IS THE USE OF NON-INVASIVE HAEMOGLOBIN MEASUREMENTS ACCURATE AND RELIABLE DURING THE TRANSFER OF SICK AND INJURED PATIENTS UTILISING AIR AMBULANCE AIRCRAFT?

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ABSTRACT

Introduction: Traditional methods for measuring haemoglobin require the drawing of blood and lab analysis, which is not an optimally timely or a risk-free process in the aeromedical transport environment. Technology that allows non-invasive and continuous monitoring of haemoglobin levels became commercially available in 2008. If this technology is not affected by altitude or the stressors of flight, its use would be advantageous for both patients and medical staff during aeromedical transfers.

Aim: This study set out to determine the precision and accuracy of a specific method of non-invasive haemoglobin (Hb) measurement and monitoring during aeromedical retrievals with a focus on the effects of altitude and flight cabin changes.

Method: This was a simple interventional before and after study design with volunteer subjects exposed to atmospheric pressure changes first while reference haemoglobin concentrations were measured. Subjects were taken rapidly to altitude in a hypobaric chamber to simulate aircraft cabin pressure (6,000 feet and 12,000 feet). Non-invasive Hb measurements were recorded every 10 seconds at both 6,000 feet and then at 12,000 feet. Ground (sea level) measurements of non-invasive and invasive Hb were also recorded for each participant. Statistical analysis compared the invasive laboratory Hb taken at sea level and the non-invasive measurement recorded at ground level and at altitude, using paired measurement methods of comparison to assess limits of agreement.

Results: A total of 64 subjects took part in the study. The mean difference (SD) between lab Hb and non-invasive Hb at ground level was -3.36 (12.87) g/L. A Bland-Altman bias plot showed that at relatively low Hb values the non-invasive measure tends to overestimate Hb, and at higher levels there is a tendency to underestimate Hb. In general, there was a small negative bias for the non-invasive (test) measure. For the measurements taken at 6,000 feet

the mean (SD) difference between lab and non-invasive Hb was -8.64 (12.93) g/L, while at 12000 feet it was -13.15 (17.52) g/L, though at this higher 'altitude' level, there was a smaller sample. A strong relationship was noted between degree of perfusion as assessed by the spectrophotometric test device at the sample site and low or high non-invasive Hb measurements.

Discussion: This is the first study we are aware of which examines effects of altitude on the accuracy of the test device, and we have found that with increasing altitude, there were small but systematic increases in the test measurement of Hb concentration. At altitude the non-invasive measurement tends to overestimate Hb in cases where Hb levels are lower, and conversely when levels of Hb are higher there is a tendency to underestimate Hb. These results are consistent with other studies analysing non-invasive Hb in different areas of medicine.

Conclusion: I conclude from these findings that the use of this new non-invasive Hb measuring technology during aeromedical retrievals shows reliability even with changes in cabin pressure which allows assessment of clinical Hb levels, and particularly to confirm approximate normal Hb levels, though not with precision and accuracy which is needed for scientific (reference) measurements. Non-invasive continuous haemoglobin monitoring, while lacking precision, is largely unaffected by the aviation environment, and has clinical application during the unusual conditions experienced during aeromedical retrieval. At least, it is no worse than traditional invasive methods, and provides clinical information that is timelier than periodic sampling. Moreover, the elimination of the need to take frequent blood samples reduces the risks to both the patient and aeromedical attendant.

To have real-time continuous Hb measurements available during aeromedical retrievals can improve medical safety for the patient and medical crews.

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LIST OF ABBREVIATIONS

AMU:	Aviation Medicine Unit
ANOVA:	Analysis of variance
CAA:	Civil Aviation Authority
CPB:	Cardiopulmonary Bypass
^{o}C:	Degrees Celsius
ED:	Emergency Department
Ft:	Feet
FDA:	Food and Drug Administration
g/L:	The amount of haemoglobin in grams (gm) per litre (L) of whole blood
Hb:	Haemoglobin
HbO_2	Oxyhaemoglobin
HR:	Heart Rate
ICU:	Intensive Care Unit
IV:	Intravenous
JR:	Junior Ranks
LED:	Light Emitting Diode
MAUDE:	Manufacturer and User Facility Device Experience
mg/L:	Milligrams per litre
mL:	Millilitres
Min:	Minutes
MT:	Massive Transfusion
MVA:	Motor Vehicle Accident
NM:	Nanometer

NCO: Non Commissioned Officer

NZDF: New Zealand Defence Force

OC: Oxygen concentration

PI: Perfusion Index

POC: Point Of Care

POCT: Point Of Care Tester

RBC: Red Blood Cells

RNZAF: Royal New Zealand Air Force

SaO_2: Saturation level of oxygen in haemoglobin

SD: Standard Deviation

SpHb: Non-invasive haemoglobin measurement

SpOC: Measurement of total arterial oxygen concentration

SpO_2: Saturation of Peripheral Oxygen

INTRODUCTION

In New Zealand and around the world, sick and injured patients are routinely transported using aircraft for the transfer of patients between regional hospitals and centres of excellence. Air Ambulance medicine and nursing is one of the most clinically demanding and time-critical form of health care practice. Patients are critically ill and in an unstable physiological state, usually made worse by environmental conditions (reduced ambient pressure, thermal stress, vibration, noise etc.) not found in usual intensive care contexts. Critical care is provided in a demanding and adverse clinical environment, while totally isolated from the normal support services that a critical care clinician could expect in a hospital setting.

An acutely injured or seriously ill patient has two major areas of physiological threat; loss of circulating blood volume and reduced tissue oxygenation due to poor tissue perfusion. Circulating blood volume may decrease as the result of internal injuries causing haemorrhage or external uncontrolled haemorrhaging. In an aeromedical environment, relatively small reductions in ambient air pressure can cause de-saturation of oxygen supply to critical tissues such as the heart and brain over and above that caused by injury or shock. Doctors, nurses and paramedics are required to transfer patients under their specialist care who require ventilation, perfusion management, and maintenance of cardiac output to ensure that patients do not experience adverse effects from either delayed treatment or the effects of transfer. Isolated from respiratory and laboratory technicians, aeromedical escorts are required to undertake periodic monitoring tests themselves.

The need to maintain adequate tissue perfusion and oxygenation require repeated and rapidly available measurements of both haemoglobin (Hb) concentrations and oxygen saturation. Direct measurements of both parameters require venepuncture and in-flight analysis; these are invasive procedures which are difficult to carry out in the aeromedical transfer environment. The current

practice for measuring haemoglobin is a procedure that involves taking a blood sample and testing it in a portable analyser. From the time the sample is taken to the time the result is produced can take up to 10 minutes and during this time the patient's haemoglobin levels can change. In addition, repeated blood sampling may increase the chance of blood-borne infections or diseases to either the clinician or patient. On the other hand integrated non-invasive haemoglobin measurement systems can provide real time instantaneous measurements of both haemoglobin concentration and oxygen saturation. Non-invasive technology updates and reports visually on accurate haemoglobin levels every 1-2 seconds. However, the susceptibility of such equipment to adverse influences from the aviation environment, and other factors that are associated with acute hypoxemia, limit the generalisability of results provided by such equipment to monitor critically ill patients in flight. Non-invasive haemoglobin testing studies have shown that this is a valid and accurate measurement tool that is more acceptable to patients. However, no studies have been completed to validate this technology at altitude or on its performance in the aeromedical environment. If this new non-invasive technology is proven not to be affected by the flight environment, instantaneous haemoglobin measurement tools will improve clinical safety for both the patient and the medical staff working in the aeromedical field.

This study involved participants being taken to altitude in the Royal New Zealand Air Force (RNZAF) hyperbaric chamber. The RNZAF altitude chamber is rated for human occupancy under reduced pressure conditions well in excess of the negative pressure to achieve simulated altitude for aircrew. It is used to take RNZAF aircrew to altitude where they are exposed to hypoxia and taught to recognise the subtle effects early and take the necessary action required. For this study participants would be taken to 6000 and 12,000 feet because this represents the altitude in a pressurised and non-pressurised aircraft. In New Zealand the worst case scenario for reduced ambient pressure during transfers would be in an unpressurised aircraft transiting the Southern Alps. This altitude is considered safe for the general public, and the NZ Civil Aviation Authority

(CAA), like other safety regulatory authorities, approves flights with fee paying passengers from the general public (including the frail and the elderly) to fly at cabin altitudes of up to 13,000 feet for 30 minutes.

BACKGROUND

In line with international best practice, centralisation of specialised clinical care has occurred, driven by cost and quality considerations. This has led to an increase in the numbers of patients who are acutely transferred to tertiary level regional centres that can provide specialist medical care. Acute medical transfers of those critically ill patients who require the highest acuity care exposes them to hazards of deteriorating clinical status during transfer, or worse still, the effects of transfer on the effects of their medical conditions. The quickest and one of the most reliable modes of transport is by air, either by helicopter or aeroplane; referred to as an aeromedical transfer [(1)]. In New Zealand thousands of aeromedical transfers are completed annually and the total completed increases each year [(2)]. Patients' medical conditions frequently change rapidly during transportation outside of the hospital, and require constant clinical and biological monitoring. For aeromedical transfers, it is important that the standard of care is maintained at the same level as expected in the hospital setting [(3)]. This includes clinical decision-making and patient monitoring.

Transporting patients at altitude incurs a physiological cost as the body's systems must compensate for the pressure changes at altitude. Lower haemoglobin levels, either due to illness or acute injury or bleeding, can potentially be important and a threat for patients when outside of the hospital (and blood bank resources). Patient well-being can be threatened by reduced oxygen-carrying capabilities. This is compounded further by being in a reduced oxygen environment during transportation. These changes can happen rapidly and can go unnoticed if the patient is not being closely and adequately monitored.

Critical changes in patient physiology that affect their clinical outcomes during and after transfer require frequently updated information on parameters such as blood gas levels and haemoglobin

levels. These measurements are vital for the on-going care and monitoring of an intensive care patient. However, there are obvious safety concerns for both the clinician and the patient by completing this procedure in a moving aircraft. Drawing a sample of blood using a needle and vascular puncture in a moving aircraft with limited space and light has a high potential for an accident or incident to occur [(4)]. In addition, the technological and commercial possibility to simply and quickly assess blood oxygen content (both haemoglobin concentration and oxyhaemoglobin percentage) quickly and non-invasively has until recently not been available.

At altitude, pulse oximetry is a key vital sign measurement due to the reduced amount of oxygen available in the air for a person to breath. During aeromedical transfers it has become standard clinical practice to measure and record oxygen saturation levels. Before pulse oximetry was commercially available for widespread patient use, oxygen levels were measured by completing a painful invasive procedure, that is, a blood test involving an arterial puncture and a sensitive and vulnerable measurement apparatus. This procedure is time consuming; taking 20-30 minutes to gain a measurement, and can introduce complications. While waiting for this measurement the patient's condition could also change or deteriorate. This delay was also problematic as severe vital organ damage due to low blood oxygen levels (hypoxemia) can occur within a few minutes. It is estimated that before pulse oximetry many patients died each year from undetected hypoxemia [(5)].

One of the strengths of pulse oximetry, as it is currently implemented, is that it involves a relatively inexpensive device (only a few thousand dollars for a durable, reliable device that can be used for years), it is non-invasive, and it provides very rapid measurements. These devices are based on transmission of light waves from a sender, through body tissue such as a finger or earlobe, and then measurement by a sensor sitting directly opposite the sender (Figure 1). The signal is derived from variations in the amount of light at two specific wavelengths that is sensed

related to pulse variation. This selected band of light that varies in pulsatile fashion has been calibrated to relative amounts of reduced haemoglobin vs. oxyhaemoglobin.

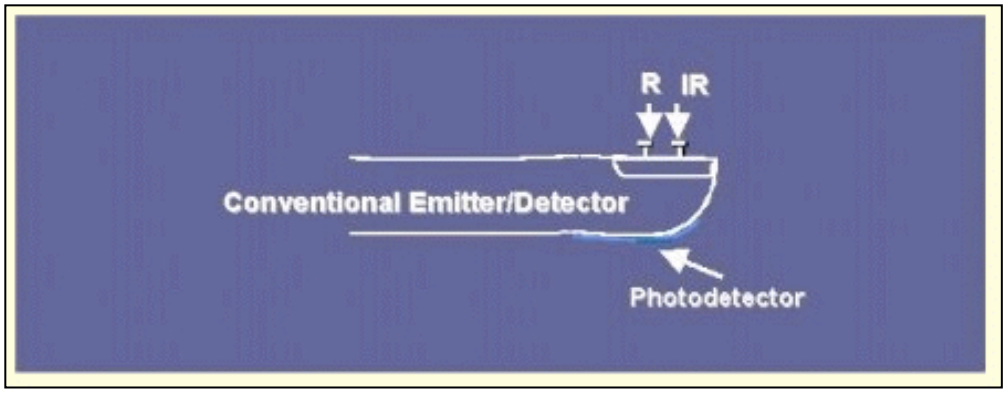


Figure 1: Conventional emitter and detector system showing basic light transmission through tissue (6).

