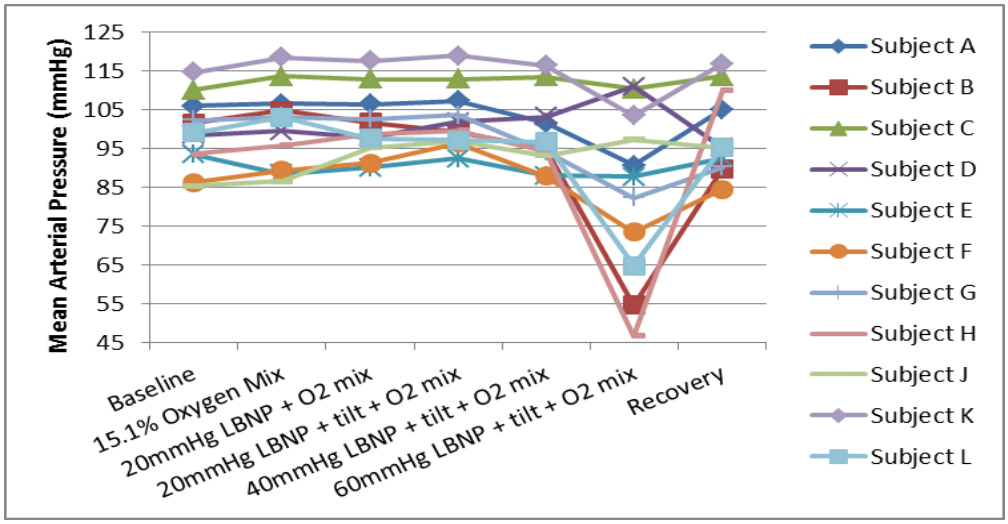


(c)

Figure 39. Mean physiological readings for the final minute of each phase of the experimental condition recorded in 11 volunteers during hypoxia altitude simulation test with lower body negative pressure test and 70 degree head up tilt
a) Peripheral arterial oxygen saturation, b) heart rate, and c) respiratory rate



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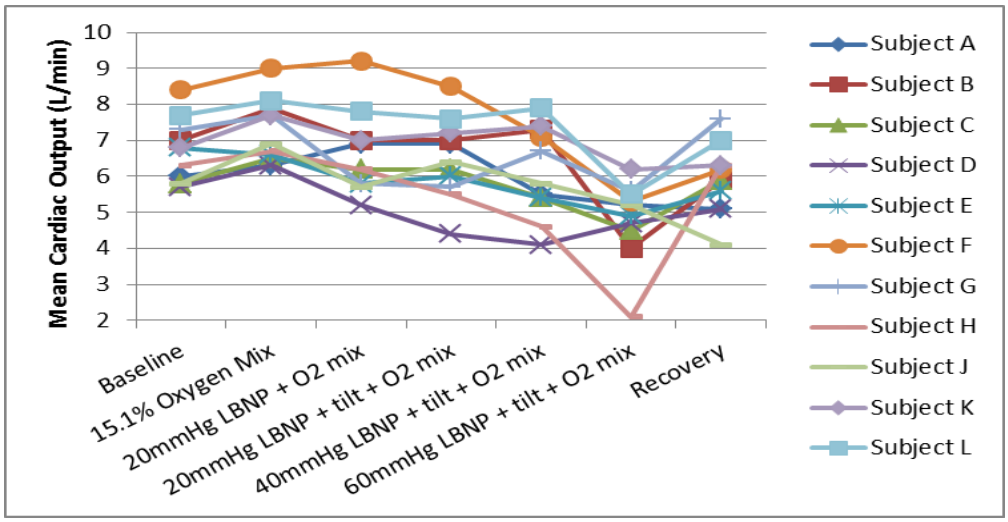

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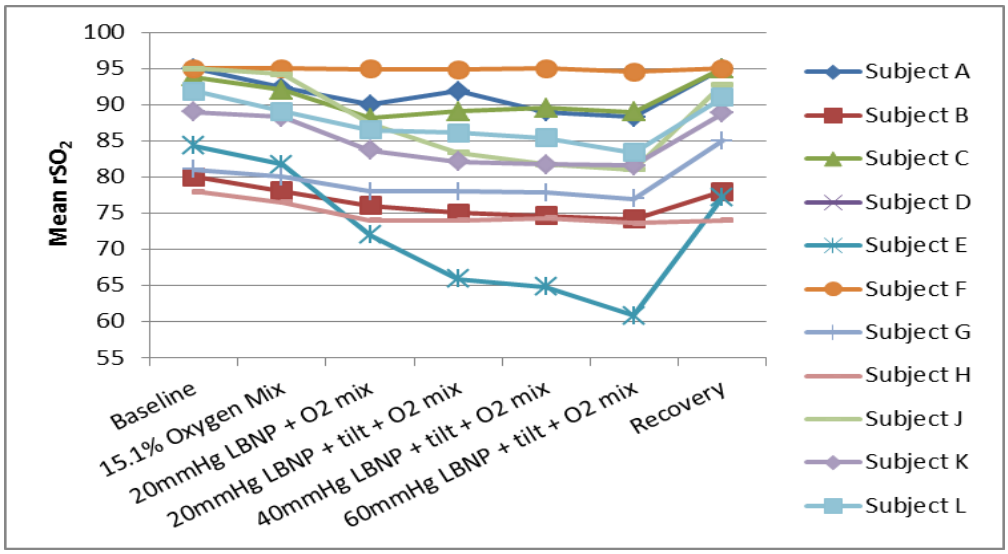

(f)

Figure 40. Mean physiological readings for the final minute of each phase of the experimental condition recorded in 11 volunteers during hypoxia altitude simulation test with lower body negative pressure test and 70 degree head up tilt
d) Mean arterial pressure, e) cardiac output, and f) tissue oxygen saturation