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Human Responses to Cold and Hypoxia: Implications for Mountaineers

A Thesis Presented for the Degree of Doctor of Philosophy

By

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"Would you know what it is to hope again
and have all your hopes at hand?
Hang upon the crags at a gradient that makes your next step a debate,
between the thing you are, and the thing you may become"

Scottish Mountaineering Journal

To my Grandfathers,

Georgios Katsigras & Vassilios *Tsianos*

Declaration

I hereby declare that this thesis has been conducted by me. All sources of information have been specifically acknowledged by means of references.

Georgios-Ioannis Tsianos

Acknowledgements

I am grateful to my supervisor-Stan Grant, assessor-Nanette Mutrie, the volunteers in my studies, as well as all University of Glasgow members of staff and outside collaborators who assisted and guided me throughout my Ph.D. research training. I have personally shown my appreciation to all. Finally, thank you to David Miller, an educator, a listener, and of course, director of the IBLS Graduate School.

Without a single doubt, my father and mother deserve my highest compliments.

I may not have gone where I intended to go, but I think I have ended up where I intended to be.

Thank you Scotland!

Contents

List of Abbreviations

ACE	*Angiotensin Converting Enzyme*
AMS	*Acute Mountain Sickness*
ANG I	*Angiotensin I*
ANG II	*Angiotensin II*
ANOVA	*Analysis of Variance*
BBB	*Blood Brain Barrier*
BC	*Base Camp*
BW	*Bubble Wrap*
^{o}C	*Degrees Celsius*
CBV	*Cerebral Blood Volume*
CNS	*Central Nervous System*
CO	*Cardiac Output*
CO_2	*Carbon Dioxide*
CI	*Confidence Interval*
CB	*Casualty Bag*
HA	*High Altitude*
HACE	*High Altitude Cerebral Edema*
HAPE	*High Altitude Pulmonary Edema*
Hb	*Haemoglobin*
HR	*Heart Rate*
HVR	*Hypoxic Ventilatory Response*
m	*Meters*
MPS	*Metallised Plastic Sheeting*
mmHg	*Millimetres of Mercury*
MOD	*Ministry of Defence*
O_2	*Oxygen*
P_aO_2	*Partial Pressure of Arterial Oxygen*
P_ACO_2	*Partial Pressure of Alveolar Carbon Dioxide*
P_AO_2	*Partial Pressure of Alveolar Oxygen*
$PETCO_2$	*Partial Pressure of End-Tidal Carbon Dioxide*
PO_2	*Partial Pressure of Oxygen*

RR	*Respiratory Rate*
SaO_2	*Arterial Blood Oxygen Saturation*
SD	*Standard Deviation*
SV	*Stoke Volume*
T_{core}	*Core Temperature*
T_{skin}	*Skin Temperature*
Vco_2	*Volume of Carbon Dioxide Produced*
V_E	*Minute Ventilation*
$VO_2 max$	*Maximal Oxygen Uptake*
VO_2	*Oxygen Uptake*

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Summary

This thesis is a compilation of 5 different projects. A brief summary for each project is presented below.

A Comparison of a Bubble-Wrap Bag and a Mountain Rescue Casualty Bag In a Cold Windy Environment

Reports from Norwegian mountain rescue teams suggest that one layer of bubble-wrap (BW) around a casualty requiring evacuation is useful in preventing loss of body heat. The aim of this study was to compare a BW bag against a previously evaluated casualty bag (CB) currently in use by some Scottish mountain rescue teams. Twelve male subjects [21±1.3 years, body mass 71.9±4.2 kg, % body fat 12.7±2.3% and height 177± 6 cm] each participated in 2 tests (one for each bag). Tests were carried out in a cold (-10°C), windy (wind speed 2.7 $m.sec^{-1}$) environment. The bags were compared using physiological and subjective responses of the participating subjects. The tests were scheduled to last 60 minutes. Core and skin site temperatures (chest, arm, thigh and calf) were recorded. Oxygen consumption (V_{O_2}), heart rate, subjective cold perception ratings and perception of shivering were also recorded at regular intervals throughout the tests. Confidence Intervals (95% CI's) showed that the mean skin temperature for the bubble-wrap was between 3.9 and 5.2°C lower than the casualty bag at 60 min. For Cold Comfort at 60 min, the bubble-wrap was between 0.7 and 3.3 units (95% CI's) higher (colder) than the casualty bag. There were no significant differences for drop in core temperature, V_{O_2} and heart rate. It was concluded that BW offers less protection against the imposed environment than the CB.

Factors Affecting a Climber's Ability to Ascend Mont Blanc

The aim of the study was to determine the factors affecting a climber's ability to ascend Mont Blanc (4807m) using a number of variables collected at the Gouter Hut (3817m) before and after an attempted ascent on the Mont Blanc summit. 285 subjects [49 females [35±11 years]; and 236 males [28±12 years]) were tested at 3817m prior to their ascent of Mont Blanc. Demographic information and height ascended in the past 14 days were recorded. End tidal CO_2 ($PETCO_2$), arterial oxygen saturation (SaO_2), heart rate (HR) and respiratory rate (RR) were measured using a Capnograph (Nellcor Patrick NPB75). Acute mountain sickness (AMS) scores were assessed using the Lake Louise scoring scale. Of the 285 subjects tested, summit information is available for 216 subjects. Of these, 198 are known to have reached summit, 12 are known to have failed, and 6 turned back in order to accompany a troubled friend. None of the subjects who attained 4000m in the previous 14 days failed to reach the summit. Previous recent exposure to an altitude of 4000m resulted in faster ascent times, higher SaO_2 and lower raw AMS scores than those who had not been above 3000m in the previous 14 days. Older climbers (>57 years) and females had slower ascent times than young males. Climbing Profile over the previous 14 days significantly affected the ascent outcome and ascent times. Recent exposure to over 4000m confers an advantage to those who wish to ascend a 4800m peak.

Performance at Altitude and Angiotensin Converting Enzyme Genotype

The 'insertion' (I) rather than 'deletion' (D) variant of the human Angiotensin Converting Enzyme (ACE) gene is associated with both lower tissue ACE activity and enhanced performance at high altitude. The aim of the study was to examine whether the onset of acute mountain sickness (AMS), and further performance on reaching the summit of Mont Blanc are influenced by the ACE I/D polymorphism. 284 climbers (86 DD, 142 ID, 56 II) had assessment of their AMS status and recording their physiological measurements ($PETCO_2$, SaO_2, HR, RR) upon arrival to

the Gouter hut (3807m) on Day 1, and again on Day 2 after an attempted ascent to the summit of Mont Blanc (4807m). Success in reaching the summit was genotype-dependent (88 % of DD, 95 % of ID, and 100% of II individuals; p=0.048); I allele frequency for those reaching the summit was 0.46 compared to 0.21 for those who did not (p=0.01). The onset of AMS on Day 1 appeared to be dependent on genotype (p=0.003), but with those heterozygous being less affected. ACE genotype was not associated either with AMS onset or severity on Day 2. Furthermore, the ACE I/D genotype was not associated with any of the tested physiological measurements on either Day 1 or 2. The II genotype is associated with successful high altitude ascent, albeit an association not explicable by genotype-dependence on AMS onset or severity.

The Effect of ACE Genotype and Hypoxic Ventilatory Response On Arterial Oxygen Saturation and other Physiological Measurements During a Staged Ascent to 5000m

The aims of this study were to consider the role of the ACE genotype on daily SaO_2, HR and AMS during gradual ascent to altitude (5000m). Furthermore, the speed of Hypoxic Ventilatory Response, measured during rest at sea level, was used to predict the daily physiological responses of SaO_2, HR, and AMS, while any ACE genotype related differences on HVR were considered. 55 subjects (33 males [36±12 years]; 22 females [32±6 years] members of a research expedition to Nepal, volunteered for the study. Their HVR and ACE genotype were determined prior the expedition, and their physiological measurements (AMS, SaO_2, HR) were recorded daily in the Nepalese Himalayas during a trek from Tumlingtar (330m) to Chamlang BC (5000m). It was found that the II genotype individuals had lower daily SaO_2 (a borderline significance p=0.4) contrary to previous research, whereas daily HR and AMS did not differ between genotypes. There were no differences in HVR by genotypes, and no differences were found in the daily values of SaO_2, HR, and AMS with respect to the speed of HVR. The slow ascent profile is likely to have acclimatized this group. Furthermore, the uneven genotype distribution (5 II, 19DD, 21 ID) may have tainted the results.

ACE Genotype and Mount Everest

The angiotensin converting enzyme gene has been previously associated with elite mountaineering status. We sought such an advantage in a prospective study of those attempting the ascent of the highest mountain on earth, Mount Everest (8850m). 64 high altitude mountaineers (58 males [36± 8.8 years] 6 females [33.1± 4.6 years]) were recruited from both Everest base camps (North side-Tibet and South side-Nepal) prior to their summit attempts in the spring of 2004. Their ACE genotype was determined, and their performance on the mountain recorded. Amongst successful summiteers (n = 42), genotype distribution was: 10 DD [24%], 22 ID [52%], 10 II [24%]; I allele frequency 0.50, and in those who failed (n=22) 4 DD [22 %], 10 ID [53%], 8 II [25%]; I allele frequency 0.59. There were no genotype differences in those who succeeded vs. those who failed, p=0.56. Although suggesting that ACE genotype may have little influence upon mountaineering success, these data may be misinterpreted by the use of supplementary oxygen (in all those summiting). Finally, it may be that ACE genotype influences success more when acclimatisation time has been limited. Further investigations are required.

Thesis Results

Chapter 2:
G. Tsianos, I. Watt, T. Aitchison, S. Grant. *A Comparison of a Bubble-Wrap Bag and a Mountain Rescue Casualty Bag In a Cold Windy Environment.*
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Chapter 3A:
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Presented at: Scottish Pulmonary Vascular Unit, Glasgow, 2003.
13th International Hypoxia Symposium, Banff, Canada, 2003.
Currently under review: European Journal of Applied Physiology.

Chapter 3B:
G. Tsianos, K. Eleftheriou, E. Hawe, L. Woolrich, M. Watt, I. Watt, A. Peacock, H. Montgomery, S. Grant. *Performance at Altitude and Angiotensin Converting Enzyme Genotype.*
Presented at: VI World Congress on Mountain Medicine and High Altitude Physiology, Xining-China & Lhasa-Tibet, 2004.
Accepted for publication: European Journal of Applied Physiology

Chapter 4:
G. Tsianos, J. Milledge, D. Collier, S. Grant, H. Montgomery. *The Effect of ACE Genotype and Hypoxic Ventilatory Response on Daily Arterial Oxygen Saturation During a Staged Ascent to 5000m.*
Presented at: 14th International Hypoxia Symposium, Lake Louise, Canada, 2005.

J. Milledge, G. Tsianos, P. Richards, P. Seal, J. Leverment, M. Morrell, A. Nickol, D. Collier. *Are Periodic Breathing and Acute Mountain Sickness Dependent Upon the Hypoxic Ventilatory Response?*
Presented at: VI World Congress on Mountain Medicine and High Altitude Physiology, Xining-China & Lhasa-Tibet, 2004.

Chapter 5:
G. Tsianos, A Mynett, T Hubbart, S Grant, H Montgomery. *ACE Genotype and Mount Everest.*
Presented at: 14th International Hypoxia Symposium, Lake Louise, Canada, 2005.

CHAPTER 1

General Introduction

1.1 Of Men and Mountains

Figure 1.1 Mount Everest, 8850m

"My darling, this is a thrilling business altogether. I can't tell you how it possesses me, and what a prospect it is. And the beauty of it all!"

George Leigh Mallory, 1921, who disappeared during the British 1924 Mount Everest summit attempt (National Geographic).

When one considers that a mountain represents something quite different from a pile of rocks to a mountaineer, only then one might ponder on the complexity of why men attempt to 'conquer' the mountains. Symbolically, a mountain will represent different things to many: challenge, courage, self-affirmation, self-discovery, accomplishment, life statement, or recognition to name a few. The concept of a 'death wish' should also be mentioned if one supports such an idea.

"The fact that either you or one of your companions may have the possibility of dying, not only doesn't stop you doing it, but it's almost one of the things that keeps you going"

Sir Edmund Hillary, first to successfully summit and descent Mount Everest along with Tenzing Norgay in 1953 (National Geographic).

To the ancient Greeks, Mount Olympus, 2917m, was the abode of the 'Gods' and any mortals venturing there, did so at their own peril. Our appreciation for the hazards in mountainous regions has changed over the centuries, and nowadays they have become the homes of many people as well as a leisure escape for others. With the increasing

popularity of climbing and hiking on mountains, hills and moorlands, the risks for casualties from injury, exposure, and high altitude, are increasing as well.

In spite of good judgment, accidents do happen and the hazards of mountainous activities include: slips on footpaths or rocks, falls caused by pitons pulling out, unexpected equipment failure, injuries from falling stones are common, as are disasters from occasional avalanches. A major concern in the mountains is hypothermia resulting from the cold, wind, and rain.

A high mountainous environment presents not only weather exposure problems but also others associated with hypoxia. Scientific interest in the physiological alterations due to high altitude boomed in the last century as climbers were exploring and climbing higher and higher mountains. High altitude laboratory and field studies, as well as high altitude research expeditions, ever since the late 1800's to the present day, have been trying to explain hypoxia's mysteries (West, 1998).

The human physiological limits were the one factor that preoccupied many, but as history has it, individual human physiology overcame scientific hypotheses and predictions. The two biggest milestones in the modern history of climbing as well as high altitude physiology were the first ascent of Mount Everest (8850m) by Sir Edmund Hillary and Tensing Norgay in 1953, and the first ascent of Mount Everest without the use of supplementary oxygen by Reinhold Messner and Peter Habeler in 1978. However, similar attempts, as well as the pursuit of other mountaineering accomplishments, have resulted in the loss of many lives. Recently, the role of genetics has been implicated in the ability of certain individuals to perform more efficiently under a hypoxic environment and thus possibly, allowing for a selective advantage. In particular the mechanisms that regulate our response to low oxygen are influenced by small (and common) variations in our genes. If it can be show that one version of a gene is more common amongst mountaineers than in the normal population, it could then be suggested that this very gene may have an important role in adapting to low oxygen. The gene focus in this thesis is on the Angiotensin Converting Enzyme (ACE) gene.