Pulse oximetry technology is based on two basic principles, the first being that a signal which is related to blood and no other tissue needs to be isolated. The second principle is that oxyhaemoglobin absorbs light at some wavelengths and reduced haemoglobin absorbs light at other wavelengths. By passing light at two different wavelengths through blood, it is possible to determine relative amounts of these two different haemoglobin species. While there is blood in arterioles, capillaries and venules that absorb pulse oximeter emitted infrared light, the blood in the arterioles is completely pulsitile. By isolating this pulsitile fraction in the light signal, one focuses largely on arterial blood, which is of interest when assessing blood oxygenation. Pulse oximetry uses two light-emitting diodes (LEDs) that emit light in specific band amplitudes. Red light is in the 600 – 750 nanometre (nm) range and infra-red is in the 850 – 1000 nm wavelength band. Oxygenated haemoglobin absorbs more infra-red light and allows more red light to pass through it, while deoxygenated or reduced haemoglobin absorbs more red light and allows more infra-red light to pass through it [(7)].

After the transmitted red light and infra-red light signals pass through the measuring site and are received at the photo detector, red and infra-red ratio is calculated. This ratio is compared to a previously established standard measurement in a table where empirical formulas then convert the ratio to a pulse oximetry (SpO_2) value set as a percentage. Most manufacturers have set their own look-up tables based on calibration curves derived from healthy subjects, though only for higher or healthy values. Typically a red/infra-red absorption ratio of 0.5 equates to a 100% SpO_2 reading, a ratio of 1.0 to 82% SpO_2, while a ratio of 2.0 equates to 0% SpO_2 [(8)].

Pulse oximetry only estimates SaO_2 levels, and even here there are physical factors which can interfere with measurements. Common problems include physical motion artefacts, inaccurate placement of the probe (poor signal), cold digits (vasoconstriction), nail polish and blood over digits. Gases that bind to haemoglobin in place of oxygen such as carbon monoxide will provide false readings by mimicking oxyhaemoglobin leading to falsely high saturation levels of oxygen in haemoglobin (SaO_2). This can be a potentially very dangerous situation for a patient if a clinician does not detect falsely high SaO_2 readings on a pulse oximeter. This is a design limitation which has been accepted in order to keep pulse oximeters simple and inexpensive. In the future, more sophisticated spectrophotometric methods may become available to test for this non-invasively.

A very relevant limitation of pulse oximetry in the ambulance setting is that it will only measure relative haemoglobin oxygen saturation, and nothing about how much haemoglobin there is in the blood. If a patient has too little haemoglobin for their needs, then the existing haemoglobin molecules in arterial blood can be completely occupied with oxygen and still there can be too little oxygen in total in the arterial blood for the body's needs. So, oxygenation (SaO_2) really tells us nothing about blood oxygen content. We must know how much haemoglobin is available for oxygen binding, in order to measure oxygen content (and hence oxygen delivery). If a clinician is confronted with a patient who has lost a lot of blood and is in haemorrhagic shock, that patient

may still show high levels of oxygen saturation. Haemoglobin levels in blood can change rapidly, though this may have no effect at all on SaO_2. Clinicians can be distracted by high SaO_2 levels in patients that are bleeding. What is needed is a simple and rapid non-invasive means for serial assessment of Hb as well as SaO_2.

Motion artefact in pulse oximetry can lead to errors in measurements and false alarms. Manufacturers have designed these devices typically for two different situations, one where patients will be moving and one where patients would be lying still (sedated or under a general anaesthetic). The tactics for reducing noise involve two compromises - filtering and averaging. Both degrade the sensitivity of the device for detecting rapid changes, but a compromise is reached where the 'response' is quick enough for clinical events (responding within some number of seconds), but where there is no alarm if there is an immediate jump or change in signals. The devices typically have two settings. An ICU setting, where there is more filtering to limit the effects of motion artefacts on the signal and number that is presented, and an 'operating room' setting which has less filtering. Averaging also increases the specificity of a change to indicate a real clinical event. This averaging is the reason for the delay that is observed when a patient (it is known) has a clear and sudden drop in SaO_2, though the pulse oximetry signal will lag some number of seconds before those values change. The same occurs when oxygenation rapidly increases. The lag is some number of seconds, and is judged by the manufacturers to be a reasonable balance for increasing the specificity of a drop in saturation to indicate a real clinical event.

Other forms of motion artefact may be of interest in these non-invasive infrared absorbance systems. There can be a lot of vibration at different frequencies in aircraft during flight. Medical devices need to be tested and validated for both high fidelity of their signals to the intended measurement as well as that they do not disturb the aircraft systems required for flight. The validation and licensing regulations for medical devices in helicopters is not as rigorous, though

clearly there are lots of physical forces on medical devices in helicopter cabins. This is an area that needs to be studied in order to describe the general reliability of this type of device in aeromedical transport use. It was part of my original plan to try to study this as well in a clinical aeromedical service, though these results will not be presented as part of this thesis.

Even though there are other species of haemoglobin where the haemoglobin molecule is in another configuration and/or is bound to another gas molecule (such as met-haemoglobin, carboxyhaemoglobin, and sulpha-haemoglobin), the simple pulse oximetry device makes an assumption that there is only reduced haemoglobin (Hb) or oxyhaemoglobin (HbO_2). As long as there is enough pulsitile flow in the tissue that is being measured by the pulse oximetry probe, then there is a result from the machine, which is an estimation of HbO_2% or oxygen saturation of arterial blood (SaO_2). If there are other species of haemoglobin present in blood (those mentioned above), then this simple and fast SaO_2 measurement can be inaccurate and misleading. Some cases where these other species of haemoglobin might be present include carbon monoxide poisoning or methemaglobinemia from drug side effects or intoxication. Even if the SaO_2 as measured by the pulse oximeter is accurate, it still says nothing about how much oxygen the blood is actually carrying and delivering to vital organs. In order to know that, then both the haemoglobin concentration as well as the SaO_2 need to be known. So, even though pulse oximeters have become widely available, by themselves they provide no complete information about how much oxygen is being carried and delivered by arterial blood flow. An example of this is that an extremely anaemic patient can have 100% SaO_2 but very little oxygen carrying capacity (very little haemoglobin in the blood), and the pulse oximeter will not give a hint of the oxygen carrying capacity problem. Conversely, a patient with normal haemoglobin concentration but a SaO_2 which is slightly below 90% can still potentially have normal oxygen delivery to vital organs, though without a recent and accurate haemoglobin concentration measurement one would be concerned. Ideally, for a patient who is being transported by air ambulance where there is

concern for vital organ oxygen delivery (concern for shock) and where there may be relatively rapid changes in haemoglobin, then just measuring SaO_2 by itself is not enough to detect changes or worsening in status.

As new patient diagnostic and monitoring technologies are developed and are being employed in hospitals, it is important that before they are also employed in the aeromedical environment they are tested and validated for accuracy and precision, particularly with relation to specific physical stressors which are relevant for the aircraft cabin in flight.

One new technological breakthrough that has been developed for hospital use is called non-invasive haemoglobin (SpHb) monitoring. This is a measurement which is related to pulse oximetry, though measuring a different parameter which is haemoglobin concentration. It is also performed by shining infra-red light which is transmitted through the skin, and the amounts of light signal at different wavelengths which are absorbed allow assessment of blood haemoglobin concentration. This is essentially a continuous signal which is analysed, though the machine programs perform point measures at predetermined intervals such as one minute. This provides the clinician with frequent serial measures of Hb which are almost real-time. This type of measurement is performed in a device which also assesses SaO_2, so that even oxygen content can be calculated simply. Serial measurements of Hb are what is needed when managing an injured or ill patient where active bleeding is suspected though must be documented (along with symptoms) in order to be able to defend a decision to move to blood transfusion during transport. When a patient is bleeding and the need for transfusion can be identified early, and where transfusion is performed and the beneficial treatment effect documented, then aggressive resuscitation with transfusion can be performed with more confidence that patient safety has been preserved. Unnecessary transfusion is considered a risk to patient wellbeing, and not transfusing or delayed transfusion when the clinical setting calls for it is also a risk for patient wellbeing.

One medical device manufacturer has introduced a non-invasive spectrophotometric device which it states assesses Hb as well as SaO_2. It was approved for clinical use by the U.S. Food and Drug Administration on May14, 2008 [(9)]. The company advertises that this device can be used to serially measure Hb in settings where serial blood tests have been used previously. While there was some clinical data used by the company to validate the machine in a clinical setting, this device was not a new technique or method and thereby could be approved (by the FDA, in the US) without vigorous clinical testing. The vigorous clinical testing is therefore left to clinicians.

The methods used to estimate total haemoglobin are based on the analysis of wavelengths of light and advanced signal processing algorithms which are proprietary. The company describes a method where 12 beams of light (red and infra-red) are shone through the tissues, and a sensor measures how much light is absorbed. The final measurement is displayed numerically as an Hb concentration per volume of blood (in grams per litre g/L) [(10)].

Pulse oximetry is considered as standard monitoring requirements for any patient where there are clinical concerns about oxygenation. Some type of Hb measurement is also considered standard, if there is concern in a patient for circulatory or respiratory insufficiency. The new non-invasive Hb assessment which is combined with pulse oximetry, if accurate and precise, could simplify the clinical collection of this important information. Unfortunately, the experience with pulse oximetry over the years is that the signal collection and analysis can be easily disturbed, and that this type of measurement can also be inaccurate and misleading since the measurement is based on some physiological presumptions (that I have mentioned) that may not be present in individual patients. Therefore, it is relevant to test this type of device in different demanding environments, where physical factors may affect both the measurement situation and the function of the device.

I have started with the setting of low atmospheric pressure that is typical for cabin pressure in flight in an air ambulance.

When transporting critically ill or injured patients by airplane or helicopter, it can become a very isolated environment for the clinical team members. They do not have the luxury of full laboratory facilities or endless resources available. They need to make clinical judgments and therapeutic decisions with the best information they have available at the time. This type of non-invasive technology, if reliably precise and accurate, could reduce the risk of unnecessary blood transfusions in flight, including risk related to repeatedly drawing blood from patients.

In setting out to do this study, two possible outcomes could be anticipated. First, that there was very strong agreement between the test device and the lab-measured values. Second, that there was a systematic difference, and if so would this difference be directly due to low atmospheric pressure? If a difference between the test value and a reference value was noted, would this be due to an effect on the machine or could there be a real physiological change in the subjects? On a practical level, it was not possible to do an POCT Hb test on these subjects, so it was necessary to make a few assumptions about what happens in subjects subjected to this type of abrupt altitude change. Before doing these altitude chamber tests, it was definitely not known what the results would be so no forms of bias were identified before collecting the data.

Since my study was started, there have been a number of publications where there has been assessment of the precision and accuracy of the device in specific patient groups; compared to invasive alternative measurements of haemoglobin [(11-21)]. These different studies report similar results in patients with (Hb) changes related to bleeding or hemodilution, where there is a consistent agreement between the non-invasive assessment of Hb and Hb measured by hospital reference devices or other to within +- 0.15-0.2 g/L. This degree of agreement was considered

generally acceptable by authors for reliability in some clinical situations, but not in others, particularly those where significant bleeding was present or expected.

Current practice in the hospital setting to determine Hb is to draw venous blood and test it in a central hospital laboratory (most accurate) or portable 'Point Of Care' (POC) analyser which is less accurate, and typically just used to follow trends. The new technology which I studied for this thesis is non-invasive and immediate in its assessment, and configured for serial measurement. This is ideal for an air ambulance setting where one wants to identify as quickly as possible rapid changes in Hb related to bleeding. This new Hb measurement technology has not been tested systematically at altitude where changes in ambient pressure or other factors related to the air ambulance environment could affect patients or the light signals or measurement. My research question concerned how robust this new technology is for the aircraft cabin environment. The first step was to examine possible effects of cabin pressure on the Hb measurements. Other aspects of the aircraft cabin environment, which I have not addressed in this thesis, could concern vibration, electromagnetic signal, or other physical factors.

AIM

This study aimed to test a hypothesis using healthy volunteers, comparing a traditional blood measurement to the non-invasive measurements at sea (ground) level and then during altitudes in a hypobaric chamber chosen to correspond to cabin atmospheric pressures in modern aircraft. There was one commercially available device at the time of my investigation which provided this type of assessment, and therefore we aimed to test only signals from this device.

HYPOTHESIS

The main hypothesis was that non-invasive haemoglobin measurements with this new technique at lower atmospheric pressures does not affect the signal and resulting non-invasive haemoglobin measurements.

METHODS

STUDY DESIGN

A simple interventional before and after study was carried out using volunteer participants. Subjects were recruited from the New Zealand Defence Force (NZDF).

An application for ethical approval was made to the Ministry of Health, Health and Disabilities Ethics Committee (Northern X region) in November 2009. The study, entitled "Is the use of non-invasive haemoglobin measurements accurate and reliable during the transfer of sick and injured patients utilising air ambulance aircraft?" gained ethical approval on 21 December 2009, PIS/Cons V#2 4/12/09 (Appendix 1).

The general study setting in which subjects were assessed was the Royal New Zealand Air Force (RNZAF) hypobaric chamber, where it was possible to simulate pressurised and unpressurised aircraft cabin altitude. Baseline or reference haemoglobin levels for the participants were determined using a traditional invasive laboratory based blood test, and then test measurements (Hb) were recorded for specific points during the altitude chamber session.

SELECTION CRITERIA

Volunteer subjects were selected from within New Zealand Defence Force personnel working in the greater Auckland area. Three target populations were identified, Royal New Zealand Air Force (RNZAF) Base Auckland, HMS Philomel (Navy) and NZ Army Camp Papakura. It was assumed that the majority of volunteers would come from RNZAF Base Auckland as this was the location for the study and it is the largest employer of NZDF personnel in the Auckland area.

Inclusion criteria for this study included:

- Male and female volunteers.
- 17 - 60 years of age.
- Non-smokers.
- Medically fit and healthy.
- Pass a Hypobaric chamber medical prior to chamber run.