1.2 Hypothermia

One of the primary risks associated with mountain accidents is hypothermia. The hypothermic effects on the individual's physical and mental state may be the primary reason why subsequent accidents happen. Ultimately, alteration of these two states can be detrimental to survival.

Hypothermia (hypo-, below & therm-, temperature) literally means low body core temperature and results from a fall in normal core temperature. Body core temperature in man is regulated around 37 Celsius (°C) by balancing the heat lost or gained. The body is divided into two different functional compartments: the 'core' and the 'shell'; the distinction is much more conceptual than anatomical. The core includes the deep regions of the body including the brain and other vital organs, and constitutes about 60% of the total body mass. The shell includes peripheral tissues such as the skin, subcutaneous tissues, and muscles, all of which make up the remaining of the body mass. Skin temperature is variable throughout the body depending on the site at which it is measured, while the mean skin temperature is calculated by weighting the regional temperatures for the areas measured (Burton and Edholm, 1955). Skin temperature is very variable and low values do not necessarily indicate hypothermia. In naked man, skin temperature is very much dependant upon the environmental conditions and its values will vary according to the body's responses.

1.2.1 Hypothermia Definitions

Core temperature in man has a diurnal variation of 1 to 2°C and therefore normal core temperature of an adult human has a range between 36 and 38°C (Clark & Edholm, 1985). For clinical purposes, and as defined by the Royal College of Physicians Committee on Accidental Hypothermia, core temperature must drop below 35°C to signify hypothermia (Lloyd, 1986). The clinical stages of a hypothermic individual adopted by the Medical International Committee on Alpine Rescue are as follows (Marsigny, 2001):

1. 35-32°C: clear consciousness with shivering (no hospital treatment)
2. 32-28°C: impaired consciousness without shivering (hospital treatment)

3. 28-24°C: unconscious, aggressive treatment and rapid transport
4. 24-15°C: appears dead, may be revived in some cases
5. <15°C: death likely due to irreversible hypothermia

1.2.2 Physiological Responses to Cold

In low ambient temperatures the body's physiological mechanisms will attempt to maintain normal core temperature both by restricting heat loss and increasing the rate of heat production. Physiological responses to help maintain core temperature and protect the individual, include:

Peripheral Vasoconstriction

Vasoconstriction is a reflex mechanism prompted by information gathered from both central and peripheral thermoreceptors. Once these receptors sense a temperature drop, the hypothalamus causes an adrenal release of noradrenaline. Noradrenaline acts on the peripheral blood vessels (smooth muscle of arterioles) resulting in vasoconstriction. The effect will be a decreased blood flow peripherally, primarily to the cutaneous circulation and to non-exercising muscle. The alteration in blood flow will produce a cold shell, which in effect encapsulates the warm core resulting in a reduced skin/environment temperature gradient and thus minimizing heat loss (Toner, 1988).

Increased Physical Activity and/or shivering

Increased voluntary physical activity, such as walking, running, or swimming, will increase the rate of heat production which may then effectively balance the heat loss in the body. Shivering, on the other hand, is an involuntary physiological mechanism, and will initially compensate for the heat lost at low ambient temperatures. The skeletal muscles contract and relax asynchronously in shivering, and as there is no purposeful movement in this process, the main objective is to increase heat production. The heat produced by the body, through any means, will aid in the maintenance of a 'normal' core temperature; although, as blood flow increases to the muscles heat loss will also increase and thus high intensity activity cannot be

sustained for long periods of time. Sometimes when the cold stress is great enough, heat balance is not achieved, and despite exercise, hypothermia is unavoidable.

1.2.3 Heat Balance

To maintain heat balance in the core, heat production must equal heat loss. If core temperature is to be maintained at equilibrium, the rate and amount of heat produced internally, must be exactly the same as the rate and amount of heat lost through convection, conduction, evaporation, and radiation from the body surface. If balance is not achieved for example, when the environment is too cold, either by a failure to conserve heat or to increase heat production, then a drop in core temperature will be observed.

The rate of heat loss in the individual will determine how fast hypothermia sets in. Continuing to exercise/walk vigorously, if it is not too cold, will protect against the development of hypothermia. The individual who maintains a high rate of body heat production through physical activity that equals or exceeds the rate of heat loss from the body will maintain heat balance. However, once one fatigues and slows down the pace of activity or stops altogether, the rate of heat production falls dramatically, and hypothermia will most likely develop. In such cases, the individual's hypothermic state is classified as *accidental*.

There are a number of characteristics associated with hypothermia, though not all may be present in all cases, the sequence of events is usually as follows: The affected person begins to slow down and lag behind. He is clumsy, stumbles, and falls frequently. Mental changes are common including apathy, incoherence, lack of co-operation and slurred speech. Muscular weakness, cramps, and collapse may follow. Death could be the final outcome (Pugh, 1966).

Heat loss can be effectively prevented through the use of clothing. Appropriate clothing can increase the body's insulation by means of a protective barrier between the body surface and the outside environment, thus allowing a state of homeothermia (Gonzales, 1988). However, when the clothing becomes wet it loses its insulative

capabilities (Pascoe, 1994), and the subsequent heat loss increases further as water conducts heat twenty-five times more than air.

1.2.4 Exposure Hazards

Some of the causes that would make a hill-walker, climber, or anyone else in the mountainous environments susceptible to exposure hazards are the following (Pugh, 1966):

- weather conditions-- overtaken by harsh conditions e.g. cold, wind, rain, snow
- being benighted--not having the appropriate equipment for night survival
- insufficient clothing--inadequate protection for cold, wet, and windy conditions
- exhaustion--muscular weakness and inability to continue on and/or to find shelter
- inexperience--lack of training, errors in judgment during hazardous situations
- inadequate body insulation--when insulation is diminished through wet clothing is diminished or in the absence of appropriate clothing, inadequate thickness of subcutaneous fat will make one even more susceptible to hypothermia

A classic and well documented sequence of events leading to accidental hypothermia is exemplified in the 1964 Four Inns Walking Competition in Derbyshire, UK, as described by Pugh (1964a). The event was held over 2 days and started at 06:00 hrs on the 14th of March 1964 with 80, three-man teams leaving at 2-minute intervals. The temperatures for that day were estimated to be between 1 and 4°C with and a wind speed of 25 knots (12.9 m$\cdot$sec^{-1}), but much stronger in the hills. By 13:15 hrs the first updates were received that some hikers were in trouble. By late afternoon five distressed hikers had been brought to safety; one subsequently died. The bodies of a further two hikers were found 2 days later, after a search was conducted by some 800 persons.

Although there were only 3 fatalities, the common features were:

- Their clothing was inappropriate for the conditions as none had waterproof outer garments such as oilskins. Any minimal insulation initially provided from their clothing was subsequently lost.
- As the insulating properties from their clothing were lost, subcutaneous fat was the only remaining insulator. In their case, were lean with little subcutaneous fat.
- They collapsed around 2 hrs after the initial fatigue symptoms set in. On the other hand the participants who finished the event were able to maintain high rates of energy expenditure, and hence high rates of heat production, for the duration of the event.

1.2.5 Mountain Rescue

When accidents happen in the hills or mountains the first to provide specialised help to the victim is usually a mountain rescue team. Most mountain rescues involve lengthy searches, carrying heavy equipment and casualties on stretchers for prolonged periods, and often in severe weather conditions. Mountain rescue teams around Britain undertake approximately 800 critical rescues a year (Mountain Rescue Council, 1998). Scottish mountain rescue call-outs are frequent. In the four-year period from 1996 to 1999, there were 1027 incidents involving 1269 people. More than half of these individuals had some form of an injury, and eight per cent of the casualties were deemed to be hypothermic (Sharp, 2001). In Scotland alone, over 30 fatalities occur yearly arising from mountain accidents (Hearns, 2000).

A major problem is finding the victim, but once located by the rescue team and treated for the sustained injuries, mountain rescue missions will most likely result in an efficient and safe evacuation of the casualty (Waddell, 1975). He/she is placed inside a rescue casualty bag (injury permitting) before being laid onto a stretcher to be carried down. The casualty bag can reduce heat loss in the victim, offering protection from environmental conditions until taken to safety.

1.2.6 Rewarming

The primary objective in the treatment of hypothermia is to rewarm the patient as safely and efficiently as possible (Dexter, 1990). The field management of a hypothermic victim requires re-warming techniques. Depending on the situation, weather conditions, and the victim's physical state, the rewarming methods can either be passive or/and active (Snadden, 1993):

Passive re-warming

Removal of the victim from the possibly exposed accident site, and transfer to a protected and safe location, will allow for core temperature to rise; this may take some time.

Active re-warming

The victim is re-warmed through the use of external means such as blankets, heat bags, airway rewarming technique, or water immersion into 40-45°C, however the latter may prove impractical in the field. Active re-warming should be a stepwise process and not an immediate and fast one. One of the dangers of rapid active re-warming of the body's surface will cause vasodilatation in the peripheries, and thus transfer of cold blood back to the core. In light of that, further cooling of the core, known as the 'after-drop', is likely to occur with the possibility for ventricular fibrillation resulting from chilling of the heart (Snadden, 1993).

1.2.7 Equipment For The Management of Hypothermia

The first aid management of accidental hypothermia in a remote location poses many problems for the rescuers. Treatment at the accident site or immediate evacuation often proves to be a critical decision. Irrespective however of the decision made, the casualty will have to be transferred to a hospital after rescue. It is important therefore to provide adequate external insulation to prevent further heat loss and a possible worsening of the casualty's condition. Such insulation can be provided by means of a casualty bag. During the 1997 Accidental Mountain Hypothermia conference in Scotland, the use of casualty bags was emphasized (Grant et al, 1998). As they probably are one of the most important equipment in keeping a rescued hypothermic victim alive, obtaining information about the effectiveness of casualty bags is

important. It was concluded that the need to test for casualty bag effectiveness is essential so that the more efficient bags can be selected for use (Grant et al, 1998).

Space Blanket

A few decades ago, the development of a revolutionary item became very popular in the treatment of a hypothermic victim; the 'space blanket'. The space blanket was developed in the 1960's to originally fulfill an 'insulator' role for industries and organizations. It is constructed of a sheet spattered with aluminium to make up a metallised plastic sheeting (MPS) otherwise known as space blanket and was introduced in the 70's for survival purposes (Chadwick and Gibson, 1997). The main heat loss avenue from the body on land is through convection, but the space blanket works by reflecting radiated heat, and whereas its an excellent insulator in the vacuum of space, theoretically it may also reflect the very small amount of infrared radiation emitted by the skin provided the vacuum can be maintained on land (Royal Air Force Institute of Aviation, 1976). Even though the space blanket is still widely used in hospital settings, review reports by Chadwick and Gibson (1997) clearly highlight that use of the space blanket is unlikely to make a meaningful contribution to the well being of the patient.

Casualty Bags

Ever since the emergence of the space blanket, bags and blankets of different makes, shapes and sizes have been developed and tested. Early developments were metallised plastic sheeting bags (Light and Norman, 1980), heavy-gauze polythene bags (bivouac bag) (Grieve, 1969; Light et al, 1980), or the more recent ones consisting of nylon and/or neoprene outer shell with or without fleece material inner lining (Grant et al, 2002). Research results provide information on which bag or blanket would protect and insulate a victim more effectively. The latest study on casualty bags, currently used by mountain rescue teams, was performed by Grant et al, (2002) who evaluated on their insulative properties by investigating the physiological responses of the participating subjects.

Some researchers may question the use of human subjects in such trials and could propose other forms of experimentation in assessing bag efficiency; those include the use of a physics laboratory for the evaluation of the best equipment in terms of

superlative insulative properties, or even the use of manikins instead of humans. However, information from such research would be of quantitative only value. The ultimate validation of any insulative equipment used by man, relies on testing with humans under actual conditions of intended use (Pascoe, 1994). It is only through this research methodology that subjective feedback and actual physiological responses can be gathered with great accuracy.

It seems though that not all rescue teams adopt the same equipment. In order to protect the victim, an effective casualty bag should have certain characteristics; it must be windproof, waterproof, and provide significant additional thermal insulation. The properties of the bag must be of high standard such that will protect a hypothermic victim. However, ideas for casualty bags made from different materials are constantly evaluated and put into effect. Therefore, the need for further testing is important in order to ensure the effectiveness of new equipment.

Bubble-Wrap Bag

Mountain rescue teams in Norway have adopted the use of bubble wrap as casualty bag material to protect their casualties. Its use may be advantageous as it is very cheap to make and very light to carry to rescue missions. However, no scientific research has thus far tested its effectiveness. Anecdotal evidence from Norwegian rescue teams suggests that bubble wrap has had satisfactory performances during their rescue missions. It is one of the aims of this thesis to test whether this is true.

1.3 Altitude Hypoxia

At altitude there is less oxygen for the same volume of gas than at sea level, despite a constant percentage of oxygen in inspired air (20.93%). Altitude hypoxia results from a decrease in barometric pressure with increasing altitude, and can be described as the less than normal-sea level amount of oxygen in the inspired air (Figure 1.2).

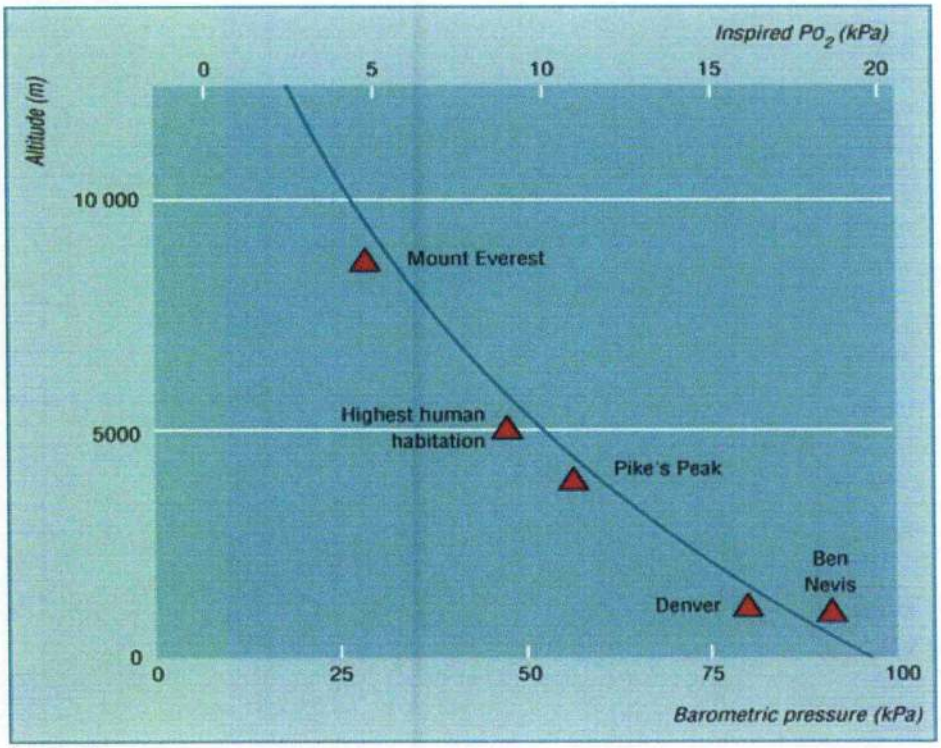


Figure 1.2 Relationship between altitude and inspired oxygen pressure (West, 1979).

Partial pressure of oxygen (PO_2) falls as oxygen is transported from ambient, to inspired, to alveolar, to arterial, and finally to mixed venous, forming a cascade of O_2 (Ward et al, 2000). These oxygen decrements are further exaggerated at altitude due to the decreased barometric pressure, Figure 1.3. The PO_2 in the mixed venous blood is maintained at approximately the same values in both at sea level and altitude; this is achieved through certain processes and changes in the physiology whilst at altitude.

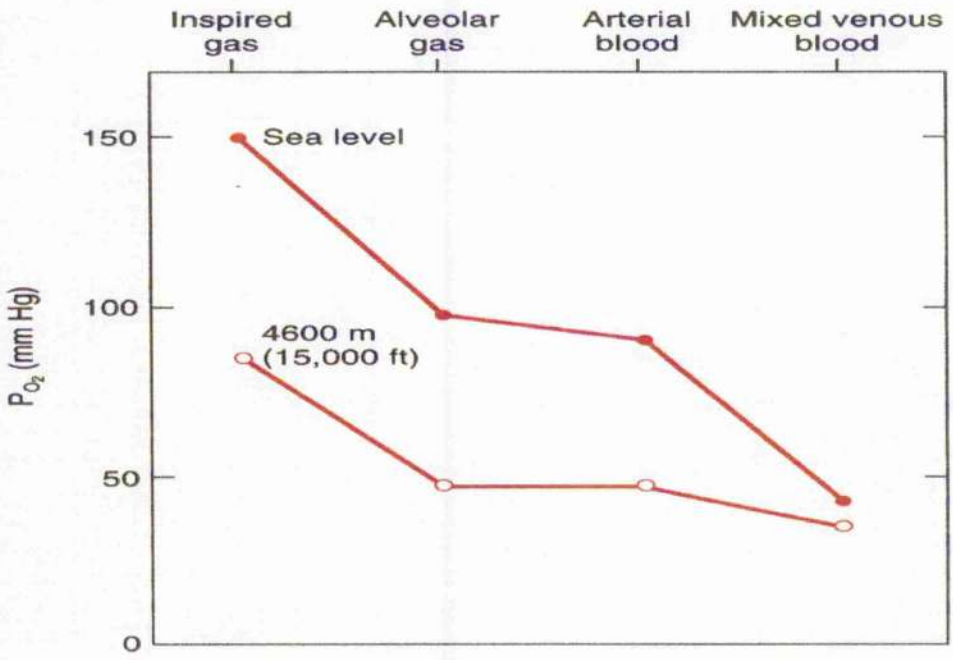


Figure 1.3 PO_2 values from inspired air to mixed venous blood a sea level and in residents at an altitude of 4600m (West, 2000).

1.3.1 Physiological Changes At Altitude

Exposure of sea-level residents to altitude evokes a series of physiological responses. In conditions of hypoxia the lungs *must* take in a greater total volume of air in an attempt to compensate for the decreased oxygen levels (West et al, 1983; Sutton et al, 1988). The most important physiological change during exposure to hypoxia is an increase in minute ventilation, otherwise called hyperventilation. The organ responsible for sensing the hypoxic condition is the carotid body. Situated above the bifurcation of the common carotid artery, the carotid body has a large blood flow and responds to decreased levels of oxygen in the arterial blood (P_aO_2), high CO_2, and low pH, while it plays an important role in the ventilatory acclimatization to hypoxia. Hyperventilation will aid in increasing alveolar oxygen levels (P_AO_2) following a decrease in ambient PO_2 when exposed to altitude. The degree of hyperventilation is represented by the value of alveolar carbon dioxide levels (P_ACO_2); as ventilation increases, P_ACO_2 values will decrease (West, 1993), and can experimentally be measured through the value of end tidal carbon dioxide ($PETCO_2$). $PETCO_2$ drops immediately with altitude exposure, and gradually continues to do so, as ventilation increases over time whilst staying at altitude, Figure 1.4.

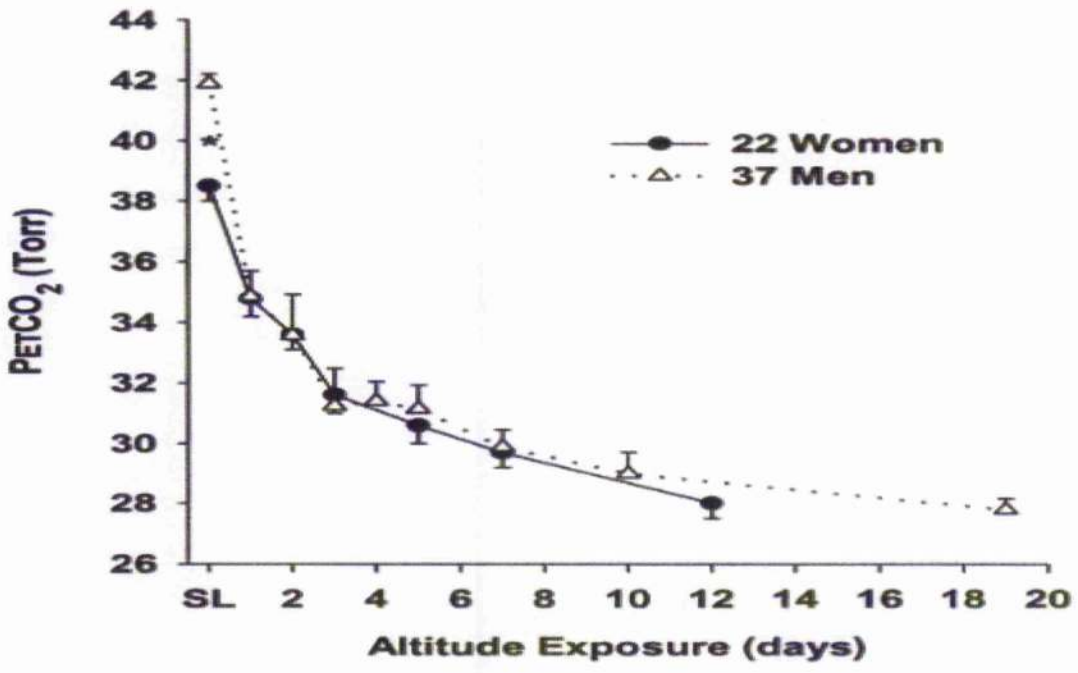


Figure 1.4 Resting $PETCO_2$ for 2 groups measured at sea level and during 12 and 19-day sojourns at 4300m. Values decrease due to hyperventilation (Muza et al, 2001).

Once the decreased PO_2 is sensed by the carotid bodies, the respiratory adjustments will take place through chemo-reflex pathways, while the reflexive increase in ventilation induced by hypoxia, is called the hypoxic ventilatory response (HVR). The increase in ventilation varies from individual to individual but does not usually start until about 3000m (Rahn and Otis, 1949). A brisk HVR on ascent to altitude will result in increased arterial oxygen saturation (SaO_2) and may therefore aid in improving performance (Schoene et al, 1984).

SaO_2 is the percentage of haemoglobin (Hb) that carries oxygen in the blood. The degree of arterial hypoxia can be measured by the SaO_2 value, and whilst at altitude (exemplified by a fall in PO_2) the saturation percentage falls. The major haematological adjustment at altitude is the increase in the Hb concentration in the blood (Pugh, 1964). Initially, Hb concentrations rise through a fall in the plasma volume due to dehydration caused by respiratory fluid loss, perspiration or diuresis. Later on though, hypoxia stimulates production of the hormone erythropoietin by the kidney, allowing Hb production to increase, leading to its concentration in the blood to rise, and resulting in an increased oxygen supply to the hypoxic tissues.

The physiological changes at altitude will aid in the individual's acclimatization to altitude. Altitude acclimatization refers to the beneficial series of physiological changes over time by which un-acclimatized individuals respond to the reduced inspired PO_2. As previously mentioned, and further summarized in Figure 1.6, hyperventilation will help maintain P_AO_2 at high enough levels in the face of falling inspired PO_2, which in turn will increase P_aO_2 thus having a direct effect achieving a raised S_aO_2. Gradual renal compensation, due to respiratory alkalosis, is another physiological change aiding in acclimatization. With the consequent increase in ventilation at altitude, arterial pressure levels of carbon dioxide will fall producing a respiratory alkalosis, an increase in pH. The kidneys then respond to the change in pH by excreting bicarbonate in urine, pH will decrease to such levels that there is less inhibition on the respiratory centers, and thus ventilation is increased to compensate towards higher pH levels again. On ascent to altitude, cardiac output (CO) will increase via an increase in heart rate so that more blood is moved rapidly to the tissues and thus increase O_2 delivery, though at high altitude (HA) each unit of blood carries less O_2. Over time however, CO returns to normal values as a higher O_2 extraction

from the blood is achieved. Capillary density increases and enhances O_2 diffusion to the muscles, whereas O_2 supply is further aided via the increased oxygen carrying capacity in the blood due to the increased Hb concentration.

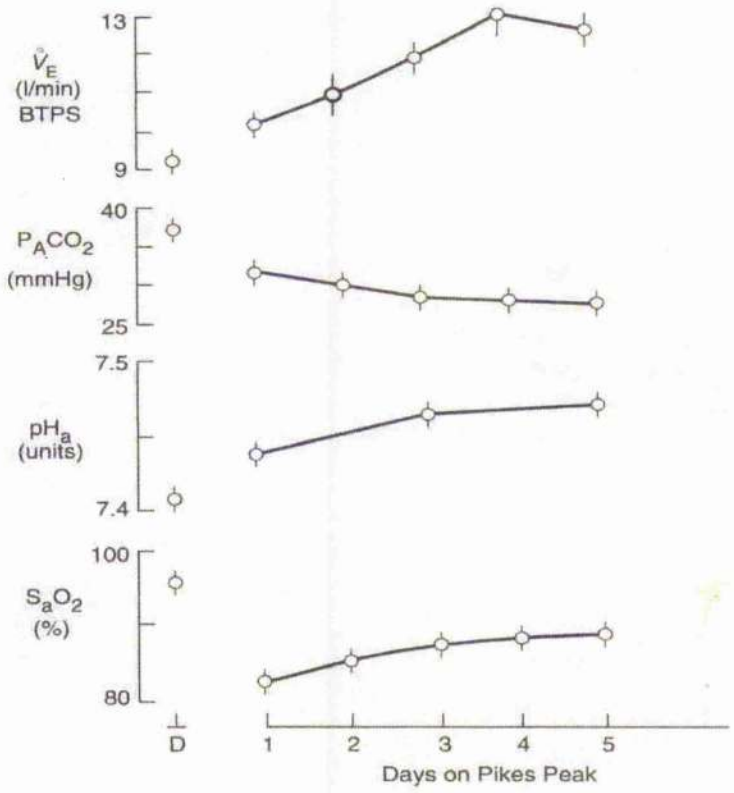


Figure 1.5 Mean changes in several variables relating to ventilation in subjects at Denver (D), 1600m, and first 5 days at an altitude of 4300m on Pikes Peak (Huang et al, 1984).

Nevertheless, at high altitudes of around 5000-6000m, one will not keep acclimatizing indefinitely to hypoxia, and as stay is prolonged, physical fitness starts to deteriorate (Pugh, 1962). This deterioration is characterized by mental and physical function

decrements such as loss of appetite, fatigue, lethargy, mental slowness, poor judgment. As humans are truly at their physiological 'ceiling' at extreme altitudes, time spent in the 'death zone', 8000m and above, should be as minimal as possible as deterioration can be severe (West, 1993).

The factors crucial to the success or failure of acclimatization are the speed by which one is exposed to hypoxia (rate of ascent), the severity of hypoxia (altitude change), as is the 'unique' physiology each individual has (Houston, 1982). Inadequate acclimatization will most likely result in Acute Mountain Sickness (AMS).

1.3.2 Acute Mountain Sickness (AMS)

The first known written report available about mountain sickness has its origins in China, and was reported by Too Kin, a Chinese official, in 37-32 B.C. The translation from the Chinese reads:

"Next, one comes to Big Headache and Little Headache Mountains, as well as Red Earth and Swelter Hills. They make a man so hot that his face turns pale, his head aches, and he begins to vomit. Even the donkeys and swine react this way"

(Gilbert, 1983).

AMS poses a significant risk to those individuals who venture to the high mountains. Of those traveling to altitudes between 2000-3000m, about 12-42% will succumb to the hypoxic stresses and develop Acute Mountain Sickness (Houston, 1985; Montgomery et al, 1989; Maggiorini et al, 1990; Honigrman et al, 1993). AMS is a self-limiting condition, which occurs to some degree in all un-acclimatized individuals who rapidly ascend to high elevations. The symptoms of AMS usually become evident after 6-12 hours of exposure (Ward et al, 2000), and reach their maximum severity during the first and second day after exposure (Carson et al, 1969). High altitude headache is the most prominent symptom in AMS (Honigrman et al, 1993) while the other common symptoms are nausea, anorexia, insomnia, fatigue, vomiting and dizziness (Hackett et al, 1976).