Exclusion criteria for this study

- Any volunteer who failed the RNZAF hypobaric medical exam.
- Any phobias, claustrophobia or fear of hypodermic needles.
- Any cultural or religious conflicts.
- Any bleeding disorders.
- Unable to draw a blood sample.

Sample size calculation

A number of assumptions were made in order to obtain the sample size required for this study. The sample size calculation was based on a null hypothesis that invasive haemoglobin level (Hb) levels are the same as non-invasive Hb measurements (i.e. both means are the same) at altitude.

Average Hb levels are different for males and females. For the proposed sample size mean Hb was assumed to be 150.39 ± SD 1.41 g/L in men and 135.39 ± SD 1.32 g/L in women [22].

The pre-specified level of statistical power for calculating the sample size was set at 0.8 for both male and female subjects based on a two-sided test for whether there was a difference between the invasive and non-invasive Hb procedure. The type 1 (alpha level) was set at 0.05.

Male subjects:

A mean of 15.0 and SD of 14.1 was assumed to define a difference between the invasive and non-invasive procedure for male subjects. It was calculated that 30 male subjects were needed to provide an 80% power. Assuming a 5% drop-out (attrition rate), it was decided at least 33 male subjects should be enrolled.

Female subjects:

A mean of 1.5 and SD of 1.32 was assumed to define a difference between the invasive and non-invasive procedure for female subjects. It was therefore calculated that 28 female subjects were needed to provide an 80% power. Assuming a 5% drop-out (attrition rate), it was decided that at least 31 female subjects should be enrolled.

Based on the above sample size calculations, enrolments of an overall minimum total of 64 subjects (33 males and 31 females) were therefore required.

STATISTICAL ANALYSIS

The main hypotheses tested for these results were that:

1. There was agreement between ground level reference laboratory and the non-invasive co-oximeter measurements of haemoglobin at ground level, 6,000 and 12,000 feet.
2. There would be differences related to 'altitude' in oxygen saturation and heart rate at different levels of altitude.

Haemoglobin laboratory assessments were regarded as gold standard and the non-invasive co-oximeter as methods of comparison. Agreement between the lab and the non-invasive measurement was completed as described by Bland and Altman [23]. Non-invasive measurements were recorded every 10 seconds at 6000 and 12000 feet. Data points were recorded as mean values and SD where a normal distribution of results was assumed.

The difference between the lab Hb and the non-invasive Hb were plotted on a scatter graph to show degrees of correlation. In the tables, a Pearson's correlation analysis is presented and a Pearson's r (correlation coefficient) result is shown.

Differences between Hb, oxygen saturation (SpO_2) and Heart Rate (HR), at ground level, 6000 and 12,000 feet were tested for significance using Analysis of Variance (ANOVA). A statistical analysis program, SPSS version 18 was used to analyse the data.

The International Standard for laboratory measurement of Hb is in grams per litre (g/L) [37], though in many countries milligrams per litre (mg/L) is the common unit used for reporting Hb. For the analysis of this study the Hb non-invasive measurements have been converted to g/L, since this result was provided by the reference laboratory for the reference measurements.

SUBJECT RECRUITMENT

An advertisement was placed in the RNZAF Base Bulletin (newsletter) over a period of three weeks prior to the planned dates for the chamber run. A group e-mail was sent out in the days leading up to the chamber run via the Base Auckland local computer network. A notice was also placed in the Army and Navy equivalent newsletters advertising for volunteers. One of the issues identified with respect to gaining enough subjects was the number of female participants needed for this study as the NZDF workforce in the Auckland area is predominately male. The advertising was aimed at non aircrew personnel who usually would not have access to the hypobaric chamber. The RNZAF hypobaric chamber is predominantly used to train aircrew in hypoxia awareness so many personnel would not normally be able to get a session in the chamber. The majority of subjects who volunteered did so in order to experience a session in the hypobaric chamber.

A total of four chamber runs were completed. The initial plan was to complete three chamber runs, but one extra run was needed to reach the total for female subjects required for the study.

RNZAF ALTITUDE CHAMBER

In 1966 the Royal New Zealand Air Force (RNZAF) transferred its Aviation Medicine Unit (AMU) from RNZAF Base Wigram to Clark House located at RNZAF Base Hobsonville in Auckland. The RNZAF purchased an American Vacudyne hypobaric chamber for aircrew training and research in aviation medicine. The chamber accommodates 12 students and two internal instructors. It can simulate conditions of flight up to 200,000 feet and rapid decompressions to 75,000 feet [(24)].

The hypobaric chamber simulates high altitude conditions by using a vacuum pump to evacuate the air out of an airtight chamber. It has a length of 10 meters (33 feet), a height of 4 meters (13 feet), a width of 4 meters (13 feet) and weighs 24.500 kg (76,000 lb). The chamber can be independently controlled in altitude from a main control panel having externally mounted aneroid instruments for indicating altitude and rate of change of altitude. In addition to the large vacuum pump, the chamber also has an air conditioning unit, an air compressor, intercom system for communication and an oxygen system for altitudes above 12,000 feet (figure 2). The RNZAF treat this chamber just like one of their operational aircraft and it needs to be certified for flight. As per RNZAF flight limitations and regulations anybody flying in RNZAF aircraft over 12,000 feet for a period longer than 30 minutes must have a supplementary oxygen supply due to the effects of hypoxia.

Figure 2: RNZAF Hypobaric Chamber

The hypobaric chamber is a useful training tool in simulating changes in barometric pressure and familiarising people with the effects of hypoxia.

ALTITUDE PROFILE

The altitude profile for the study was determined in consultation with the RNZAF Flight Surgeon and the RNZAF Chamber Controller, and it was agreed that participants would be taken to 6,000 feet and 12,000 feet with no supplementary oxygen.

The flight profile consisted of ascending to 6,000 feet and sitting at 6,000 feet for a period of 10 minutes. This period was to allow for the participants to physiologically settle and their bodies to adjust to the environmental conditions that they were being exposed to. After the 10 minute period non-invasive measurements were started. The monitors were attached to the subjects and once the monitor's measurements had stabilised, measurements were started for a period of one minute per subject. Each subject's measurements were recorded every 10 seconds for one minute. The time was measured by the Chamber Run Recorder whose role it is to keep the time that the chamber is at any given altitude during the run. After all participants had the monitor on for one minute at 6,000 feet and the measurements were recorded, the chamber ascended to 12,000 feet. At 12,000 feet measurements were started right away due to the RNZAF limitation of only being at 12,000 feet for a period no longer than 30 minutes and the participants' physiological state would have stabilised after being at 6,000 feet for a long period of time.

DATA COLLECTION

Data was recorded and collected using a combined pulse oximeter/non-invasive haemoglobin concentration device (RAD 7, Masimo Corporation, Irvine, California) (figure 3) with MASIMO SET V7.6.0.4 software. The finger sensor E version (RAD 7, Masimo Corporation, Irvine, California), which is disposable, was used. The probes were not reused (single use on each subject) and were provided free of charge for this study by Pro Medical Ltd, the New Zealand Masimo distributors. A trained representative from Pro Medical was present at each chamber run to place the finger probes on each subject as per the manufacturer's (Masimo) instructions. The probes where placed on the same arm that the blood sample was taken from, and a black plastic pouch was placed over sensor and finger to reduce ambient light effecting the measurement, as recommended by Masimo. Five measurement parameters were recorded from the device (see Table 1).

Figure 3: The test device Masimo RAD 7 non-invasive monitor

Table 1: RAD 57 measurements

Measurement	Abbreviation	Action
Haemoglobin	SpHb	Measures haemoglobin level in circulating blood
Heart rate	HR	Measures heart rate per minute
Pulse oximetry	SpO_2	Measures oxygen saturation of arterial blood
Perfusion Index	PI	Assessment of arterial perfusion at measurement site
Arterial oxygen concentration	SpOC	Circulation of total arterial oxygen concentration

DATA COLLECTION PROTOCOL

A strict data collection protocol was adhered to for every participant prior to each chamber run; the protocol is summarised in Table 2.

Table 2: Data collection protocol

Study task	Description
Database	Participant given a study number and personal details loaded into database by RNZAF Aviation Medicine Unit (AMU) Training Officer.
Documentation	Study information sheet (Appendix b), consent sheet (Appendix c) filled out by participant and signed , chamber medical form (Appendix d), blood form
Study brief	Overview of research study and outline of data collection completed by principle investigator
Chamber brief	Completed by RNZAF Chamber operator about chamber run and flight profile
Ground data measurement	Disposable finger probes placed on each participant, same arm as blood drawn from, non-invasive measurement recorded
Blood drawn	Blood taken and send to lab for invasive measurement
Chamber medical	Chamber medical forms reviewed by RNZAF Flight Surgeon participant medically cleared for chamber run
Chamber run	Once all of the above was completed participant was placed inside the chamber

The study database was managed by the training officer at the Aviation Medicine Unit (AMU). They were the single contact to register for the study and when the invasive Hb results were sent back from the laboratory they entered the result into the study database.

Figure 4: Manually recording non-invasive measurements inside the chamber

Only one female participant was unable to complete the data collection protocol due to being unable to provide a blood sample and she was withdrawn from the study.

COLLECTION OF NON-INVASIVE DATA

The collection of non-invasive data was accomplished by manual and automatic data recording. For manual recording, two people were placed inside the chamber with two monitors to record data over a minute at 10 second intervals on each participant (Figure 4).

A maximum total of twenty participants were placed inside the chamber at any one time. Automatic recording was completed by the monitor (RAD 57) at two second intervals and then downloaded to a computer immediately after each chamber run. The manual and automatic data was later compared to rule out any human error in the recording process.

CHAMBER RUNS

The first chamber run completed had a total of nineteen participants and the second run had a total of sixteen. The third chamber run consisted of eighteen participants and the last chamber run had a total of ten females only to reach the required sample size for this study. While completing the first chamber run, at 12,000 feet it was noted that the recordings on the monitor were taking a long time to stabilise. The cold temperature inside the chamber combined with slight hypoxia, reduced blood flow to the extremities, was making it hard for the finger probe to pick up a signal. It was taking longer per person for the monitors to gain a reading of the Hb although it did pick up on the other parameters much earlier. The average autumn temperature in Auckland over this time of year is 20° degrees Celsius (^{o}C) high and 11°C low. The chamber itself has very little heating available and it is made out of thick steel. This problem was reduced during the other runs by getting the participants to wear gloves. The gloves were worn while the participants were inside the chamber and ascending to altitude, they were removed to attach the finger probe ensuring the participants maintained adequate digital perfusion.

A total of six participants required supplementary oxygen at 12,000 feet and one participant had an inner ear problem while descending. Out of the six participants who became hypoxic only one participant became hypoxic before data was collected. Once the participants were placed on oxygen data recordings were no longer recorded. All made a full recovery and no participants made contact with the RNZAF Flight Surgeon after any of the chamber runs with medical problems (see table 3).

Table 3: Participants requiring assistance during chamber runs

Subject Number	**Chamber run**	**Male/ Female**	**Age in years**	**Time at 6000Ft**	**Time at 1200Ft**	**Symptoms**	**Treatment**
3	One	Male	20	60 minutes (min)	28 min	Light headed	O_2 recovered in 4 min
8	One	Female	21	60 min	23 min	Felt sick	O_2 recovered in 3min
33	Second	Male	22	90 min	20 min	Light headed	O_2 stayed on oxygen
52	Third	Female	20	36 min	20 min	Felt sick and light headed	O_2 recovered in 3 mins no data collected
53	Third	Female	21	36 min	23 min	Light headed	O_2 recovered in 2 min
54	Third	Female	30	36 min	16 min	Light headed	O_2 recovered in 4 min
62	Fourth	Female	45	18 min	2 min	Inner ear pain	Nasal decongestant recovered 5 min

TOTAL DATA

A total of 64 participants enrolled in this study, as calculated by the sample size requirements. One was withdrawn as we were unable to gain a blood sample for an invasive measurement of Hb. All 63 participants provided non-invasive measurements at 6,000 feet and a total of forty eight participants provided data at 12,000 feet. Only 48 participants were able to provide non-invasive measurements at 12,000 feet due to the time limitation by the Air Force at altitudes over 10,000 feet. The Air Force do not allow any personnel at 10,000 feet or above for a period longer than 30 minutes without supplementary oxygen. Data was recorded only for a 60 second period at intervals of 10 seconds to ensure the 30 minute time frame was adhered too.

ANALYSIS

Haemoglobin laboratory assessments were regarded as gold standard and the non-invasive Hb oximeter as methods of comparison. Agreement between the lab and the non-invasive measurement was explored using a version of the method described by Bland and Altman to plot the difference between Lab Hb and measured Hb (Lab Hb – measured Hb) at ground level. Most method comparison studies seem to use single observations by each method for each individual. There are, however, considerable advantages in collecting replicate observations so that the repeatability of the methods can be compared. The limits of agreement method is most easily applied to the simple, un-replicated case. Limits of agreement provide a straightforward and intuitive approach to agreement between different methods for measuring the same quantity. When pairs of observations using the two methods are independent, i.e. on different subjects, the calculations are very simple and straightforward. The 95% limits of agreement, estimated by mean difference 1.96 SD of the differences, provide an interval within which 95% of differences between measurements by the two methods are expected to lie [23].

Where the difference was negative, this meant that the measured Hb was greater than the Lab Hb, while a positive value meant the measured Hb is lower than the Lab Hb. Non-invasive measurements were recorded every 10 seconds at 6000 and 12000 feet. Data points were reported as mean values and SD when normally distributed. Analysis of the differences between Heart Rate (HR), oxygen saturation (SpO_2) and Hb at different levels of altitude were tested using Analysis of Variance (ANOVA, SPSS 18)..