As agreed upon at the 1993 International Hypoxia Symposium at Lake Louise, Canada, AMS is diagnosed when an individual has a headache and at least one more symptom due to a recent ascent in altitude. A diagnostic AMS scoring scale (Appendix A) was further proposed (Roach et al, 1993). Prior to that, classification of AMS during scientific research usually depended on the protocol of the study and the investigator's personal assessment of the tested individual's physiological status. The Lake Louise consensus AMS scoring scale has since then been validated and found effective in assessing the incidence of AMS (Maggiorini et al, 1998).

As previously stated the incidence and severity of AMS will depend on the ascent profile, particularly the rate of ascent and total height difference achieved. In skiing resorts in Colorado, at altitudes between 2000 and 2800m a 12% incident was observed (Houston, 1985). In the Southern Alps of New Zealand, around the region of Mount Cook (3754m), there was a 26% incidence of AMS, with the incidence rising to 50% for those who slept above 2500m (Murdoch and Curry, 1998). In the Swiss Alps at refuge huts the incidence of AMS was 9% at 2850m, 13% at 3050m, 35% at 3650m, and 53% at 4559m (Maggiorini et al, 1990). In the Nepalese Himalayas (Pheriche, 4243m) it was found that 43% of the trekkers were affected (Hackett et al, 1976). Moreover, at the same location, the incidence was higher in those who started their trek at 2800m (Lukla airport) than those who trekked from 1200m (Kathmandu), 49% versus 31% (Hackett et al, 1976). Despite the current knowledge on the illnesses caused by high altitude hypoxia the reasons why some subjects are more susceptible to HA illnesses still remain unclear.

1.3.3 Arterial Oxygen Saturation and Acute Mountain Sickness

AMS severity has been correlated to the levels of SaO_2; the lower the SaO_2 the higher the degree of AMS. On arrival to an altitude of 4200m, low SaO_2 measurements are associated with a higher AMS onset (Basnyat et al, 1999) and are a good predictor for subsequent AMS development (Roach et al, 1998), as are low levels during normobaric or hypobaric exposure to pikilocapnic hypoxia (Burtscher et al, 2004), or even nocturnal levels the night of arrival at an altitude of 4459m (Erba et al, 2004). However, one study has failed to show a correlation between low SaO_2 levels and AMS at an altitude of 3080m (O'Connor et al, 2004). Low arterial oxygenations at altitude have been attributed to hypoventilation (Hackett et al, 1982; Moore et al, 1986) and impaired gas exchange (Kronenberg et al, 1971; Sutton et al, 1976). Moreover, SaO_2 further decreases with exercise at high altitude (West et al, 1983) and such worsening hypoxemia have been attributed to both ventilation/perfusion inequality and diffusion limitation in the lung (Wagner et al, 1986; Wagner et al, 1987). Even though the decrease of SaO_2 with an increase in altitude is an immediate one, the onset of AMS symptoms is not as rapid.

1.3.4 Hypoxic Ventilatory Response (HVR) And Acute Mountain Sickness

It seems appropriate to infer that increased ventilation at altitude through a brisk HVR and a consequent increase in SaO_2 levels, would protect one from AMS and enhance performance at altitude (Schoene et al, 1984). The documented findings however are divided with either a positive evidence for an HVR-AMS correlation (King and Robinson, 1972; Moore et al, 1986) or a lack of it (Milledge et al, 1988; Milledge et al, 1991; Bartsch et al, 2002). High altitude residents have a blunted HVR response (Severinghaus et al, 1966; Milledge and Lahiri, 1967) yet seem to be less affected by AMS to the same degree as lowlanders when venturing to altitude. To make matters more confusing, it has been shown that high altitude climbers have a more brisk HVR when compared to non-climbers (Schoene et al, 1982) but, it is interesting to mention that one of the first two climbers to reach the summit of Everest without the use of supplementary oxygen had a blunted HVR (Schoene et al, 1987).

1.3.5 Acute Mountain Sickness Susceptibility And Prediction

The incidence of AMS appears to affect from about a quarter of the people who travel to high altitude at around 2500m to almost half at around 4000m. The physiological responses between individuals at altitude do not seem to be consistent (Murdoch, 1999). Susceptibility most likely depends on the individual and there is no easy way to identify and predict who will succumb to the ill effects of hypoxia. Athletic fitness and an increased aerobic capacity do not make one 'safe' from AMS onset (Savourey et al, 1995). Anecdotal evidence reports that many elite athletes and physically fit individuals are more prone to AMS than are relatively unfit people when both ascending the same mountain. It is likely that fit mountaineers may overexert themselves more readily without paying attention to any warning symptoms of AMS and therefore are at a higher risk of developing the sickness. A similar distribution for AMS incidence has been reported between males and females (Hackett et al, 1976; Hackett, 1980), whereas older people tend to be less susceptible than younger ones (Roach et al, 1995). As climbing mountains is a vigorous exercise, high intensity exercise has been shown to further exacerbate AMS symptoms (Roach et al, 2000).

Prediction of susceptibility on the incidence of AMS through various physiological measurements has been attempted through various laboratory and field studies. Because AMS susceptible individuals may have low ventilation at altitude, HVR has been investigated whether or not it can predict AMS, as previously discussed (1.3.4). Other investigators have proposed alternative methods for predicting AMS and have showed positive correlations with low end-expiratory PO_2 in normoxia (Savourey et al, 1995), short apnea time and a hypersensitive gag reflex (Austin and Sleigh, 1995), or ventilation measurements in acute normobaric hypoxia (Hoefer et al, 1999); however, their methods are questioned for their validity and sensitivity, and their findings have yet to be reproduced (Bartsch et al, 2001). Grant et al, (2002) attempted to predict AMS at altitude from physiological variables measured in acute normobaric hypoxia, but the results offered limited predicative information. Measurement of the arterial oxygen saturation (SaO_2) upon arrival at altitude has also been implemented as means of predicting consequent AMS (Roach et al, 1998), although the specific study results are only applicable for the tested altitude as SaO_2 levels vary at different altitudes.

1.3.6 Acute Mountain Sickness Treatment

AMS is a self-limiting condition and relatively well tolerated. Prophylactic treatment through the use of drugs is not usually taken up, as most cases will improve after 24-48 hours (Ward et al, 2000). However, therapy for those with a history of AMS is recommended. Acetazolamide (Diamox), a carbonic anhydrase inhibitor, is the medication of choice. It has been shown to be effective for the prevention of AMS through an increase in ventilation (Greene et al, 1981). The usual oral dose is 250mg every 8-12 hours, starting one day before ascent and continuing for 48-72 hours at altitude (Greene et al, 1981). High altitude headache can be effectively treated with paracetamol. If symptoms arise, ascent should be stopped until they resolve, but if they persist a short descent of about 500m should be implemented until they disappear (Peacock, 1998).

1.3.7 Central Nervous System (CNS) Model Of AMS Pathophysiology

Alternative attempts to determine the development of AMS have been suggested. The most recent attempt to explain the pathophysiology of AMS is through a CNS model (Roach and Hackett, 2001). Hypoxia will cause swelling of the brain. This swelling has been attributed to development of cerebral oedema (Hackett et al, 1998), an increase in blood brain barrier (BBB) permeability (Abbott and Revest, 1991), and possibly an increase in cerebral blood volume (CBV) (Roach and Hackett, 2001). At the same time, peripherally, there is an increase in extra-cellular water levels and once at the brain level intracranial pressure develops by means of compression to the brain. Inability to buffer the pressure through cerebrospinal volume capacity (Shapiro et al, 1980) will most likely cause AMS symptoms. The current and future technological experimental techniques may make it possible in the near future to prove whether or not this model can be verified. The "tight fit" hypothesis of Ross (1985) that anatomical differences, smaller intracranial and intraspinal fluid capacities, could justify the unsystematic nature of AMS susceptibility in individuals is very attractive, yet not experimentally proven.

1.3.8 High Altitude Pulmonary And Cerebral Edemas (HAPE and HACE)

Ascent to high altitude may make one prone to AMS, but the two most serious potential illness developments are High Altitude Pulmonary Edema (HAPE) and High Altitude Cerebral Edema (HACE). Although they are presented as separate entities, they share many clinical features but represent different degrees of severity of a common, yet still undiscovered, pathophysiological process (Hackett et al, 1981; Hackett et al, 1988).

HAPE occurs in otherwise healthy individuals who ascend to high altitude, and is a non-cardiogenic form of pulmonary edema resulting from a leak in the alveolar capillary membrane. Its development usually arises in association with rigorous exercise, and develops after the first day (Hackett and Roach, 1990). Past HAPE history will most likely result in a future episode, while high pulmonary arterial pressure (due to hypoxic vasoconstriction) is a marker for HAPE susceptibility in hypoxia (Gibbs, 1999). Further, HAPE susceptible subjects tend to have a low HVR (Hackett et al, 1988; Matsuzawa et al, 1989). Its clinical features, in addition to those of AMS, are crackles at the site of edema in the lungs, shortness of breath which is usually exaggerated during the night, dry cough with further development of production of a frothy white-yellowish or bloody sputum. Figure 1.7 shows a chest radiography of a patient with HAPE (left illustration) and the same patient 4 days later (right illustration). Typical features are asymmetrical and irregularly positioned 'cotton wool' blotches in both lungs. In treated cases, radiographic lesions clear rapidly (Ward et al, 2000).

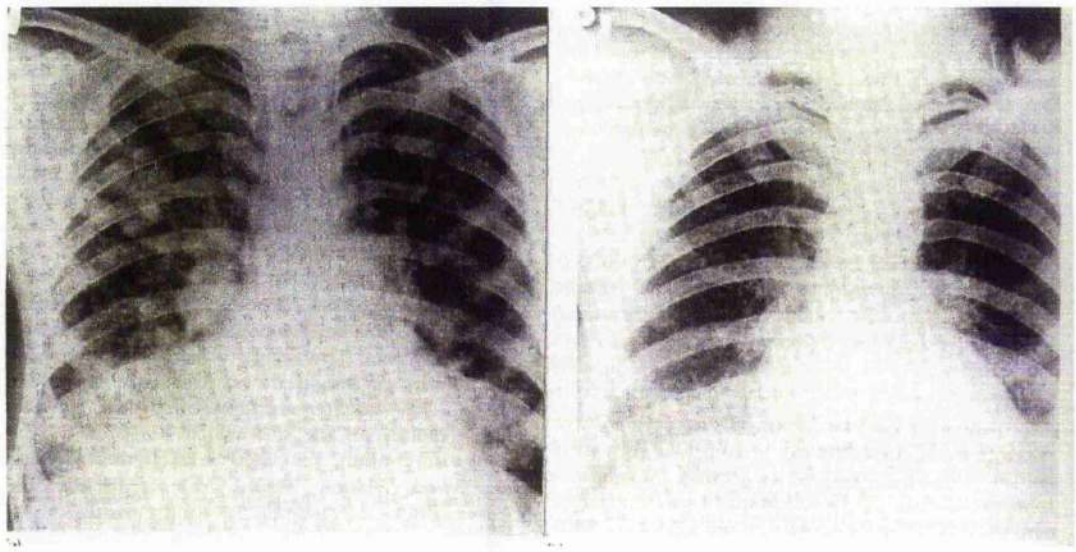


Figure 1.6 Radiograph of patient with HAPE (left) and 4 days later (right) (Ward et al, 2000).

Furthermore, there is a decrease in exercise performance, chest tightness and pain, weakness, lethargy, tachycardia, and cyanosis (Sartori et al, 1997). Recommendations for prevention include allowing enough time for acclimatization and implementing a slow ascent rate. As HAPE is a life threatening condition, the best management and treatment is immediate descent. Unless descent is impossible to implement immediately, alternatives include oxygen administration (Hackett and Hornbein, 1988) or the use of a portable hyperbaric bag (Shimada et al, 1996). Administration of vasodilators such as Nifedipine or Nitric Oxide is also an effective way of treatment (Oelz et al, 1989; Scherrer et al; 1996). The objective of the treatment is to improve arterial oxygenation, reduce pulmonary hypertension and clear the edema. Similarly to AMS, there is great variability to the individual susceptibility for HAPE, and a prediction for the condition has also yet to be found.

HACE on the other hand is considered to be the more malignant form of AMS and will affect un-acclimatized individuals on ascent to high altitude (Hackett, 1981). HACE is characterized by the same symptoms as AMS, but developing to altered consciousness, ataxia, coma, and even death. The most vital treatment is immediate descent. In addition the use of supplemental oxygen and hyperbaric bag are certainly recommended, as is the use of the drug Dexamethasone, all of which have been

shown to be aid in the treatment of HACE (Johnson et al, 1984; Montgomery et al, 1989).

1.3.9 Recommendations For Safe Ascent To Altitude

Despite the seriousness of all mountain illnesses, it may be possible to prevent their unwanted consequences, and if caution is practiced, then an ascent can be as risk free as possible. To date, no tests are available that can accurately predict high altitude tolerance. However, precautions are advised when venturing to high mountains; recommendations that should be considered are the following (Ward et al, 2000; Bartsch et al, 2001):

- Ascent profile should be gradual, and above 3000m the ascent rate should be no more than 300-500m/day with a rest day every 3-4 days, however, a safe ascent cannot be 'engraved in stone' as it varies amongst individuals
- Previous altitude illness history needs to be considered; precautions should be taken to avoid a future illness episode
- Medical support should be available within the team and emergency evacuation plans should be available
- Flexibility in itinerary in order to allow for any insufficient acclimatization as well as treatment of any medical problems
- Preventative methods through the use of prophylactic drugs may be implemented
- Knowledge on how to identify AMS symptoms and when to stop the ascent, is also deemed important

1.4 Genetics

Genetic predisposition undoubtedly plays a role in the development of a particular physical performance under a particular condition. The data presented and the research undertaken in this thesis focuses and examines the role of the angiotensin converting enzyme (ACE) gene during performance at altitude.

1.4.1 Angiotensin Converting Enzyme (ACE)

The renin-angiotensin system (RAS) is known to play a significant role in circulatory homeostasis. The liver produces angiotensinogen, a globulin, which is acted upon by the protease renin, produced by the kidney under conditions of salt or volume loss, or sympathetic activation, and converts it into the peptide angiotensin I (Ang I). ACE, circulating and membrane bound, cleaves Ang I into angiotensin II (Ang II). Ang II is a potent vasoconstrictor and stimulator of adrenal aldosterone release which leads to water and salt retention. Moreover, the RAS has a tissue-based diversity and has been observed in areas such as the human myocardium (Dzau, 1988), adipose tissue (Jonsson et al, 1994), lung (Pieruzzi et al, 1995), and skeletal muscle (Dragovic et al, 1996).

In the human ACE gene, found on chromosome 17, a common genetic variance is observed. The absence (deletion, D allele) rather than the presence (insertion, I allele) of a 287 base pair fragment at intron 16 in the ACE gene, is associated with higher ACE activity. The frequency of the alleles, I and D, is roughly equally distributed, but variations do occur between populations of different ethnic origin. A large scale population study on British people, showed the ACE genotype to be divided into 24% of the population having the II genotype (low ACE activity), 26% having the DD genotype (high ACE activity), and 50% having the ID genotype (intermediate ACE activity) (Miller et al, 1996).

Human pathological and physiological responses have been observed and recorded under various stimuli in regards to a specific ACE genotype.

1.4.2 ACE I/D Polymorphism And Human Physical Performance

The I allele has been associated with athletic endurance performance and has been observed in excess in rowers (Gayagay et al, 1998), distance runners (Myerson et al, 1999), marathon swimmers (Tsianos et al, 2004), and elite athletes in a variety of sports (Alvarez et al, 2000). Other studies however (Karjalainen et al, 1999; Taylor et al, 1999; Rankinen et al, 2000b), have not been able to reproduce similar outcome, and this may be the result of their 'athletic populations' not being truly endurance based. In the Myerson et al, (1999) study, the I allele frequency shows a linear trend increase with running distance, hence aerobic ability; in Olympic standard runners of the distances ≤200m, 400-3000m, and ≥5000m, the respective I allele frequencies were 0.35, 0.53, and 0.62. On the other hand, the D allele has been associated with power-oriented performance, being found in excess in short-distance swimmers (Woods et al, 2001), power athletes (Nazarov et al, 2001), and as has been linked with a greater strength gain in the quadriceps muscles during training (Folland et al, 2000).

It may appear that the I allele and II genotype may be of benefit in endurance events via its effects on the cardio-respiratory system. However, examination of the ACE genotype and VO_2 *max* relationship has resulted in contradictory evidence, and while some investigators show as association (Hagberg et al, 1998), others do not (Rankinen et al, 2000a). Furthermore, even though the I/D polymorphism may play a role in an enhanced endurance performance, it is not mediated by differences in the cardio-respiratory response to training (Woods et al, 2002).

In view of the fact that a physiological link between the ACE I/D polymorphism and 'endurance' or 'power' performance is unlikely to involve the cardio-respiratory system, it is probable that an alternative lies at the skeletal muscle level. It has been stated that the tissue RAS metabolic involvement plays an important role in regulating human skeletal muscle and metabolism (Montgomery et al, 1999). Jones and Woods (2003) discuss how through the existence of a functional renin-angiotensin system (RAS) in the skeletal muscles, raised ACE activity (DD genotype) will promote greater strength gains perhaps via muscle hypertrophy, although Sundgren et al (2003) showed an in vivo hyperplasia of cardiomyocytes after stimulation by Ang II. On the other hand lower ACE levels may promote enhanced endurance performance possibly

via changes in substrate availability, muscle fiber type and efficiency. These findings suggest that the role of ACE I/D polymorphism can be of great importance beyond sporting activities, given the therapeutic treatments by means of ACE inhibitors; a pharmacological manipulation of this kind could benefit in muscular diseased states, such as congestive heart failure (Williams et al, 2000) as well as in other diseases causing low levels of O_2 in the blood. To what extent endurance or power performance is dependent on the RAS at the muscle level, remains to be elucidated in future studies.

1.4.3 ACE I/D Polymorphism And Hypoxia

High altitude climbers demonstrate an association with the I allele. Elite British mountaineers, who had ascended over 7000m without the use supplemental oxygen, had a significant excess of the I allele and II genotype with respective frequencies of 0.7 and 0.48 (Montgomery et al, 1998). Of those climbers who had ascended over 8000m without supplemental oxygen, none were of the DD genotype, while the top performer was of II the genotype. Even though this group sample is rather small to strongly support a gene association, it does suggest a performance advantage of the I allele at high altitude and more specifically in conditions of low oxygen.

In view of the fact that an increased arterial oxygen saturation (SaO_2) is of benefit at high altitude, the RAS is probably of great importance. Ang II facilitates pulmonary vasoconstriction (Kiely et al, 1995), and high ACE activity is associated with an increased pulmonary hypertensive response in conditions of hypoxia (Kanazawa et al, 2000). It may therefore be speculated that a lower ACE activity will enable better oxygenation and more efficient alveolar ventilation during hypoxic conditions where supply of oxygen is scarce. Additionally, and as previously stated, the compensatory increase in alveolar ventilation also known as HVR, promotes an increase in arterial oxygen saturations and tissue oxygen delivery. In fact, II genotype is associated with an increased ventilatory response during hypoxic exercise (Patel et al, 2003).

Finally, the concept of a genetic advantage in those carrying the I allele in hypoxic conditions is further supported by a finding of better-preserved SaO_2 amongst those of the II rather than DD genotype during rapid ascent to altitude, Figure 1.8, but the absence of such when ascent is more gradual (Woods et al, 2002).

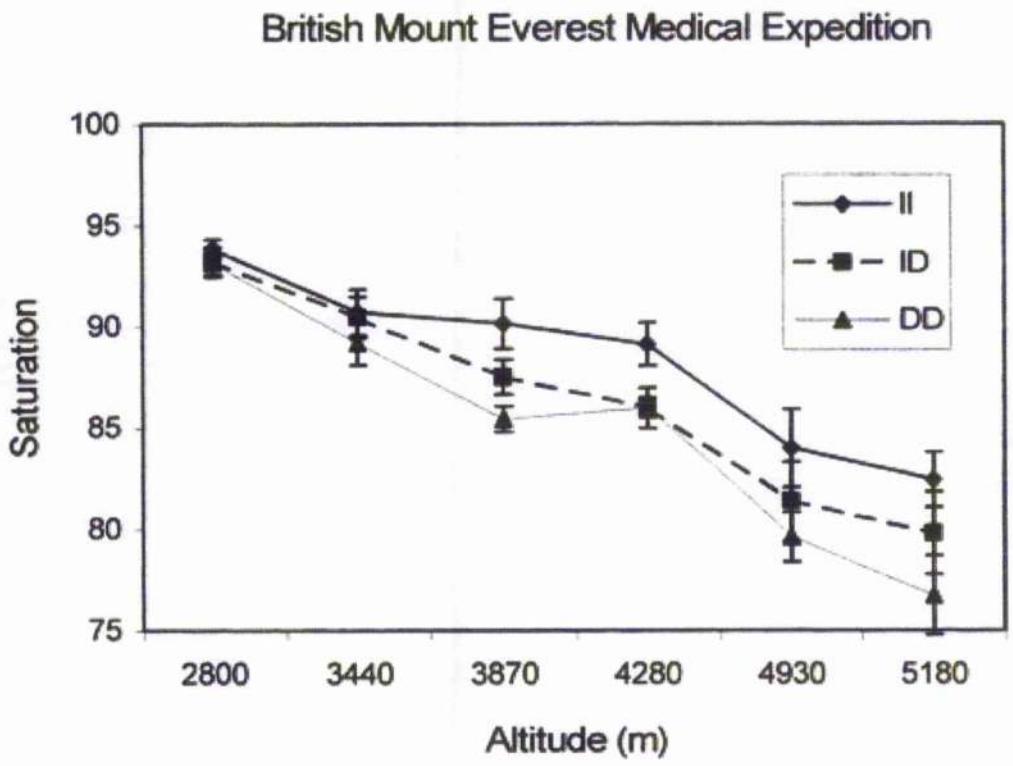


Figure 1.7 Oxygen saturation at various altitudes by ACE genotype during the 1994 British Mount Everest Medical Expedition (rapid ascent group). The initial saturation on arrival at a higher altitude is shown. Sa_{O2} with ascent was better sustained in the II-allele subjects (Woods et al, 2002).

1.4.4 ACE And AMS

Is it possible then that the ACE I/D polymorphism influences AMS? A speculation lies directly through alterations in blood volume and pressure by ACE elevation of Ang II levels, which would in turn, stimulate aldosterone production, leading to water and sodium retention. Individuals with AMS have been examined and found to retain more fluid and have increased plasma levels of aldosterone (Hackett et al, 1982; Bartsch et al, 1988). Given the role of the renin-angiotensin system in fluid retention, in addition to the ACE expression in the tissues of the lung, it may be possible that the DD genotype is associated with a higher prevalence of AMS.

It could be inferred that the I allele advantage at high altitude may mediate a reduced AMS occurrence. However, Dehnert et al, (2002) found no relationship between ACE genotype and AMS. A limitation of the study was that AMS assessment was made only a few hours after arrival at the tested altitude and no evidence of a better tolerance by any of the genotypes is available on the following day at altitude. As onset of AMS symptoms is considered, for most individuals, to begin between 6 and 12 hours after arrival at altitude, concrete evidence of a specific ACE genotype and tolerance to AMS still remains unclear.

To date, no study has prospectively attempted to investigate the above. This is mainly due to cost of field studies as well as the need for a larger cohort in order to have a reliable association for a link between a genetic marker and a physiological response. It is one of this thesis' aims to address AMS onset in a prospective study where the subjects would be tested upon arrival at altitude, and while their performance during further climbing would be monitored, they would be assessed again on their AMS status the following day.

1.5 Aims Of Thesis

The aims of this thesis were to assess an innovative mountain rescue equipment, to observe performance of individuals whilst undergoing fast and slow ascents to altitude, and to investigate what role the ACE genotype plays in individual performance at high altitude. The aims were achieved through the following studies:

Study 1

To compare a mountain rescue casualty bag used by the Norwegian mountain rescue teams with a casualty bag currently used by the Scottish mountain rescue teams. This was achieved through the use of physiological and subjective responses of the participating subjects in each of the two bags.

Study 2

To compare the physiological responses of climbers assessed during a fast ascent altitude profile to the summit of Mont Blanc (4807m). Reference is given to those who became ill and were unable to perform under a hypoxic environment. Demographic information from the participating subjects was used in an attempt to explain the reasons for those who underperformed on the mountain. Furthermore, an investigation of the climbers' ACE gene profiles was made to assess a possible genetic predisposition both in those who became ill and those who performed successfully.

Study 3

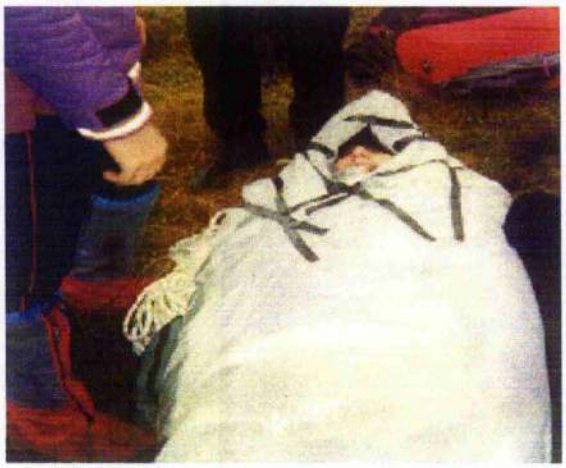
To compare the physiological responses during a slow ascent profile to 5000m in relation to the trekkers' ACE gene profiles. Reference was also given to pre-exposure testing in an attempt to predict performance during exposure to altitude.

Study 4

To investigate the ACE genotype in those climbers who successfully summit Mount Everest (8850m).

CHAPTER 2

A Comparison of a Bubble-Wrap Bag
And a Mountain Rescue Casualty Bag
In a Cold Windy Environment



INTRODUCTION

Mountain rescue team call-outs occur frequently in the UK with over 800 emergency rescues each year (Hearns, 2000). During the period 1993 to 1995, there were 604 incidents in the Scottish mountains in which 13% of the casualties became hypothermic, and 7% of hypothermic victims died (Scottish Mountaineering Journal, 1993-1995). While casualties wait for rescue teams to arrive, they may encounter inclement weather including cold, wet and windy conditions. These harsh conditions may result in rapid body heat loss and lead to hypothermia in addition to the victims' injuries.

The first plan of action in the treatment of a hypothermic individual is to prevent further heat loss and to reduce the possibility of a hypothermic state. To achieve this, several casualty rescue bags and blankets have been developed. The effectiveness of such equipment has been studied in settings such as hospitals, laboratories and in the outdoors (Grieve, 1969; RAF Inst of Aviation, 1976; Light and Norman, 1980; Light et al, 1980; Benner, 1988; Goodlock, 1995; Smith, 1996). While heat loss may be prevented using casualty bags, their insulating qualities will depend upon the environmental conditions. Criticism of some bags includes the fact that they are bulky, difficult to carry, and offer limited protection from the cold.

Anecdotal reports from Norwegian mountain rescue teams suggest that a single layer of bubble-wrap around the casualty may help prevent heat loss. Possible advantages of a bubble-wrap (BW) bag include its lightweight and low cost. However, there is no scientific evidence to substantiate the claim that a bubble-wrap bag is effective in preventing loss of body heat.

The aim of this study was to compare the BW bag against a standard casualty bag (CB) used by Scottish mountain rescue teams, in a cold (-10°C) and windy (wind speed 2.7 $m \cdot sec^{-1}$) environment using physiological and subjective responses of the participating subjects.