RESULTS

DEMOGRAPHICS OF STUDY PARTICIPANTS

Participants for this study were selected from volunteers and there was no exclusion criteria based on age. All volunteers were employed by the New Zealand Defence Force (NZDF), either as service men/women or civilian employees. The range of age for study participants was 18 to 60 years, with an average age of 31 years (see Table 4).

Table 4: Average age of participants

Gender	Min Age	Max Age	Average Age	Std Dev Age	Total number
Female	18	53	31	11	31
Male	19	60	30	12	33
Overall	18	60	31	11	64

Table 5: Different ranks held by study participants

RANK	Female	Male	Total
Captain (A/Capt)	1		1
Aircraftsman (AC)	8	11	19
Seaman (AWES)		1	1
Civilian (CIV)	4		4
Corporal (CPL)	1	4	5
Flight Sergeant (F/S)		1	1
Flying Officer (FGOFF)		2	2
Leading Aircraftsman (LAC)	6	6	12
Lance Corporal (LCPL)	1		1
MR		5	5
MRS	4		4
Pilot Officer (PLTOFF)	1		1
Private (PTE)	2		2
Sergeant (SGT)	2	3	5
Squadron Leader (SQNLDR)	1		1
TOTAL	31	33	64

As evident in Table 4 there was a range of participants across the study population in terms of military rank and structure. A total of 13 participants were civilian employed workers while the remanding 51 were military serving personnel in the Army, Air Force or Navy. The largest single group of military personnel to participate were Aircraftsmen. In terms of military rank and structure, seven were Commissioned Officers, 11 were Non Commissioned Officers (NCOs) and 33 were Junior Ranks (JRs). The JR group is the largest group out of the NZDF population in Auckland and reflects the largest group of people employed by the NZDF.

STUDY PROCESS

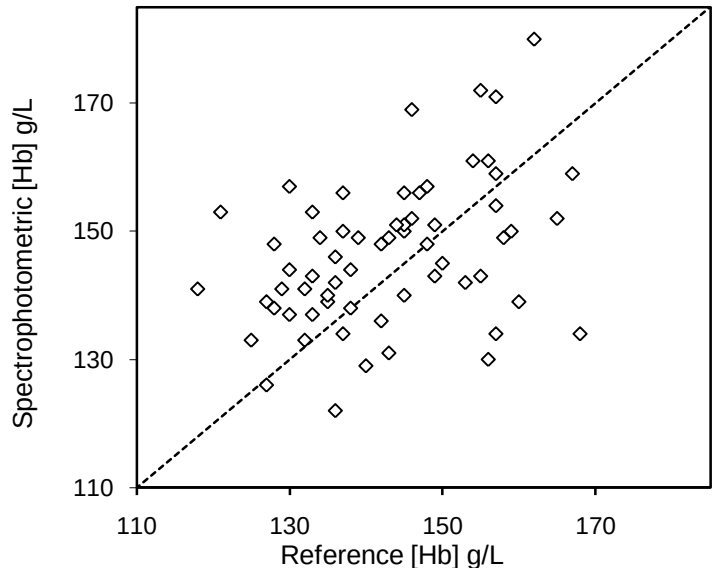
All participants had measurements recorded at sea level (ground) and then the same measurements were recorded at 6,000 and 12,000 feet (simulated altitude). The key measurement for this study was haemoglobin (Hb) but the monitor also collected other useful measurements. The ground measurement was used as baseline measurement with all other measurements used as a comparison. All measurements were non-invasive with only one blood sample drawn for a haemoglobin level. Pulse Oximetry (SpO_2) measures the amount of oxygen saturated haemoglobin in the tissue capillaries. The Perfusion Index (PI) is the ratio of pulsating blood to non-pulsating blood where the sensor is attached. Total arterial oxygen content (OC) is the measurement of oxygen in arterial blood.

Table 6: Mean (SD) values between ground and altitude measurements

Measurement	**Ground**	**6000 feet**	**10000 feet**	**P value**
Heart Rate (beats per minute)	72.3 (11.4)	71.1 (10.4)	75.3 (12.6)	0.03
Pulse Oximetry (%)	98.6(1.1)	94.5 (1.6)	88.2 (4.1)	0.0001
Perfusion Index	3.1 (2.0)	3.4 (1.8)	3.5 (2.6)	0.28
Haemoglobin (g/L)	0.146 (11)	0.151 (13)	0.157 (18)	0.002
Oxygen Content (mL O_2 per100 mLs of blood)	17.8 (1.4)	17.3 (2.6)	17.2 (2.1)	0.38

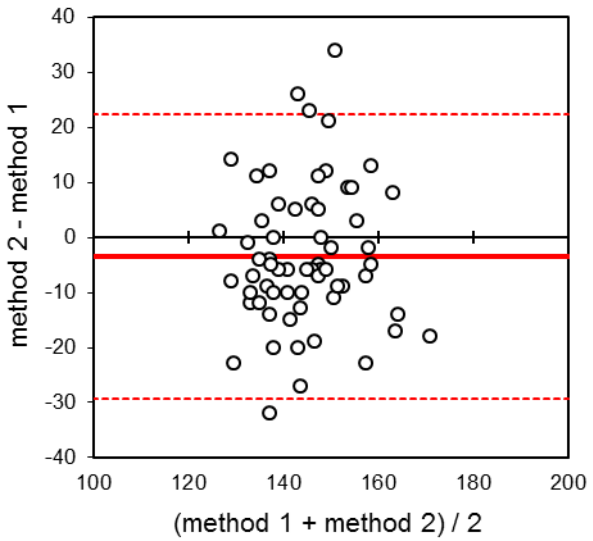
In Table 6 mean (SD) values are shown for ground, 10 second measurements at 6000 feet and 10000 feet. These show significant changes in Heart Rate (HR), oxygen saturation decreases at tissue level (SpO_2) and haemoglobin (Hb) increasing with altitude. Statistical analysis was completed by using analysis of variance (ANOVA).

Table 7: Combined data at ground level



	Spectrophotometric Hb	Reference Hb (lab)
n =	63	63
min	122	118
max	180	168
SD	11.34	11.95
range	58	50
r =	0.390	

Figure 5a: Correlation plot for Hb values (g/L), males and females combined at ground level (n = 63).

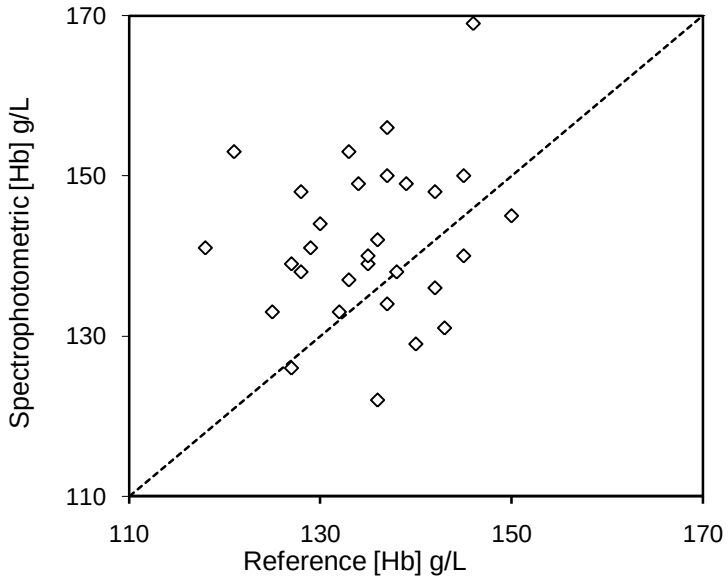


	mean	M2-M1
n =	63	63
min	126.50	-32.00
max	171.00	34.00
SD	9.71	12.87
range	44.5	66.0

bias value	**-3.46**
+2SD	22.29
- 2SD	-29.21

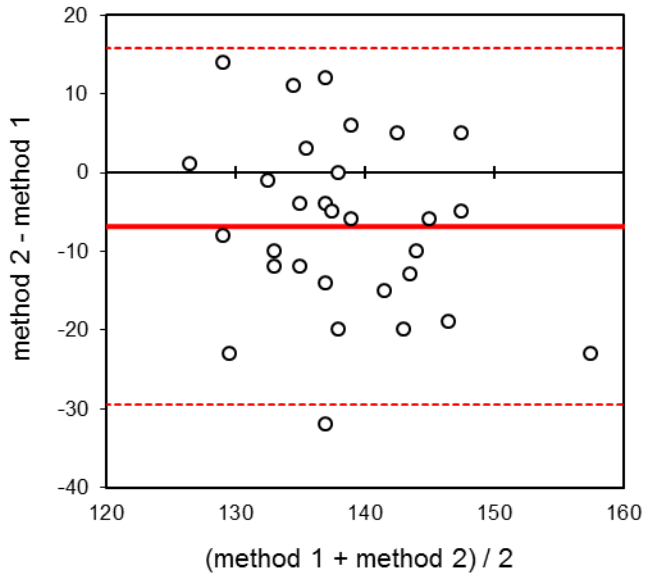
Figure 5b: Bias plot for Hb values (g/L) combined male and female subjects at ground level. Method 1 (M1) as the test method (Masimo spectrophotometric Hb concentration) and method 2 (M2) the reference (laboratory standard) method. There is a small tendency for overestimation with the test method (method 1) with precision estimation shown with the 2 SD limits.

Table 8: Female data at ground level



	Spectrophotometric Hb	Reference Hb (lab)
n =	30	30
min	122	118
max	169	150
SD	9.77	7.57
range	47	32
r =	0.171	

Figure 6a: Results for the subgroup of female subjects only, Hb (g/L) at ground level (n = 30).

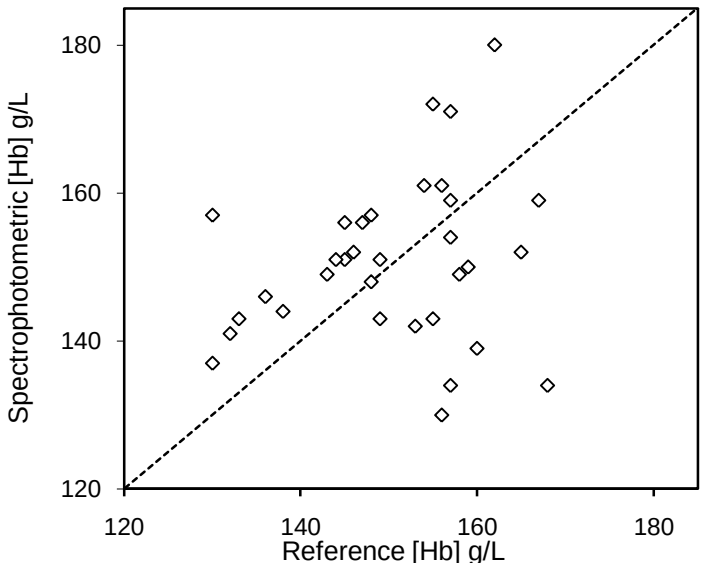


	mean	M2-M1
n =	30	30
min	126.50	-32.00
max	157.50	14.00
SD	6.67	11.29
range	31.0	46.0

bias value	**-6.83**
+2SD	15.75
- 2SD	-29.41

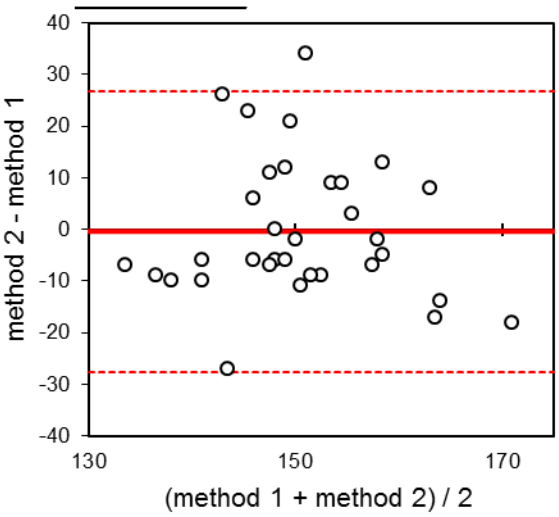
Figure 6b: Bias plot for Hb values (g/L) for the subgroup of female subjects at ground level. Method 1 (M1) as the test method (Masimo spectrophotometric Hb concentration) and method 2 (M2) the reference (laboratory standard) method. There is a tendency for overestimation with the test method (method 1) with precision estimation shown with the 2 SD limits.

Table 9: Male data at ground level



	Spectrophotometric Hb	Reference Hb (lab)
n =	33	33
min	130	130
max	180	168
SD	11.13	10.44
range	50	38
r =	0.205	

Figure 7a: The subgroup of male subjects only, Hb (g/L) at ground level.