METHODS

Subjects

Twelve healthy male volunteers (age 21 ± 1.3 years, body mass 71.9 ± 4.2 kg, body fat 12.7 ± 2.3%, height 1.77 ± .1 m) who were regular exercisers participated in the study. The subjects were hill-walkers, swimmers and canoeists and all had encountered cold conditions in the past, whether in the mountains, or the rivers and seas. Each subject completed a medical history and physical activity questionnaire. Subjects were informed about the nature, purpose and effects of the study before giving their written consent to participate. They were asked to avoid consumption of alcohol and coffee for at least 12 hours prior to testing, and to report in a fasted state (overnight and morning) before each test. All subjects were randomly allocated into two groups. Half of the subjects were tested first using the CB and half were tested first using the BW. One week later the subjects crossed over to the other bag for testing. Ethics approval for the study was obtained from the University of Glasgow Ethics Committee.

Preliminary measurements

The following measurements were made: height (meters), body mass (kilograms), and body fat (%). Body fat was estimated at four sites (biceps, triceps, subscapular, and suprailliac) using the procedures outlined by Durnin and Womersley (1974).

Study Design

The experimental procedures for all the subjects were undertaken at the University of Glasgow Environmental Research Chamber. All trials were carried out between 8:00-10:00am to avoid any circadian rhythm variations. Each subject underwent 2 exposures in the environmental chamber while lying inside one of two bags: one in the standard mountain rescue CB, and one in the BW bag. Each exposure was planned to last 60 minutes. The exposures were at least one week apart to avoid any acclimatisation effects. After the equipment (thermistors) were attached to the subjects, they were dressed in the study clothing (see below). Thereafter resting measurements were taken. Resting (lying in a supine position) baseline measurements

were made during a 10-minute period in an anteroom before the subjects entered the environmental chamber. The casualty bags were exposed and opened inside the chamber 10 minutes before the subject entered the chamber. When inside the chamber, the subjects lay in a supine position on a mountain rescue stretcher, and were placed inside the bag. The bag was then closed and sealed, and fans were turned on. The stretcher was at a height of 110 cm from the floor. Throughout both tests, skin and core temperatures were continuously monitored and recorded every 5 minutes. Heart rate (every minute) and oxygen consumption (5 minute periods), subjective cold comfort and shivering (every 5 minutes) were measured throughout the test. At the end of the trial, the subjects were moved into a warm area (ambient temperature ~35°C) where blankets and warm drinks were provided. They were allowed to leave the laboratory only when their core temperature was above 36.0°C and rising.

Bags

Mountain Rescue Casualty Bag (Marshall bag)

The casualty bag (CB), Figure 2.1, consists of an outer shell constructed of neoprene/nylon material. This wind and waterproof outer shell wraps around an inner 'duffel' bag. The subject lay on the inner layer, which was wrapped around him and secured, with Velcro strips. The outer layer was also wrapped around the subject and secured using straps attached the outer layer. A hood was attached to the rescue bag. The overall weight of the bag was 6.4 kg.

Figure 2.1 Casualty Bag

Bubble-Wrap Bag

The bubble-wrap bag (BW), Figure 2.2, consisted of a single layer of bubble-wrap supplied by the company *Sealed Air* (New Jersey, USA). The BW was delivered by the company in roles BW; a prototype was designed according to the dimensions and make of the CB. The bubbles were 'small' as classified by the company, and measured 9.5mm in diameter and 4.2mm in height. The bubbles had a high-density polyethylene (HDPE) film laminated covering which enhanced puncture and tear strength. Once the subject was in position on the bubble-wrap, it was wrapped around him and held together with the use of elephant tape (sellotape). A hood, also made of bubble-wrap, was attached to the topside of the bag. The overall weight of the bag was 0.6 kg. 12 identical BW bags were made, one for each experimental trial.

Figure 2.2 BW bag during experimental trial (with subject permission).

The surface areas of the casualty and bubble-wrap bags were virtually the same. The surface area of the Bubble Wrap was $5.12m^2$ and the inner layer of the casualty bag was $5.13m^2$.

Clothing

All subjects in both experimental trials wore their own underpants. They all wore the same thermal underwear (leggings and long sleeved top), Ministry of Defence (MOD) issue khaki trousers and zipped jacket (no hood) with draw strings, MOD issue khaki hat with protective ear flaps and wool lining, MOD issue mitten gloves with wool inner lining, 2 pairs of wool socks and military boots.

Physiological Measurements

Heart rate was monitored using a PE3000 (Polar Vantage Kemple, Finland), and recorded every minute.

Four skin thermocouple wires (Comark Ltd, Hertfordshire, UK) were used for measurement of skin temperature at the chest, arm, thigh and calf; all attached to the skin with 3M micropore tape. The thermocouple wires were connected to a portable temperature logger (KM 1242, Comark Ltd, Hertfordshire, UK), and values were recorded every 5 minutes. Mean weighted skin temperature was calculated as described by Ramanathan (1964).

$$M.T_{sk}=0.3t_{chest}+0.3t_{arm}+0.2t_{thigh}+0.2t_{calf}$$

Core temperature was measured with the use of a rectal probe (Mechanical workshop, University of Glasgow, Institute of Biomedical and Life Sciences), inserted 10 cm beyond the anal sphincter, connected to the portable logger (KM 1242, Comark Ltd, Hertfordshire, UK) and recorded every five minutes, but monitored continuously.

Respiratory and metabolic measurements (V_E, Vo_2) were made by means of open-circuit system spirometry in 5 minute intervals (at minutes 5-10, 15-20, 25-30, 35-40, 45-50, 55-60) as the subject breathed atmospheric air and expired through a mouthpiece and hose into 150 L Douglas bags (polyurethane, Harvard Apparatus Ltd, Kent, UK). The Douglas bags were connected to the mouthpiece using a 2700 valve (Hans Rudolph), tubing and a 2100 3-way stopcock valve (Hans Rudolph). Gas analysis (O_2%, CO_2%) was carried out using an Oxygen Analyser (Servomex 570A, Crowborough, UK) and a Carbon Dioxide Analyser (PK Morgan Ltd, Rainhamm, UK). The gas analysers were calibrated before every test. V_E was measured using a

Harvard dry-gas meter. V_{O_2} was calculated using University of Glasgow computer software.

Baseline measurements were taken in a room adjacent to the environmental chamber (ambient temperature ~20°C), while the subjects lay quietly on an examination table for 10 minutes. They wore all their experimental clothing. Values were recorded for 10 minutes and then averaged for the last 5 minutes for heart rate, skin and core temperature. Respiratory measurements were taken during the second 5 minutes of the 10-minute period. Shivering and cold comfort scales were recorded at the end of baseline measurements.

Assessment of Cold Comfort and Shivering

Subjective comfort level responses were recorded every five minutes (from time 0 to 60 minutes) using a Whole-Body Cold Comfort Scale (Table 2.2, page 67), and a Shivering Scale (Table 2.3, page 68). The subjects were shown the scale and asked to indicate perceived cold comfort and shivering states. The values for both scales were indicative of a whole body cold comfort and shivering, and not of specific body areas.

Environmental Chamber

The environmental conditions inside the chamber were: -10 °C $\pm$ 1°C (dry bulb temperature) maintained using a Cool Guard Refrigeration Unit (C&M Refrigeration Ltd., Glasgow, UK) fitted with a cyclical thermostat. A continuous airflow at 2.7 $m \cdot sec^{-1}$ (measured at feet of subjects) was provided by three Vent Axia (Vent Axia, Glasgow, UK) wall mounted fans. The wind chill index was estimated to be - 17°C.

Termination of Experiment

The criteria for termination of the trials were as follows:

1. subject's voluntary withdrawal
2. subject's core temperature reaching 35.5°C
3. completion of experimental procedure

Statistical Analysis

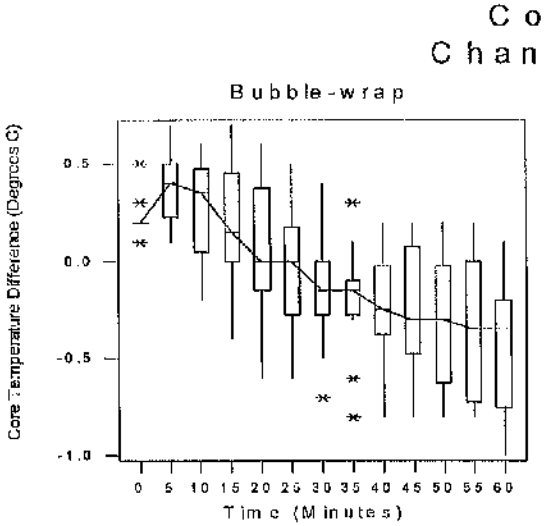
A Repeated Measures Analysis of Variance (ANOVA) was used to investigate the effects of bag, time, bag/time, order and subject effects. All variables were adjusted for baseline by subtracting each baseline from the respective score at each time point. In addition, Bonferroni multiple comparisons (with 95% Confidence Intervals) were carried out in order to provide an interval estimate of the true mean difference for those response variables where there was evidence of a significant difference between the bags. The shivering scale was reformulated. Originally the scale had a range of 0 to 3, but 3 was never used and 2 only very sparingly. Therefore shivering was analysed using the following: no shivering corresponding to 0, and shivering which encompassed the scale numbers 1 and 2. The reconstituted Shivering variable (i.e. no shivering vs. shivering) was analysed using McNemar's test for the data at 60 minutes. Data in Figures 2.3A-11B are presented as median, 25% and 75% quartiles. Statistical significance was declared at $P<0.05$.

RESULTS

All subjects completed the experimental procedures for both bags, as described in the Methods. Core temperature, skin temperatures (chest, thigh, triceps, calf), and heart rate have negative values (denoting a decrease from the baseline values), whereas oxygen consumption, cold comfort scale and perception of shivering have positive ones (denoting an increase from the baseline values). Figures 2.3A-12 give a visual representation of the changes in the tested measurements from baseline until termination of the experiment. Sample means, at three selected time points (20, 40, and 60 minutes) into the study are given in Table 2.3 together with the results of the corresponding Bonferroni follow-up multiple comparisons.

Core temperature

The core temperature increased from the baseline measurement between 0 and 5 minutes for both bags. Thereafter, core temperature decreased throughout the tests (Figure 2.3A-B). There was no significant difference (p=0.57) in the decrease from baseline between the bags.



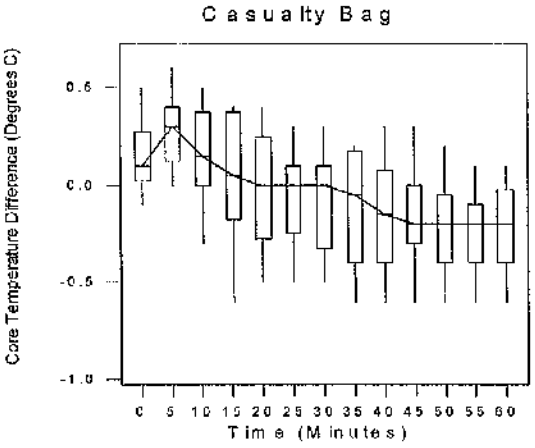


Figure 2.3A

Box-plot showing the core temperature changes during exposure in the BW.

Figure 2.3B

Box-plot showing the core temperature changes during exposure in the CB.

Mean skin temperature

The decrease in mean skin temperature was much greater in the BW compared with the CB (Figure 2.4A-B). The 95% CI shows that on average the BW mean skin temperature was significantly lower ($p<0.005$) than the CB with the BW being between 3.9°C to 5.2°C lower than the CB at 60 minutes.

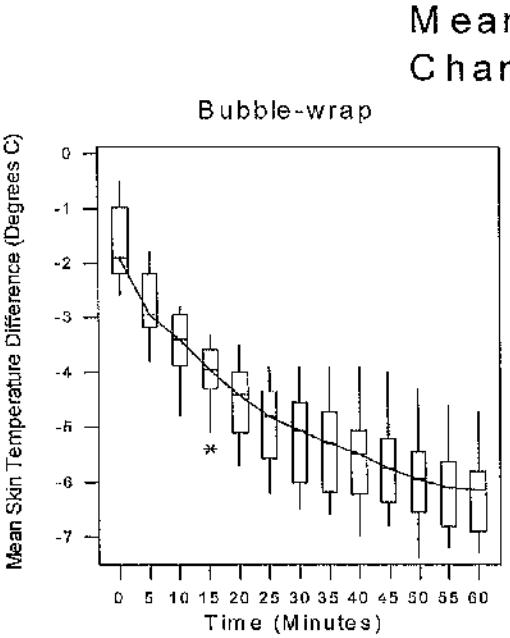


Figure 2.4A

Box-plot showing the mean skin temperature changes during exposure in the BW.

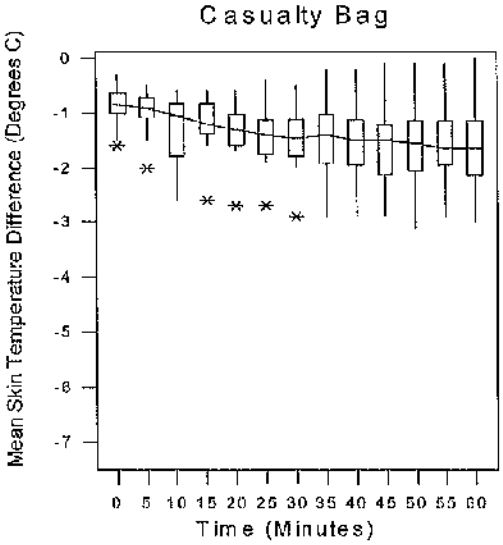


Figure 2.4B

Box-plot showing the mean skin temperature change during exposure in the CB.

Individual skin site temperatures

The skin temperature decrease in all four sites tested (chest, arm, thigh, and calf) was significantly greater ($p<0.005$) in the BW compared with the CB. At 60 minutes the temperatures for all sites in the BW were lower than in the CB by: 3.7 °C to 6.4 °C for the triceps (Figure 2.5A-B), 3.5 °C to 5.4 °C for the chest (Figure 2.6A-B), 3.4 °C to 5.3 °C for the thigh (Figure 2.7A-B), and 3.1 °C to 5.1 °C for the calf (Figure 2.8A-B).