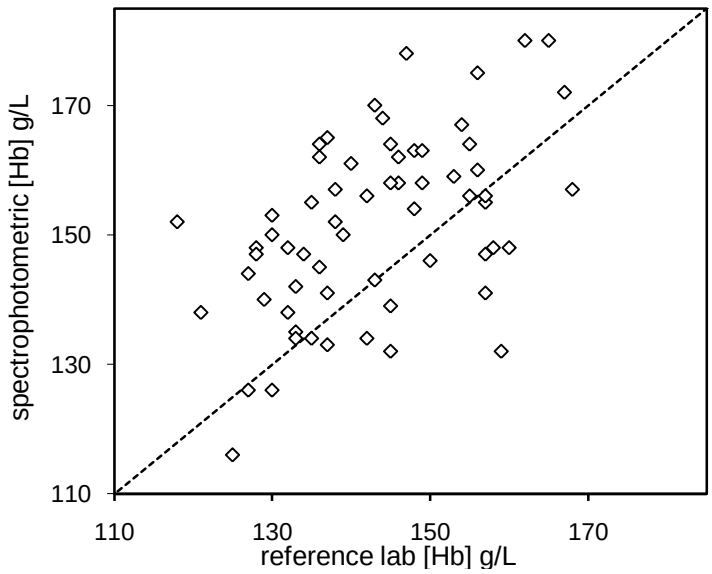


	mean	M2-M1
n =	33	33
min	133.50	-27.00
max	171.00	34.00
SD	8.38	13.61
range	37.5	61.0

bias value	**-0.39**
+2SD	26.83
- 2SD	-27.61

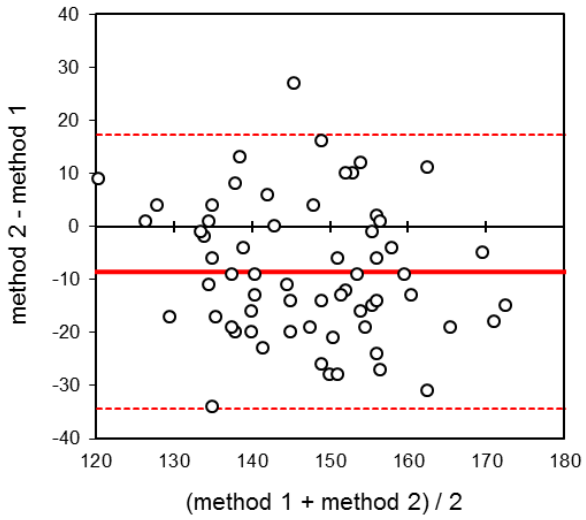
Figure 7b: Bias plot for Hb values (g/L) for the subgroup of male subjects at ground level. Method 1 (M1) as the test method (Masimo spectrophotometric Hb concentration) and method 2 (M2) the reference (laboratory standard) method. There is almost no bias demonstrated for this subgroup with the test method (method 1), with precision estimation shown with the 2 SD limits.

Table 10: Combined data at 6000 feet



	Spectrophotometric Hb	Reference Hb (lab)
n =	63	63
min	116	118
max	180	168
SD	13.87	11.95
range	64	50
r =	0.507	

Figure 8a: Combined male and female subjects at 6000 feet.

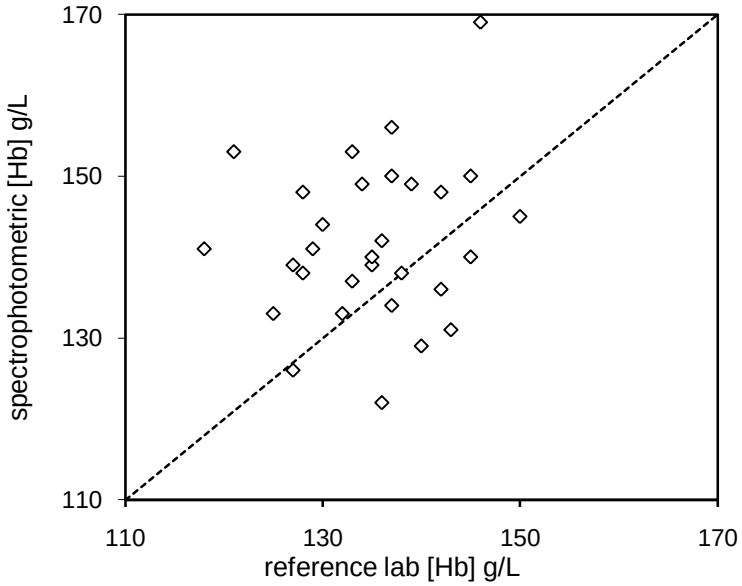


	mean	M2-M1
n =	63	63
min	120.50	-34.00
max	172.50	27.00
SD	11.21	12.93
range	52.0	61.0

bias value	**-8.56**
+2SD	17.30
- 2SD	-34.41

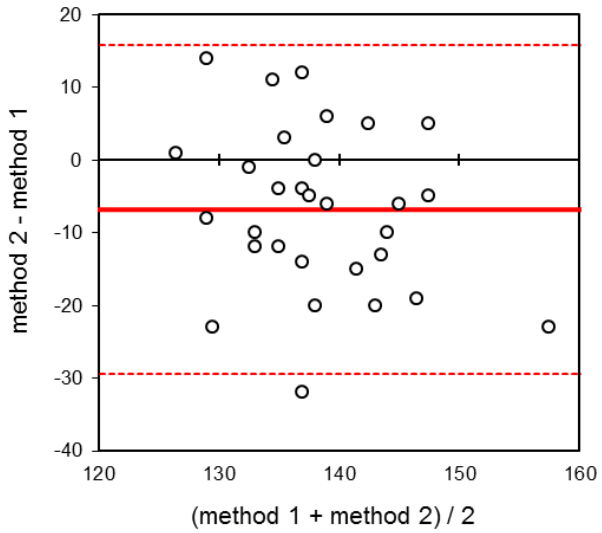
Figure 8b: Combined male and female subjects at 6000 feet. Method 1 (M1) as the test method (Masimo spectrophotometric Hb concentration) and method 2 (M2) the reference (laboratory standard) method. There is some overestimation demonstrated with the test method (method 1), with precision estimation shown with the 2 SD limits.

Table 11: Female data at 6000 feet



	Spectrophotometric Hb	Reference Hb (lab)
n =	30	30
min	122	118
max	169	150
SD	9.77	7.57
range	47	32
r =	0.171	

Figure 9a: A correlation plot the Hb results for the subgroup of female subjects at 6000 feet.

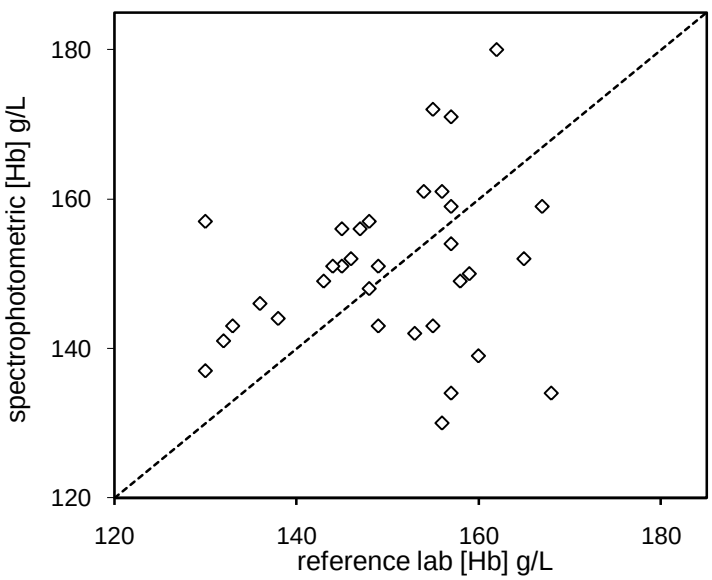


	mean	M2-M1
n =	30	30
min	126.50	-32.00
max	157.50	14.00
SD	6.67	11.29
range	31.0	46.0

bias value	**-6.83**
+2SD	15.75
- 2SD	-29.41

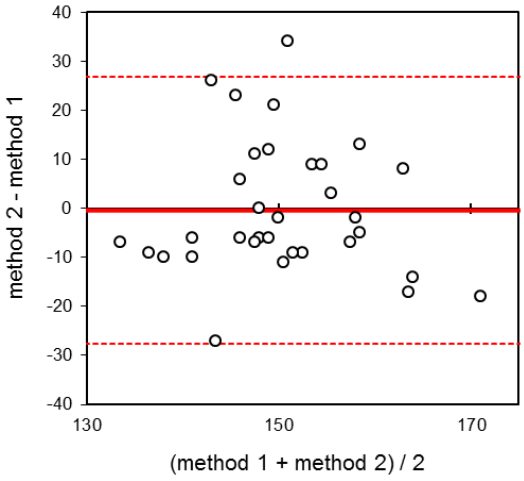
Figure 9b: Bias analysis for the subgroup of female subjects at 6000 feet. Method 1 (M1) as the test method (Masimo spectrophotometric Hb concentration) and method 2 (M2) the reference (laboratory standard) method. There is some overestimation demonstrated with the test method (method 1) for this subgroup, with precision estimation shown with the 2 SD limits.

Table 12: Male data at 6000 feet



	Spectrophotometric Hb	Reference Hb (lab)
n =	33	33
min	130	130
max	180	168
SD	11.13	10.44
range	50	38
r =	0.205	

Figure 10a: Correlation plot for the subgroup of male subjects only at 6000 feet.

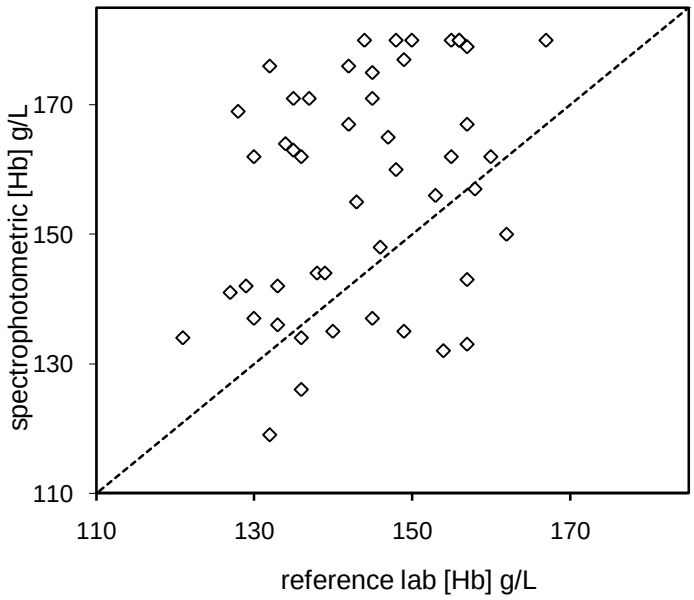


	mean	M2-M1
n =	33	33
min	133.50	-27.00
max	171.00	34.00
SD	8.38	13.61
range	37.5	61.0

bias value	**-0.39**
+2SD	26.83
- 2SD	-27.61

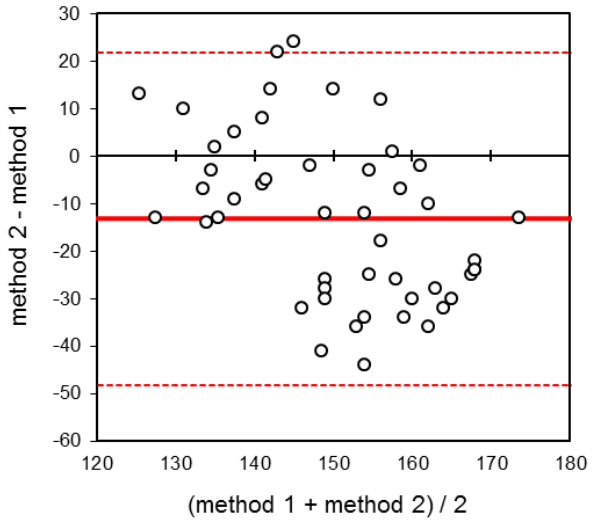
Figure 10b: Bias plot for the subgroup of male subjects at 6000 feet.Method 1 (M1) as the test method (Masimo spectrophotometric Hb concentration) and method 2 (M2) the reference (laboratory standard) method. There is almost no bias with the test method (method 1) for this subgroup, with precision estimation shown with the 2 SD limits.

Table 13: Combined data at 12000 feet



	Spectrophotometric Hb	Reference Hb (lab)
n =	48	48
min	119	121
max	180	167
SD	17.91	10.95
range	61	46
r =	0.341	

Figure 11a: Results for Hb measurements at 12000 feet, all subjects.

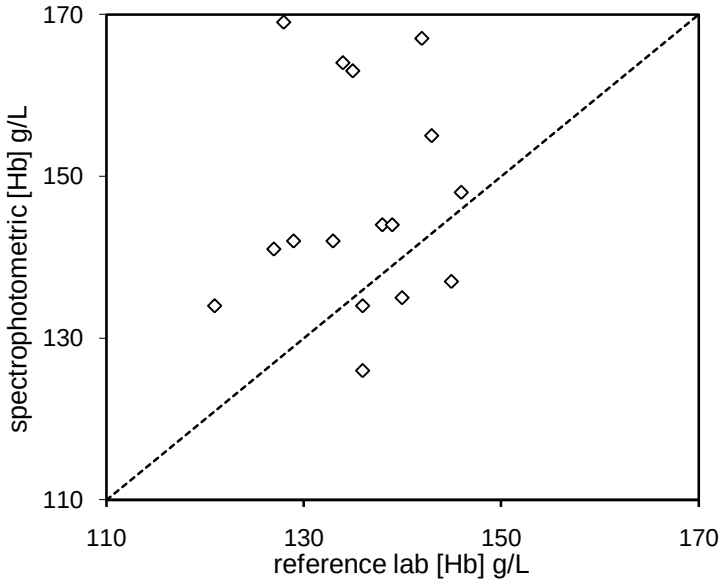


	mean	M2-M1
n =	48	48
min	125.5	-44.0
max	173.5	24.0
SD	11.98	17.52
range	48.0	68.0

bias value	**-13.15**
+2SD	21.89
- 2SD	-48.18

Figure 11b: Bias plot for Hb measurements at 12000 feet, all subjects.Method 1 (M1) is the test method (Masimo spectrophotometric Hb concentration) and method 2 (M2) the reference (laboratory standard) method. There is an overestimation with the test method (method 1) for this group of measurements, with precision estimation shown with the 2 SD limits.