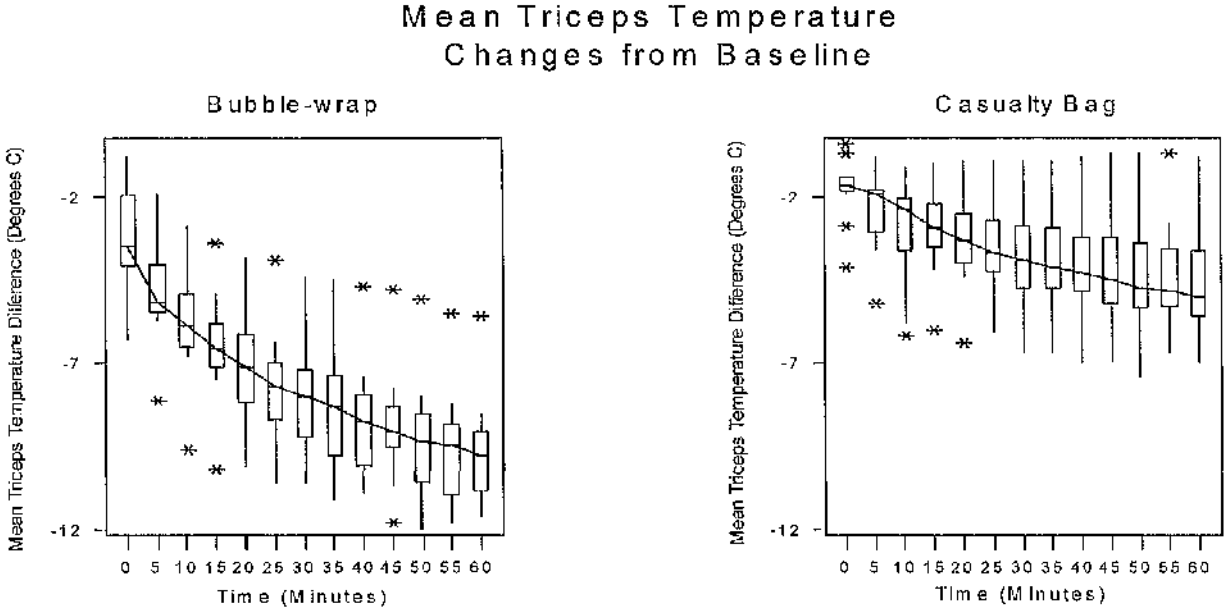


Figure 2.5A

Box-plot showing the triceps temperature changes during exposure in the BW.

Figure 2.5B

Box-plot showing the triceps skin temperature chang during exposure in the CB.

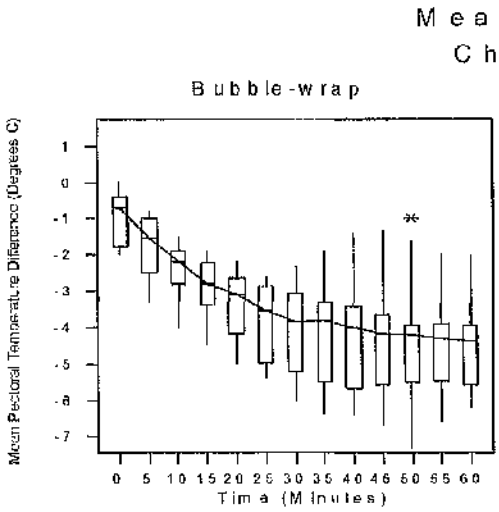


Figure 2.6A

Box-plot showing the pectoral temperature changes during exposure in the BW.

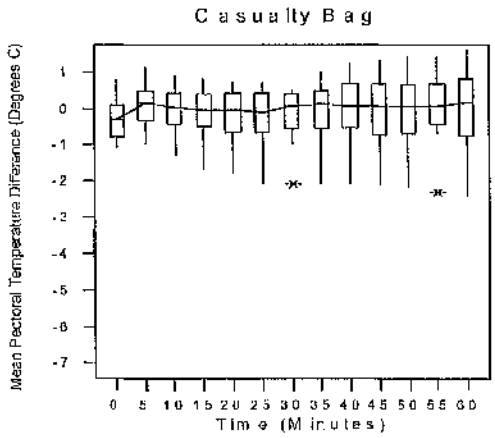


Figure 2.6B

Box-plot showing the pectoral temperature change during exposure in the CB.

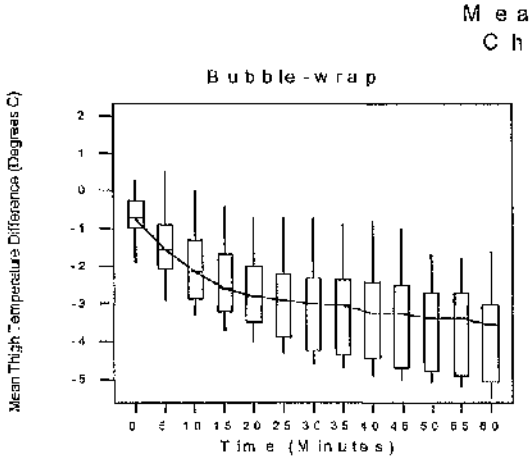


Figure 2.7A

Box-plot showing the thigh temperature changes during exposure in the BW.

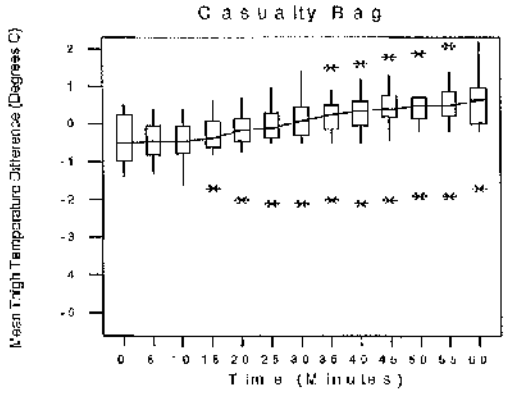


Figure 2.7B

Box-plot showing the thigh temperature changes during exposure in the CB.

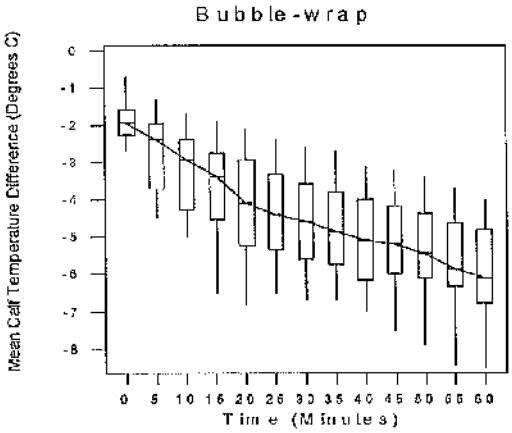


Figure 2.8A

Box-plot showing the calf temperature changes during exposure in the BW.

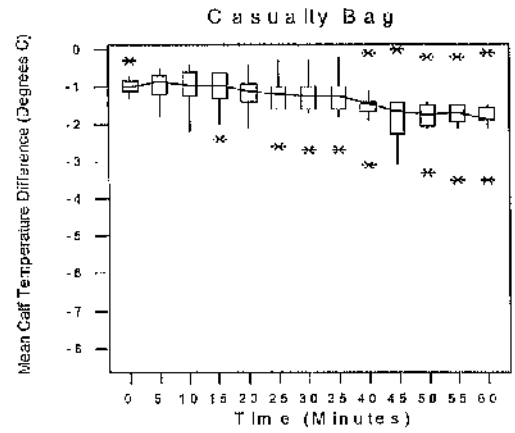


Figure 2.8B

Box-plot showing the calf temperature changes during exposure in the CB.

Heart rate

There was a general decrease in heart rate for both bags until the latter stages of the tests when both bags showed an increase (Figure 2.9A-B). There was no significant difference (p=0.98) between the bags.

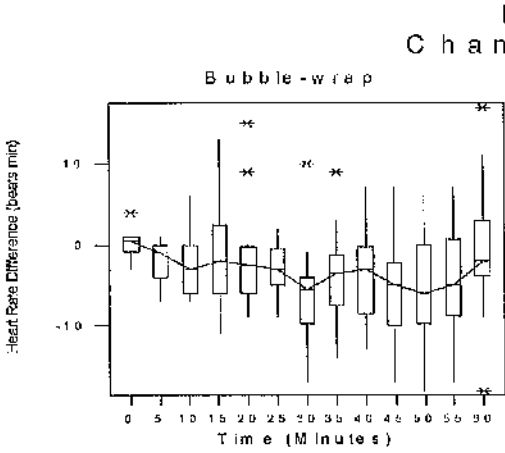


Figure 2.9A

Box-plot showing the heart rate changes during exposure in the BW.

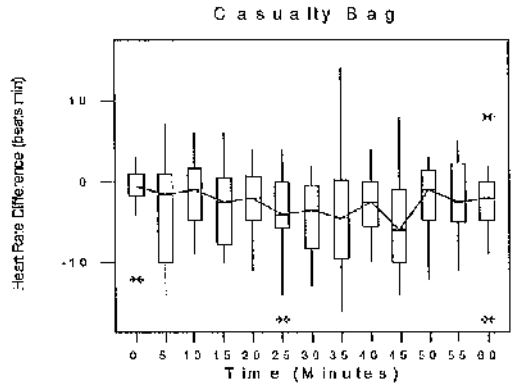
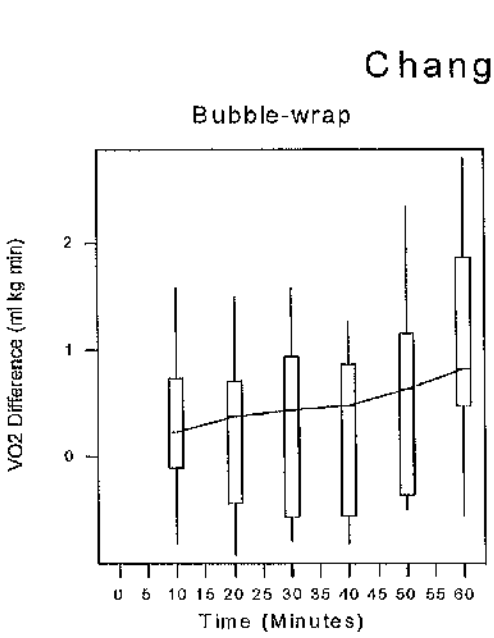


Figure 2.9B

Box-plot showing the heart rate changes during exposure in the CB.

Oxygen consumption

There was a trend for V_{O_2} to rise in both bags over time (Figure 2.10A-B), while there was a tendency for V_{O_2} in the BW to be higher than the CB. There was no significant difference (p=0.12) between the bags.



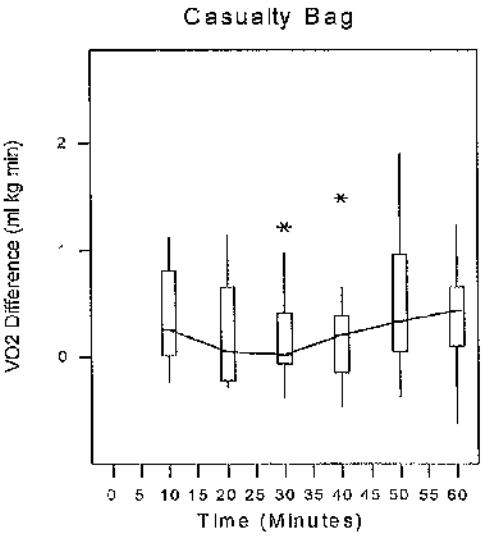


Figure 2.10A

Box-plot showing the $\dot{V}O_2$ changes during exposure in the BW.

Figure 2.10B

Box-plot showing the $\dot{V}O_2$ changes during exposure in the CB.

Cold comfort

For CB, the median score did not rise after 35 minutes whereas there was a fairly regular rise in cold comfort throughout the test (Figure 2.11A-B). The cold comfort score in the BW was significantly higher ($p<0.005$) than in the CB. The 95% CI, at 60 minutes for the BW was higher than the CB by 0.7 to 3.3 units.

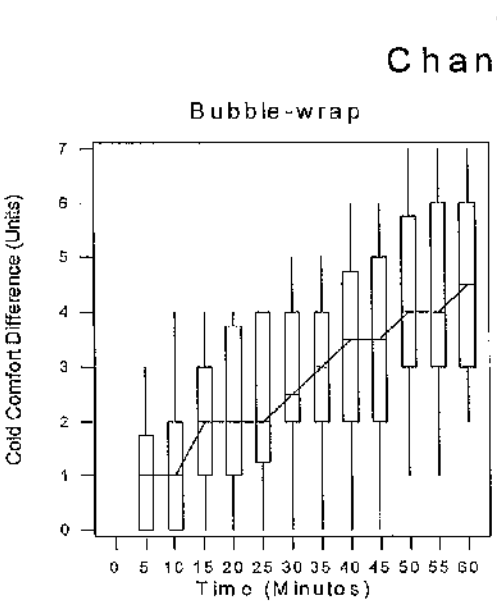


Figure 2.11A

Box-plot showing the cold comfort changes during exposure in the BW.

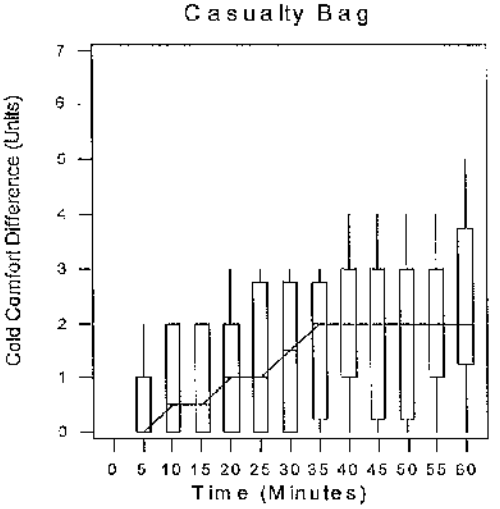


Figure 2.11B

Box-plot showing the cold comfort changes during exposure in the CB.