Table 14: Female data at 12000 feet



	Spectrophotometric Hb	Reference Hb (lab)
n =	22	22
min	126	121
max	180	150
SD	17.13	7.03
range	54	29
r =	0.287	

Figure 12a: Correlation plot for Hb measurements for the subgroup of female subjects at 12000 feet. Some degree of overestimation by the test measurement is apparent even in the correlation plot for this somewhat reduced subgroup.

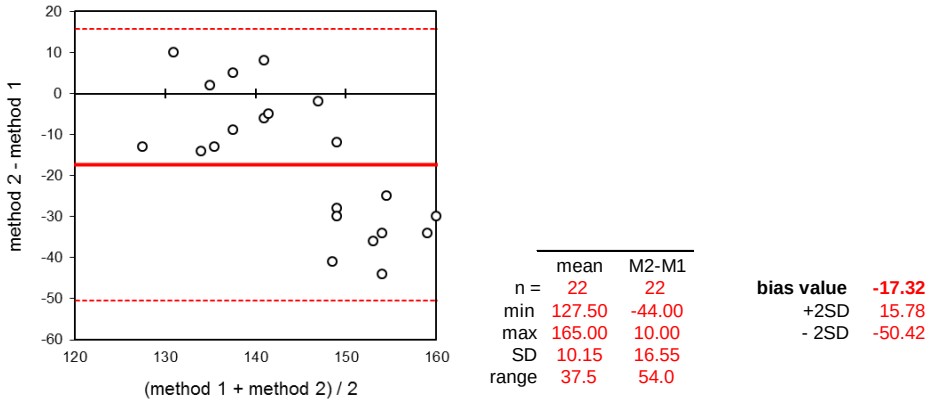
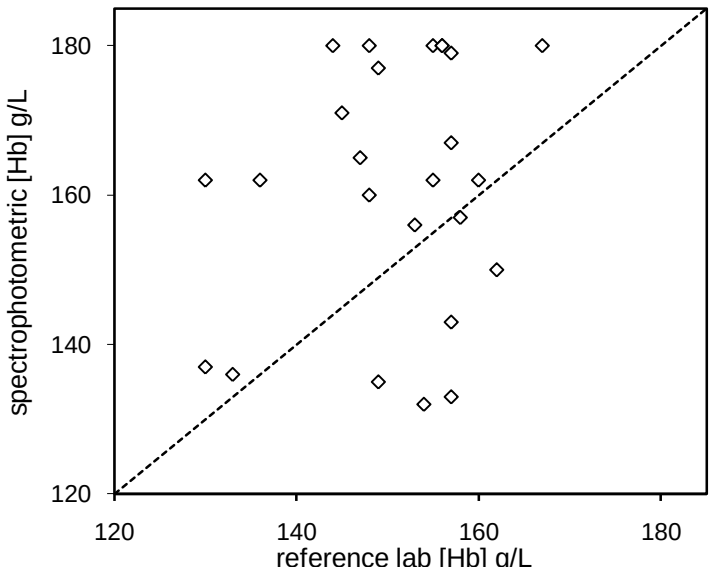


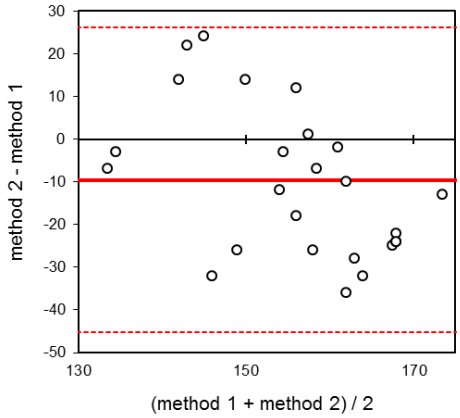
Figure 12b: Bias plot for Hb measurements for the subgroup of female subjects at 12000 feet. Method 1 (M1) is the test method (Masimo spectrophotometric Hb concentration) and method 2 (M2) the reference (laboratory standard) method. In this more extreme condition, there is a larger overestimation (bias) with the test Hb measurement compared to the reference measurement. The precision estimation is shown with the 2 SD limits. There seems to be worse less agreement between the 2 methods (more overestimation by the test measurement) at the higher values for Hb in this subgroup.

Table 15: Male data at 12000 feet



	Spectrophotometric Hb	Reference Hb (lab)
n =	26	26
min	119	130
max	180	167
SD	18.54	10.25
range	61	37
r =	0.343	

Figure 13a: A correlation plot for the subgroup of male subjects at 12000 feet. Some tendency for overestimation by the test measurement is apparent in the correlation plot also for this subgroup.



	mean	M2-M1
n =	26	26
min	125.50	-36.00
max	173.50	24.00
SD	12.03	17.84
range	48.0	60.0

bias value	**-9.62**
+2SD	26.07
- 2SD	-45.30

Figure 13b: A bias plot for subgroup of male subjects at 12000 feet. Method 1 is the test method (Masimo spectrophotometric Hb concentration), and method 2 the reference (laboratory standard) method.

DISCUSSION

To the authors knowledge this study is the first of its kind to access the accuracy of this new technology at altitude and the main findings are twofold. First, the findings demonstrate the limits of agreement between the test (non-invasive Hb) measurement and the reference lab measurements, as shown by the pre-altitude chamber measurements, as well as tendencies for more overestimation by the test devise at higher true Hb levels and underestimation at lower true Hb levels. The second main finding is that rapid 'ascent' to 'altitude' in the hypobaric chamber led to increases in group mean values for (Hb) estimation by the test machine, which was concurrent to decreases in oxyhaemoglobin saturation, though with (at the same time) no changes in 'perfusion index' or oxygen content. The oxygen saturation estimation decreased by approximately 10% at 10,000 feet altitude, and if 'perfusion' and (Hb) had remained constant, this should mean that oxygen content should have decreased by approximately 10%. Total haemoglobin and oxygen carrying capacity appears to have increased during the rapid change to altitude, and this seems to have counterbalanced the decrease in SpO_2% so that the estimation of oxygen content was unchanged. This balance was expected, since the parameters are mathematically dependent on each other - oxygen content is calculated from Hb and SpO_2.

There was an effect of low atmospheric pressure on the test (Hb) estimation which showed a clear positive bias (overestimation) compared to the reference measurement which was even greater at the higher altitude. One question that arises is whether there was a meaningful change in Hb that occurred, or if it was measurement error in the test device. Due to practical considerations, the crowded conditions, and short intervals at altitude, repeated blood drawing in the altitude chamber was not performed. There are reports that some manoeuvres, for example in diving, with hypoxia, hypercapnea, and apnoea, can lead to some degree of splenic contraction and some amount of auto transfusion which leads to increased (Hb), the same way that diving seals maintain oxygenation during diving through some redistribution of blood cells. Our experimental design included

hypobaric atmosphere exposure, but no clinically relevant hypoxia or hypercapnea as in the above mentioned studies. There are no reports that I can find to date that describe immediate changes in Hb or splenic contraction related to a brief hypobaric (12,000 ft altitude) exposure. Therefore, one may speculate that there are other possible explanations for the change in the test device signal for Hb [25-27]. The increases in Hb that were observed in the non-invasive measurement were very small and clinically irrelevant. The degree to which there were group-wise changes was relatively small but also comparable to the limits in precision observed in the bias plots. We interpret therefore the measurement to be reliable for clinical Hb measurement in reduced atmospheric pressure conditions, even though it there is may be a minimal accuracy issue.

Spectrophotometric devices sense blood in arteries, capillaries and veins, particularly the small vessels. Signals can be affected in theory if there are changes in blood amounts in the microcirculation in the area interrogated by the sensor. The method by which the device calculates (Hb) is proprietary, and it is not within the goals of this study to analyse the exact methods of the device. But it is possible that if blood flow in fingertips changed in response to 'altitude', then this would be detected by the device. It is probably technically difficult to be completely specific when trying to separate blood amount and flow for Hb since none of these things are measured directly or with certainty.

Still, the strength of agreement of the 'altitude' measurements to the reference value for Hb was in the same range as has been reported for repeated measures of Hb and comparisons to reference values when true (Hb) levels have been altered by bleeding or hemodilution [11-21]. This allows an interpretation that the device has a relatively high degree of reliability even during altitude changes related to aeromedical conditions, even if one must also have some reservations for the degree of variability in the test device performance if a patient was acutely bleeding. The device appears, based on these findings, to provide the degree of accuracy that would allow one to reliably identify a change of more than Hb of .015 g/L. In this way, our findings agree with

previous findings from other clinical settings. Despite these limitations in agreement with a reference method, the precision and accuracy are still good enough to identify high and normal ranges of hemoglobin (low ranges not tested here), which are the clinically relevant determinations. For clinical use, and particularly in the pre-hospital environment, this performance should be sufficient until other measurements (hospital-based) can be performed using reference methods.

The clinical applications of the findings in this study are mostly for the aeromedical setting, though they can possibly also be extrapolated to other clinical settings. Research has been completed looking at this technology during different types of surgery, in the Emergency Department (ED), Intensive Care Units (ICU), and on different genders and ages [13-16,19]. It is likely that there is a high degree of variability in extremity (hand and finger) blood flow which can affect this type of non-invasive spectrophotometric device, and this must always be remembered when trying to interpret clinical measurements. Aeromedical teams routinely transport patients who are critically sick or injured, either from accident scenes or transfer them between hospitals for definitive care. During these transfers it is important to measure and monitor haemoglobin concentration and oxygen concentration. These patients can have many different pathophysiological processes which could affect hand/finger circulation as well as blood volume shift and even intravascular shift of fluids. These can all affect Hb concentration. Patients need to have an adequate Hb level along with adequate oxygenation in order to maintain the needs of the vital organs. These are at risk when patients are quickly placed at high altitude, in an aeromedical transfer. Ready availability and non-invasiveness in a moving ambulance is a strong clinical advantage.

Reduction in Red Blood Cells (RBC's) or haemoglobin is called anaemia, and causes of anaemia can be hereditary, intrinsic or extrinsic [28]. Extrinsic anaemia is usually caused by rapid blood loss or haemorrhage and is a common challenge for aeromedical transfer teams [29]. Patients who are

admitted to Intensive Care Units (ICU) for longer than three days have a ninety per cent chance of developing anaemia due to blood loss from phlebotomy sites [30]. Other potential causes of extrinsic anaemia from blood loss could be due to trauma, gastrointestinal bleeding, obstetric emergencies and various surgical procedures.

IDENTIFYING ANAEMIA IN THE AEROMEDICAL SETTING

The current best practice adopted by aeromedical teams to gain haematology measurements during transfers is by using a Point Of Care (POC) device. Two of the more popular devices used by transfer teams are the HemoCue and i-STAT handheld analysers. They both work by drawing a small amount of blood and placing it in a cassette. Then the cassette is placed in the analyser and the result takes about 90 seconds [(31)]. Point of care testing in the aeromedical environment has its limitations and safety concerns which will be discussed later.

POC testing is usually only used during secondary (inter-hospital) or tertiary (international) aeromedical transfers. During primary aeromedical retrievals the clinician uses clinical judgement to identify hypovolemic shock (anaemia from rapid blood loss) to start a transfusion protocol. These are typically in situations with prolonged extrication due to high speed Motor Vehicle Accidents (MVAs) or if the patient is trapped inside industrial machinery [(32)].

MANAGEMENT OF ANAEMIA

The most commonly used treatment for anaemia is a blood transfusion while trying to identify the source of the haemoglobin loss. Most aeromedical retrieval teams will have a Massive Transfusion (MT) protocol or transfusion protocol for anaemia. For critically ill and perioperative patients, Napolitano (2004) advocates that for haemoglobin levels under .07 g/L, Red Blood Cell (RBC) transfusion is strongly indicated. For Hb levels over 0.1 g/L a blood transfusion is unjustified and for Hb levels between .07- 0.1 g/L clinical judgement should prevail [(33)].

There are differing views on the benefits of administering transfusions to critically ill patients. A large study in the United States enrolled 838 critically ill patients all with normal blood volume after initial treatment. One group of 418 patients only received RBC transfusions if their Hb level dropped below 0.7 g/L. The other patients received transfusions if their Hb level fell below 0.1 g/L. The study concluded that the patients who had transfusions below 0.7 g/L had a mortality rate of 22.2% compared with a mortality rate of 28.1% for patients who received transfusions with an Hb of 0.1 g/L or below. They concluded that a restrictive strategy was as effective or superior to a liberal transfusion strategy in critically ill patients [(34)].

RBC transfusions can also produce other complications such as immunosuppression, biochemical and physiological disturbances, infections and reduced or impaired microcirculatory blood flow. Gould et al. (2007)[(29)] completed a retrospective review of published studies between 1999 and 2006 and concluded that critically ill patients who received RBC transfusions had worse outcomes because of these complications [(29)].

The average total cost of a blood transfusion ranges from $522.45 to $1183.32 USD per unit of RBC, with a mean of three to four units used per patient [(35)]. Most critical care clinicians now avoid large RBC transfusions where possible because of these complications. Even if a patient is

actively haemorrhaging they will not receive large amounts of RBCs. The clinical practices being developed from current military conflicts have identified that keeping patients hypotensive in the field and the ED until they reach the operating theatre where their haemorrhage can be controlled is more effective. This has led to an overall decrease in mortality and morbidity rates during current modern military conflicts [(36)].

Many aeromedical retrieval teams will carry between two and four units of RBCs or blood products depending on their Massive Transfusion (MT) protocol. They are transported in a chiller or refrigerated box with frozen liquid pads to maintain a constant temperature. This allows them to start a RBC transfusion at the origin of the retrieval or during the retrieval if required.

In clinical practice there are three common methods of gaining an Hb result; from a laboratory Hb analyser, Point Of Care (POC) testing, and non-invasive co-oximetry. Each method has its own limitations, strengths and weaknesses.

Laboratory

The most common technique for obtaining an Hb measurement is to take a sample of blood and send it to the laboratory for analysis, which is also considered a reference measurement. Once at the laboratory they will use a number of different methods to gain an Hb measurement. The most common method uses spectrophotometric analysis, based on the Beer-Lambert law. The other methods involve using chemicals to convert the Hb and then calculate the amount using red and infra-red light [(37)].

A number of studies have questioned the accuracy of these methods and the analysers that complete this testing. A large Canadian laboratory (Gamma-Dynacare) wanted to standardise their laboratory analysers across their company. They completed a four-way evolution trial; they compared the results on four different analysers that the company were using at the time. The average systematic error was between 1.9-3.0% [(38)]. Another preliminary report looked at the blood samples from 33 liver transplant patients using a conventional Coulter counter and the spectrophotometric method, where they found some significant limits of agreement between the two methods [(39).]

The laboratory Hb result is considered by most clinicians to be the gold standard when it comes to blood results. This is the measurement that will provide the basis of their clinical decision making

and treatment. Yet these studies show statistically they are not accurate and could have a significant result in the mortality or morbidity of seriously ill patients.

Point Of Care Testing (POCT)

POC testing is completed at the patient's bedside and a result is delivered within one minute allowing a true reflection of the patient's condition, unlike the laboratory test that is ordered by the doctor, taken by the nurse, delivered to the laboratory, test completed and then the doctor informed of the result. During the time it has taken to receive the result, the patient's clinical condition could have changed. Most large Emergency departments (EDs) and Intensive Care Units (ICUs) now use these devices for that exact reason; they provided quicker results which reflect the current clinical condition of their patient [(40)].

While these devices provide a fast result their accuracy can also be questioned. Multiple studies have been completed looking at the accuracy of POC analysers, mainly the i-STAT and the HemoCue. These studies show that human error and damage to the cassettes if not stored in the correct environment will cause measurement errors [(41-46)].

A search on the Food and Drug Administration (FDA) website shows several reports and issues arising with i-STAT analyser. On the FDA site you can search a database called Manufacturer and User Facility Device Experience (MAUDE). There are several reports showing discrepancies between the results from the i-SAT and laboratory. For example, a report dated 24 September 2007 presented a case where the i-STAT measured an Hb at 0.075 g/L and haematocrit at 22%. The patient was re-tested an hour and a half later and it showed an Hb of 0.068 g/L and haematocrit of 20%. Then the same sample was sent to the laboratory showing a result of Hb 0.079 g/L and haematocrit of 22.5%[(47)].

A study using whole blood but with differing Hb levels compared the i-STAT, HemoCue and a traditional laboratory analyser (GenS). The i-STAT discrepancies between measurements increased as the Hb levels decreased, though this was less the case with the HemaCue measurements. Haemodilution was simulated using normal saline or lactated ringers solution. The i-STAT discrepancies increased as the Hb and haematocrit levels deceased with a lower protein content. To rectify this problem the manufacturer added a Cardiopulmonary Bypass (CPB) that automatically adjusts the haematocrit for decreased plasma protein levels usually associated with haemodilution [41].

NON-INVASIVE PULSE CO-OXIMETRY

Clinical studies comparing non-invasive pulse co-oximetry and laboratory analysers use the Bland-Altman method for assessing agreement between two methods of clinical measurement. The Bland-Altman statistical approach compares two different methods for measuring the same thing examining the measured difference between the test measurement and the reference measurement, over a range of measured values.

A large study of 300 Emergency Department (ED) patients compared non-invasive Hb (Masimo RAD 7) results with a traditional invasive laboratory (lab) method (ADVIA 2120). The median age was 49 years (range 35 to 69), 139 males and 161 females where enrolled in the trial with typical ED presentations. The only exclusion criteria was finger burns which would affect the RAD 7 finger probe. The finger probe was placed on the patient while a nurse gained a blood sample, only one non-invasive measurement was recorded and the blood sent to the lab. The non-invasive values were significantly lower than the lab values, with a mean difference of 0.15 g/L (95% CI –18.2 to -13.7, *P*<.0001). Limitations of the study include not targeting patients suffering from anaemia and only recording one non-invasive measurement per patient. They also did not study the other large benefit of this non-invasive technology which is real time continuous Hb levels [(16)].

A smaller study of sixty patients from surgical and Intensive Care Units (ICU) also compared non-invasive and invasive Hb values. The mean age of the patients was 64 with 55% being male. What makes this study different is that 44% of these patients were actively bleeding. For the purposes of this study active bleeding was considered to be 200 mls or more of blood; five patients required intraoperative blood transfusions during the study. The overall correlation of the non-invasive value and the lab value was 0.78 (*P*<.001), with a mean difference of 0.15 (95% CI, -.03 to .32, *P*=.10). The limitations of this study were the variability of the measurements reported

with both the non-invasive and invasive methods. The other limitation was that only one area of the surgical patients (general surgery) provided a sample size large enough to determine the true difference in the actual measurements [14].

Frasca et.al (2011)[15] compared non-invasive Hb measurements with the HemoCue (PCOT), a satellite bedside lab co-oximeter (Siemens RapidPoint 405) and a traditional lab analyser (Symex XT-2100i). They recorded data from 62 ICU patients from a surgical intensive care unit at a university hospital. Any patient who required arterial blood to be drawn for Hb testing was included in the trial. When the case-by-case variation was assessed, the limits of agreement were 0 – 0.01 g/L for the non-invasive method, 0.003 – 0.013 g/L for the POCT (HemoCue), and 0.006 – 0.009 g/L for the satellite co-oximeter when compared with the reference method (lab Hb). The limitations of this study were that less than 10% of the patients had an Hb concentration below 0.80 g/L so Hb accuracy at lower levels may be different. None of the patients in this study had active bleeding and the study did not assess the potential advantages of continuous Hb monitoring or the early detection of bleeding [15].

Non-invasive Hb, POC (HemoCue) and traditional lab measurements were again compared for accuracy with patients undergoing spinal surgery. The correlation between Perfusion Index (PI) and non-invasive measurements was also investigated, Masimo advise not to obtain non-invasive measurements if the PI is <1.4. Perfusion Index (PI) is a measurement of the strength of signal where the non-invasive probe is located. Twenty patients, aged between 40 to 80 years of age were included in this study. All samples were taken from an arterial line; all patients had between three to five blood samples taken, this was completed on the hour during their surgery. Differences between non-invasive Hb and lab Hb were <0.015 g/L for 60% of observations, between 0.016 to 0.020 g/L for 16% of the time and >0.020 g/L for 22% of the time. The study showed a definite relationship between PI and non-invasive Hb. When perfusion diminishes (PI

<1.4) non-invasive Hb underestimates Hb and as perfusion improves (PI >1.4) the Hb becomes a more accurate measurement [19].

Macknet et al. (2010)[13] completed a study looking at the accuracy of non-invasive Hb measurement by human subjects undergoing hemodilution. Twenty healthy volunteers had 500 mls of blood withdrawn and replaced with crystalloid Intravenous (IV) fluid to compensate for the decrease in intravascular volume and to reduce haemoglobin concentration. The non-invasive method was compared to a conventional blood analyser (radiometer BL820) in the laboratory. The results showed that the difference between the non-invasive Hb and the lab Hb was <0.020 g/L for 97% of the measurements. The difference was <0.015 g/L for 97% of the measurements when the lab Hb was <0.1 g/L. Limitations to this study include evaluating no critically ill patients, patients with low perfusion, or those with known peripheral vascular disease [13].

All the studies completed advocate a place for non-invasive co-oximetry Hb measurements and monitoring. The studies completed so far include a variety of patients where Hb recording and measuring are important in the clinical management of patients, with surgery, ICU, and to a lesser extent ED, being the logical clinical areas to benefit from this technology. This is possible due to the availability of real time continuous non-invasive Hb measurements which allows for the trending of values. It enables the clinician to formulate an on-going clinical picture of the patient's condition. The research studies completed on co-oximetry show a trend of statistical inaccuracy with an average of 0.015 g/L difference when compared to the lab measurement.

Is a difference of <0.015 g/L clinically significant? Some clinicians would argue that maybe it is not. As long as the clinician was aware of the difference and this consideration was included when deciding on the clinical management of the patient. This technology could be used in areas where patients are closely monitored and observed. This information could help decide if and when a blood transfusion was necessary. The non-invasive measurement on its own would not be

used to make that decision in isolation, as a number of other factors would be taken into consideration. It is a relatively big clinical decision to make, knowing the complications and issues that arise with blood transfusions. Non-invasive Hb measurements along with other vital signs, lab Hb measurements (if available) or POCT Hb, estimated blood loss and the patient's current clinical condition would help formulate a clinical decision when and if to complete a blood transfusion [48, 49]. All of the studies thus far on non-invasive Hb acknowledge that there is limited data and research looking at its accuracy with patients who are actively haemorrhaging and have low Hb levels. Given that this technology would benefit patients who are actively bleeding, more research is required in this area.

Only one study, Miller et al., looked at trending of non-invasive Hb during spinal surgery; all the other studies discussed the benefits of trending and that more research was required. They provided no statistical data on trending although they did provide a graph of one patient [19 figure1] who completed six hours of spinal surgery. Non-invasive monitoring continued throughout the surgery, and invasive (lab) Hb was recorded on the hour. A total of four invasive Hb data points were plotted with two points being identical with the non-invasive Hb measurement. The other two invasive values were not. One was underestimated and the other was overestimated when compared to the trended non-invasive data points. Miller et al. also found a direct relationship between non-invasive Hb and Perfusion Index (PI). PI is a numerical number given to the plethysmographic pulse wave and amplitude, PI is assumed to reflect the perfusion at the finger and the origin of the measurement. As one would expect, as PI decreased so did the variability of the Hb measurements. The study concluded that PI and non-invasive Hb have a close relationship and that even though Masimo advocate not relying on measurements <1.4 that this figure should be increased to reduce variability in measurements [19].

There has been no research or literature published on the use of non-invasive pulse co-oximetry Hb monitoring in the pre-hospital or aeromedical retrieval fields. Studies using non-invasive pulse

oximetry monitoring have been completed in both the pre-hospital and aeromedical environments with positive results in accuracy and use [50-51].

ACCURACY OF HAEMOGLOBIN TESTING

The studies previously discussed provide comparisons between haemoglobin results from laboratory tests (haematology analysers), Point Of Care (POC) analysers, and non-invasive pulse co-oximetry. Laboratory Hb measurements are considered the gold standard of Hb measurements but studies have challenged this concept. Bourner et al. found when comparing haematology analysers the average error to be between 1.9 to 3% [38].

POC testing using analysers like the HemoCue and the i-STAT provide a quick measurement faster than a laboratory. Human error and cartridges that are stored incorrectly can create incorrect results. When gathering a blood sample from a finger or heel prick the first drop of blood may be contaminated by alcohol or prep solutions used to clean the skin, these can also affect the Hb result.

Pulse co-oximetry can be affected by similar things that affect SpO_2 measurements. Both systems use infra-red light so they can be both affected by ambient light sources. Conditions that affect circulation to the distal aspect of fingers like hypothermia or cold digits and peripheral vascular disease will reduce blood flow and peripheral pulsations. As previously discussed, there seems to be a relation between reduced or increased Perfusion Index (PI) affecting non-invasive co-oximetry measurements. Co-pulse oximetry readings can also be affected motion artefact, patient movement, nail polish and incorrect placement of the sensor [52].

ACCURACY AT ALTITUDE

At the start of this study a set of ground measurements were recorded to form a baseline measurement or reference for comparison, only one non-invasive measurement was recorded at sea level. A venous blood sample was taken and sent to a commercial laboratory for measurement and analysis. The type of analyser and its bias is not known or what type of analysis was used (Spectrophotometer or Hemiglobincyanide method [37]). The other unknown factor was how the blood sample was handled before analysis. The sample is collected at the end of the day by a lab technician and transported by car into town for analysis in the lab.

Measurements taken at ground level (Figure 5a) for this study show a regression towards the mean. There are a large number of negative values showing that the non-invasive Hb measurements were greater than the laboratory Hb measurements. There are fewer positive values, when the non-invasive measurement is higher than the laboratory Hb measurement. There is a trend that shows at relatively low Hb values the non-invasive measurement tends to overestimate the value. At higher levels the non-invasive measurement tends to underestimate the value. The mean difference was -3.46, with a SD of 12.86 g/L.

This trend continues at 6000 feet (Figure 6a) with more negative values than positive, with a mean difference of -8.65 and SD of 12.93 g/L. At 12000 feet (Figure 7) the trend continues to grow with even less positive values. The mean difference at 12000 feet was -13.5, with a SD of 17.52 g/L.

LIMITATIONS OF THIS STUDY

The main limitation of this study was that we were not able to take blood samples for reference measurements during the altitude chamber runs. Only one spectrophotometric Hb blood measurement was taken just prior to the start of the chamber run. Ideally another spectrophotometric Hb test at 6,000 and 12,000 feet would have produced more reliable data for comparison. We did not make the absolute assumption that Hb would remain absolutely unchanged, but we made the assumption that changes that would occur would be small, and well within the error range for the test device. We detected a possible overestimation of Hb by the test device, though this must still be confirmed by further testing.

A further limitation, now in retrospect, is that it would have been ideal to have a plethysmographic measurement of finger blood volume and flow. This is not an easy measurement, but it would have allowed us to have a reference measurement in which to compare the test devices estimation 'perfusion' and oxygen content. In a future study, it would be ideal to measure finger volume as well as a regional or global indication of blood flow.

Another limitation is that we did not include a positive control test; that is, a test where we had a known change in Hb. To have a positive control test would be ideal, but our study was a first step where the number of test steps, once the study question was established, was determined by a reasonable study sized and measurement number for what I could manage in the frame of a first (Master's) study.

CONCLUSION

In summary, I found that this test device, in the setting of rapid ascent to 'altitude' which simulates the setting of an aircraft cabin, appears to slightly overestimate Hb values, though observed measurements are within limits of agreement to reference measures that are previously described for the test device. I conclude that this device will probably be helpful to confirm over time that major bleeding is not occurring, but that some caution should be used with the device when trying to identify very acute changes of Hb, particularly when the changes are in the range of plus or minus 15 g/L. I further conclude that this device is worthy of further study to determine the relation of Hb measurements, 'perfusion' and oxygen content in relation to changes in the local small vessel circulation in the tissue that is being measured. Altitude change is a relevant provoking factor for negative circulatory changes, and caution must be taken when assessing patients with circulatory instability and possible bleeding when in the aeromedical transfer setting. This type of device for close and serial measure of haemoglobin continues to show promise for both identifying need for acute transfusion, as well as for giving a clinician confidence to avoid unnecessary patient exposure to blood products when transfusion is not needed.

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Health and Disability Ethics Committees

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650 Great South Road, Penrose
Private Bag 92 522
Wellesley Street, Auckland
Phone (09) 580 9105
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Please note postal address is : Northern X Regional Ethics Committee, C/o Ministry of Health, PB 92 522 Wellesley St Auckland

21 December 2009

Dr Rob Griffiths
Occupational and Aviation
Medicine University of Otago
Wellington P O Box 7343
Wellington South 6242

Dear Rob

NTX/09/11/106 **Study title: Are instantaneously reporting, non-invasive haemomglobin measurements using the Masimo finger probe unaffected by changes in ambient pressure and oxygen concentration or other air ambulance-related environmental factors that indicate that they would be sufficiently reliable for use on patients during routine aeromedical transfers? PIS/Cons V#2, 4/12/09**

Principal Investigator: Dr Rob Griffiths, RNZAF
Co-Investigators: Dr Russell Clarke, Dr Ben Johnston, Dr Michael Haney
Locality: RNZAF

Thank you for your letter dated 12 December 2009 and the attached Committee requirements. The above study has now been given ethical approval by the **Northern X Regional** Ethics Committee.

Approved Documents

- Information Sheet/Consent Form Part One, V#2, dated 4 December 2009
- Information Sheet/Consent Form Part Two, V#2, dated 4 December 2009
- Protocol dated May 2009

Certification
The Committee is satisfied that this study is not being conducted principally for the benefit of the manufacturer or distributor of the medicine or item in respect of which the trial is being carried out.

Accreditation
The Committee involved in the approval of this study is accredited by the Health Research Council and is constituted and operates in accordance with the Operational Standard for Ethics Committees, April 2006.

Final Report
The study is approved until **30 April 2010**. A final report is required at the end of the study. The report form is available on http://www.ethicscommittees.health.govt.nz (forms – progress reports) and should be forwarded along with a summary of the results. If the study will not be completed as advised, please forward a progress report and an application for extension of ethical approval one month before the above date.

Requirements for SAE Reporting
The Principal Investigator will inform the Committee as soon as possible of the following:

- Any serious adverse events occurring during the study which are considered related to the study.

All SAE reports must be signed by the Principal Investigator and include a comment on whether he/she considers there are any ethical issues relating to this study continuing due to this adverse event. It is assumed by signing the report, the Principal Investigator has undertaken to ensure that all investigators are made aware of the event.

Amendments
All amendments to the study must be advised to the Committee prior to their implementation, except in the case where immediate implementation is required for reasons of safety. In such cases the Committee must be notified as soon as possible of the change.

Please quote the above ethics committee reference number in all correspondence.

The Principal Investigator is responsible for advising any other study sites of approvals and all other correspondence with the Ethics Committee.

It should be noted that Ethics Committee approval does not imply any resource commitment or administrative facilitation by any healthcare provider within whose facility the research is to be carried out. Where applicable, authority for this must be obtained separately from the appropriate manager within the organisation.

We wish you well with your study.

Yours sincerely

Pat Chainey
Administrator
Northern X Regional Ethics Committee

Cc: Dr Russell Clarke

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www.otago.ac.nz/aviation_medicine

Patient Information Sheet

Non Invasive Red Blood Cell (Haemoglobin) Measurement Trial at Altitude Part One

Investigators:

Flight Sergeant Russell Clarke Senior Medic/Flight Paramedic Royal New Zealand Air Force, Post Graduate Masters student in Health Sciences endorsed in Aeromedical Retrieval and Transportation, phone 09 417 8932, e-mail russell.clarke@nzdf.mil.nz

Squadron Leader Ben Johnston Medical Officer Royal New Zealand Air Force, MBCHB, MAvMed, PG Dip Occ Med, Officer Commanding Aviation Medicine Unit, Royal New Zealand Air Force, phone 09 417 8932, e-mail ben.johnston@nzdf.mil.nz

Dr Rob Griffiths Director, Director of Occupational and Aviation Medicine University of Otago, Phone 04 385 5592, e-mail rob.griffiths@otago.ac.nz

Introduction:

I would like to invite you to participate in this research project that I am completing to gain my Masters in Health Science (endorsed in aeromedical retrieval and transportation) through the University of Otago.

In the human body red blood cells (haemoglobin) carry oxygen around our body delivering it to the tissues and vital organs. When a person becomes ill it is important to be able to measure the amount of red blood cells circulating around the body. This measurement is completed by taking a blood sample and counting how many red blood cells there are per millimetre of blood, usually done in a laboratory. New advances in technology have led to the development of a non invasive (not having to enter the body) red blood cell (haemoglobin) measurement. This non invasive measurement is taken by

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placing a finger probe over your finger and allowing a small amount of infrared lights to pass through your finger, a totally painless procedure. This method has been formally introduced and established, and today is used in general health care.

Every day around the world, hundreds of patients are transported by air ambulances to hospital. If this new technology is accurate and reliable to use at altitude and in the air ambulance environment, it will result in better access to important medical information for the treatment of ambulance patients which could potentially save lives and reduce potential complications. The aim of this trial is to test the accuracy of this new non invasive method of measuring red blood cells (haemoglobin) while at altitude or in an air ambulance.

The Study:

Prior to the start of your altitude (hypobaric) chamber session a small blood sample will be taken. A small needle will be used to gain the blood sample, between 3-5 ml of blood will be drawn into a standardised blood test tube. There is a small risk of bleeding which is minimised by pressing on the puncture site for a short period after taking the blood sample. It will feel like a small scratch or a small insect bite, no more painful than having a standard blood test completed. The blood sample will be taken by a trained health professional that is qualified to complete this procedure. The blood sample will be tested to ensure your red blood cell (haemoglobin) levels are within normal ranges before for this trial. You will be taken to 12,000 feet inside the altitude (hypobaric) chamber and after a short period of time (about 10-15 minutes). During this time a finger probe will be placed on one of your fingers and this will also measure your haemoglobin level. A number of infrared lights will pass through your tissues and calculate the amount of haemoglobin in your blood; this is a totally painless procedure. The data from both tests will be recorded and the data will later be compared for agreement.

Study Risks: The study should not involve any risks for you.

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Participants in the study will not receive any payment.

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention, Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends upon a number of factors such as whether you are an earner or a non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is the result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators.

If you have any questions about ACC, contact your nearest ACC office of the investigator.

If you are currently serving in the New Zealand Defence Force (NZDF) you are covered by the NZDF workplace insurance.

Participation in this trial:

You are invited to participate in this trial and participation is entirely voluntary (your choice). If you do agree to take part in the study, you are free to withdraw from this study at any time, without having to give a reason. If you chose not to participate in this trial it will not effect your employment or your career management within the RNZAF.

General

Your participation in the study will be totally confidential.

Any results gained during the study will be available to you on request. Any abnormal results (measurements outside the normal range) will be passed onto the Base Medical Officer (BMO) or a clinical follow up appointment.

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If you would like more information regarding the study, then you are able to discuss the study with any of the investigators.

You may have a friend or member of your family present to help you understand the study.

You must fit and well to go into the hyperbaric chamber. If you currently have a cold or any respiratory illness (cough etc) you will need to be checked by a doctor before entering the chamber. Please inform the researchers if you need to be cleared or if you are unsure.

If you have any queries or concerns regarding your rights as a participant in this study, you may wish to contact an independent health and disability advocate
Free phone: 0800 555 050
Free fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz

Confidentiality

No material which could identify you personally will be used in any reports of this study. The data we collect will be stored on computer, but this data will not identify you, and will only be available to the study investigators. Once the study is finished, this data will be stored securely on CD-ROM.

This study has received ethical approval from the Northern X Regional Ethics committee.

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CONSENT FORM – Non invasive haemoglobin measurements at simulated altitude.

REQUEST FOR INTERPRETER

English	I wish to have an interpreter.	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.	Ae	Kao
Samoan	Ou te mana'o ia i ai se fa'amatala upu.	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea.	Io	Ikai
Cook Island	Ka inangaro au i tetai tangata uri reo.	Ae	Kare
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.	E	Nakai

- I have read and I understand the information sheet, version 2 dated 04 December 2009 for volunteers taking part in the study designed to evaluate haemoglobin levels at simulated altitude.
- I have had the opportunity to discuss this study I am satisfied with the answers I have been given.
- I have had the opportunity to use whanau support or a friend to help me ask questions and understand the study.
- I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time, and this will in no way affect my subsequent health care.
- I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study.
- I have had time to consider whether to take part.
- I understand that the investigation will be stopped if it should appear harmful to me.
- I have had time to consider whether to take part.
- I agree to my blood sample being destroyed at the end of this study.
- I agree to my doctor or clinical provider being informed of my participation in this study.
- I agree to my doctor or clinical provider being informed of the results of my participation in this study.

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I _____ (full name) hereby consent to take part in this study.

Signature _____ Date _____

This research is being conducted by:

Russell Clarke, student, Masters in Health Science endorsed in Aeromedical Retrieval and Transportation, University of Otago

Dr Ben Johnston, Aviation Medicine Officer, Royal New Zealand Air Force

Dr Rob Griffiths, Director Aeromedical and Occupational Medicine, University of Otago

Project explained by _____

Signature _____ Date_____

OCCUPATIONAL AND AVIATION MEDICINE UNIT
UNIVERSITY OF OTAGO, WELLINGTON
MEIN STREET, NEWTOWN. PO BOX 7343, WELLINGTON SOUTH 6242, NEW ZEALAND
TEL 64 4 385 5590 ● FAX 64 4 389 5427

MEDICAL QUESTIONNAIRE & DISCLAIMER FOR CIVILIAN HYPOXIA TRAINEES

NAME: _____

ADDRESS: _____

_____

_____

PART 1 – MEDICAL HISTORY

(*Delete any statements and discuss with the Medical Officer*)

1. I have attended lectures and briefings relating to Hypoxia Training at Aviation Medicine Unit
2. I understand the nature and risks of Hypoxia Training
3. I hold a current CAA Medical Certificate
4. I am currently well
5. I am not suffering from:
    a. A cold or flu
    b. Difficulty clearing the ears
    c. Asthma or a chest complaint
    d. Heavy menstruation
    e. Heart problems
6. I have not been SCUBA diving in the last 48hours
7. I have not been above 10,000ft (cabin altitude) in the last 24 hours
8. I am not on any medication
9. I am not pregnant
10. I have never had decompression sickness or similar problems
11. I will not fly for 12 hrs and I will not fly above 10,000ft (cabin altitude) for 24 hours

12. I consent to experience Hypoxia in the Aviation Medicine Unit Altitude Chamber

SIGNED: _____

DATE: _____

PART 2 – DISCLAIMER

I acknowledge that I am participating in hypoxia training of my own free will and entirely at my own risk. I accept that this training has inherent risk.

I understand that neither the Crown, the New Zealand Defence Force or the Royal New Zealand Air Force nor any officer or employee of the Crown of New Zealand Defence Force accept any liability whatsoever for any loss or damage whatsoever, including the loss of or damage to personal equipment, clothing or possessions generally, injury or death sustained as a direct or indirect result of any activity carried out during this training.

AND I unconditionally and irrevocably indemnify and hold harmless the Crown, the New Zealand Defence Force and its servants and agents against all claims, actions, suits, damages, liabilities, losses, demands, charges, proceedings, expenses and costs which the Crown, the New Zealand Defence Force and its servants and agents may incur or be put to as a result of my participating in Hypoxia Training.

I understand that I may not be eligible to receive ACC employment related compensation in respect of any injury I sustain in the course of participating in this training.

SIGNED: _____

DATE: _____