Shivering

Shivering was analysed in terms of reported shivering (yes or no). By 15 minutes, none of the 12 subjects were shivering in the CB while two subjects were shivering in the BW. By 30 minutes, 1 person was shivering in the CB and 5 were in the BW, (Figure 2.12). At 60 minutes, 3 out of the 12 shivered in neither bag, 3 shivered in both, and, most importantly, 6 shivered in BW but not in the CB (p= 0.02).

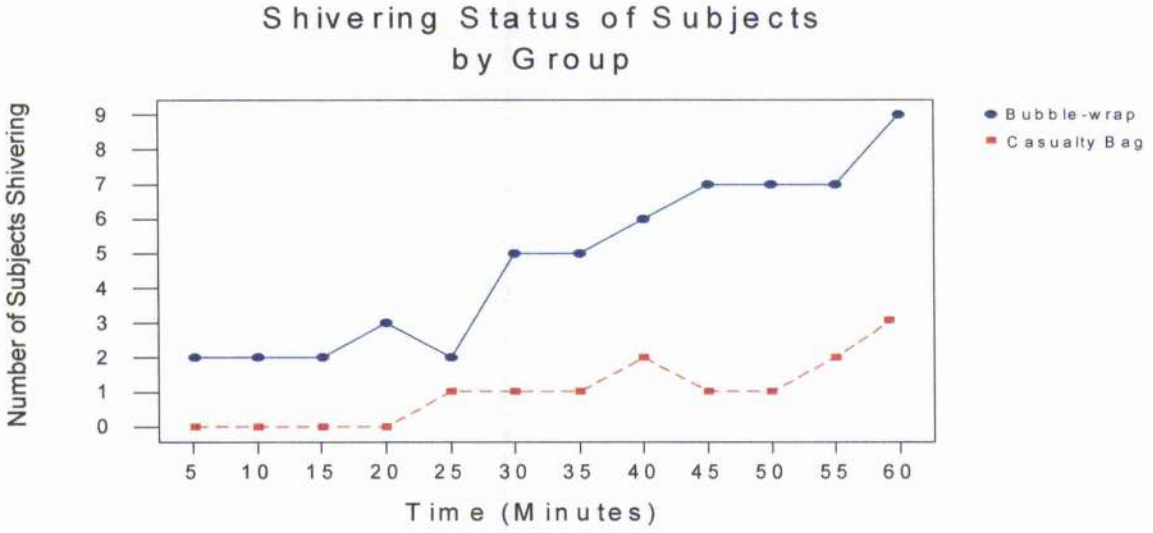


Figure 2.12

Graph showing the shivering status of subjects by group.

Order of testing

A significant effect was observed for the order by which the trials took place, BW first or CB first. The first test tended to generate more marked responses (increases or decreases) than the second test; for core temperature p=0.03, for mean skin temperature p<0.005, for $\dot{V}O_2$ p<0.005, and for cold comfort p<0.005.

Sample mean differences and 95% confidence intervals (shown in brackets) for the selected variables of Core Temperature, Mean Skin Temperature, Heart Rate, Oxygen Consumption, and Cold Comfort of each bag at three selected time points (20, 40, and 60 minutes) into the study, are presented in Table 2.1.

Variable	Material	Time		
		20 minutes	**40 minutes**	**60 minutes**
Core Temperature (°C)	*BW*	0.075	-0.233	-0.408
	CB	-0.017	-0.158	-0.233
95%CI		*(-0.18,0.36)*	*(-0.31,0.16)*	*(-0.42,0.07)*
Mean Skin Temperature (°C)	*BW*	-4.53	-5.54	-6.18
	CB	-1.36	-1.51	-1.63
95% CI		*(-3.7,-2.7)*	*(-4.7, -3.4)*	*(-5.2, -3.9)*
Heart Rate (beats. min^{-1})	*BW*	-1.42	-3.42	-0.75
	CB	-2.33	-2.42	-2.92
95% CI		*(-4.1, 5.9)*	*(-5.3, 3.3)*	*(-4.3, 8.7)*
$\dot{V}O_2$ **(ml.kg^{-1}.min^{-1})**	*BW*	0.253	0.253	0.973
	CB	0.191	0.218	0.415
95% CI		*(-0.48,0.60)*	*(-0.52,0.59)*	*(-0.11,1.23)*
Cold Comfort (0-10 unit scale)	*BW*	2.17	3.25	4.42
	CB	1.00	1.83	2.42
95% CI		*(0.1, 2.3)*	*(0.1, 2.8)*	*(0.7, 3.3)*

Table 2.1 Sample mean differences and 95% confidence intervals. *(The values have been calculated as follows: Bubble Wrap minus Casualty Bag differences of changes from baseline).*

DISCUSSION

The major finding of this study was that the bubble-wrap bag (BW) did not protect the subjects as effectively as the casualty bag (CB) under the selected environmental conditions of -10°C ambient temperature and wind speed of 2.7m·sec^{-1}. The four individual skin sites and mean skin temperature were lower for the BW. Cold comfort scores (i.e. subjects felt colder) and perception of shivering were higher for the BW compared with the CB.

There was no difference for core temperature between the bags. The subjects defended the decrease in core temperature in both bags by vasoconstriction in order to increase insulation (Toner and McArdle, 1988). However, it is likely there was greater vasoconstriction in the BW. Evidence for this comes from the greater decrease in skin temperature for the BW in all four sites (triceps, calf, chest and thigh) and the mean skin temperature compared with the CB (Table 2.1). With the CB, the much higher skin temperatures demonstrated that there was a significantly smaller decrease in skin temperatures. It is speculated that the insulation of the BW material is less than that of the CB, resulting in lower skin temperatures. As the skin temperatures were much lower in the BW, it seems plausible to suggest that, had the conditions been harsher or the experiment lasted longer, it is likely that the core temperature in the BW would have become lower than the CB. In both bags, the core temperature showed a slight rise in temperature at the start of the trials, (Figures 2.3A and 2.3B). The initial increase in core temperature was most likely due to the initial vasoconstriction and redistribution of blood to the core. It may be attributed to a time lag in measurement through the use of a rectal thermistor (Lloyd, 1986) and the possible warming effect of a fairly long period (15 min) in a warm anteroom while wearing the protective clothing.

While there was no significant difference in oxygen consumption (V_{O_2}) between the bags, there was a tendency for V_{O_2} to increase more in the BW compared with the CB (Table 2.1, and Figures 2.10A & 2.10B). A fall in skin temperature is associated with the onset of shivering (Iampietro et al, 1960). Thus, it is to be expected that the lower mean skin temperature for the BW would initiate shivering sooner than the CB. The core temperatures in both bags were very similar but the mean skin temperature at 60

minutes in the BW was much lower than the CB, 28.2°C vs. 31.1°C, and was well below the uniform cutaneous temperature of 29.0°C, at which shivering begins (Mercer, 1991). Based on the mean skin temperature at 60 minutes, it is to be expected that shivering intensity would be greater in the BW. While there was no significant difference in $\dot{V}O_2$ between the BW and the CB, the subjects perceived that they were shivering much more in the BW than in the CB. By 60 minutes, in the CB, 2 out of 12 subjects were shivering compared with 9 out of 12 in the BW, (Figure 2.12). Although the subjects did 'shiver' more in the BW, this was not reflected in their $\dot{V}O_2$ values as they did not differ significantly between the bags. Errors on gas collection or analysis are unlikely to have occurred, as all equipment were checked and calibrated prior to every trial.

There were no differences for heart rate (HR) between the CB and the BW, (Table 2.1). There was a general trend for HR to decrease in the first half of the tests. Possible contributory factors for the decrease in HR included the supine position of the subjects, peripheral vasoconstriction and cooling of the face (Le Blanc et al, 1976). The adoption of a supine position would enhance baroreflex sensitivity and result in a decreased HR (Vander, 1994). A greater central volume and increased central venous pressure would result from cold induced sympathetic vasoconstriction. The enhanced ventricular filling and larger end-diastolic volume results in a greater stroke volume. Consequently the HR is reduced to maintain a constant cardiac output (Graham, 1988). Cooling of the face has been associated with an increase in parasympathetic activity and a resulting decrease in HR (Smith, 1996). There was a trend for HR to increase in the second half of the tests particularly with the BW in the last 10 minutes. This increase may be attributed to shivering (Haymes and Wells, 1986).

The perception of cold increased in both bags, the increase being significantly higher in the BW (Figures 2.11A & 2.11B and Table 2.1). A drop in skin temperature is probably the signal for cold sensation (Toner and McArdle, 1988). Thus, it may not be unexpected that the lower mean skin temperature in the BW resulted in a greater perception of cold.

There was a significant effect in the order of which the trials took place, regardless of which bag was used first. The first test tended to produce more marked responses (increases or decreases) in the measurements than the second test. This may be due to a slight acclimatization effect that may have taken place (Leppaluoto et al, 2001). These findings highlight the need for an order effect to be considered in the design of similar studies.

There were a number of possible sources of heat loss in this study. The face was directly exposed to a continuous airflow produced by the fans. Most subjects reported that they had a cold face. Respiratory heat loss in a cold environment has been shown to account for around 8% of total body heat loss (Doubt, 1991). Some subjects reported that their feet were cold and some experienced a tingly-cold sensation primarily in their big toes. In almost all the BW trials heat loss took place in the chest, triceps, thigh, and calf areas as evidenced by a fall in skin temperature at these sites. The most marked decrease in skin temperature between the BW and the CB was at the triceps. It is speculated that this may have been due to contact with the stretcher's metal rail, which induced conductive heat loss.

It would be appropriate to emphasize the fact that the BW, although had the same surface area as the CB, its weight was $1/10^{th}$ that of the CB. It was important to test the BW the exact way it is used by the Norwegian teams in their rescue missions, and not add on a second or third layer in an attempt to standardize bulkiness or weight.

In conclusion the BW bag was found to be less effective compared to the CB in protecting subjects under the imposed environmental conditions. This was evidenced by significantly lower skin temperatures (mean and individual skin sites), an increased feeling of cold, as well as a higher perception of shivering in the BW compared to the CB. This study demonstrated that the Casualty Bag offers more protection from cold and wind than the Bubble-Wrap.

Table 2.2

Whole-Body Cold Comfort Scale

0-Comfortable

1-

2-Slightly Cold

3-

4-Fairly Cold

5-

6-Moderately Cold

7-

8-Very Cold

9-

10-Unbearable

Table 2.3

Shivering Scale

0-Absence of Shivering

1-Slight Shivering

2-Moderate Shivering

3-Severe Shivering

CHAPTER 3A

Factors Affecting a Climber's Ability to Ascent Mont Blanc, 4807m

INTRODUCTION

Many sea level dwellers venture to altitude to climb high mountains including the highest peak in Western Europe, Mont Blanc, 4807m. Anecdotal evidence from Alpine guides indicates that a considerable number (~30%) of those who aspire to reach the Mont Blanc summit fail to do so mainly as a result of the adverse effects of hypoxia. This fairly high failure rate may not be too surprising as the literature highlights that exercise at altitude results in a decreased physical work capacity with a fall of around 30% of V_{O_2} max at 4000m compared with sea level values (Buskirk et al, 1967). In addition, acute mountain sickness (AMS) is a common characteristic at altitudes >2500 m (Hackett and Roach, 2000) and has been shown to have an incidence of over 50% at 4300 m (Hackett et al, 1976). Monitoring subject responses to altitude may, along with subject characteristics, allow the identification of poor responders to a hypoxic environment and, for such subjects, precautions could be taken to avoid problems at altitude.

A number of variables may be predictive of success at altitude including recent altitude history of the individuals. Altitude acclimatisation is considered to be an important factor for 'success' at altitude and is strongly linked to ventilatory acclimatisation. A brisk hypoxic ventilatory response (HVR) is considered to be advantageous as it leads to an enhanced arterial oxygen saturation (SaO_2), and has been associated with less severe AMS (King and Robinson, 1972; Sutton et al, 1976; Hackett et al, 1982), although this in not observed at all times. In addition, an increased hypoxemia has been shown in those with AMS and has been associated with hypoventilation (Anholm et al, 1979; Hackett et al, 1982; Moore et al, 1986) and impaired gas exchange (Kronenberg et al, 1971; Sutton et al, 1976).

The aim of the study was to assess performance (i.e. success/failure and time to summit if successful) on the ascent of Mont Blanc (4807m) based on subject characteristics, recent climbing history and physiological variables measured at the Gouter Hut (3817m) before and after an attempted ascent on the Mont Blanc summit.

METHODS

Subjects

Between the 14th-19th of August 2002, 285 subjects (49 females [35±11 years]; and 236 males [28±12 years]) who visited the Gouter Hut, Figure 3A.1, prior to an attempted ascent of the Mont Blanc summit volunteered to take part in the study. A small number of subjects refused to be tested as they felt unwell. Subjects taking acetazolamide or steroids (used in AMS prevention/treatment) were excluded from the time of the study. Of the 285 subjects, 199 were tested on two occasions, before and after the attempt to the summit. The remaining 86 subjects did not report back to us at the Gouter Hut for various reasons. Some descended by another route and some did not want to delay their descent by being tested at the Gouter Hut. Some subjects provided summit information by post or e-mail at a later date. Thus, summit success or failure information was available from 216 subjects. Ethics permission was granted from the Glasgow University Ethics Committee and informed consent was obtained from all volunteers.

Figure 3A.1 Gouter Hut, 3817m.

Study Design

The normal ascent route starts in from the Chamonix valley (1100m), and includes and overnight stay at the Gouter hut (3817m) on Day 1, and thence to the summit (4807m) and back to the hut on Day 2. The experimental procedures took place in the Gouter Hut (3817m), France. The subjects were tested on the day of arrival at the hut (Day 1) and the following day (Day 2) once they had attempted to reach the Mont Blanc summit (4807m), if their descent route was via the Gouter Hut. An attempt was made to make sure that all subjects were tested after they had been in the hut and rested for at least one hour. For all the pre-summit testing this aim was successful, whereas for the post-summit testing it was not possible to comply rigidly with this guideline as some climbers were pressed for time and did not want to wait 30 minutes before being tested. Nevertheless, all climbers were tested upon arrival at the hut from their descent and had at least 20 minutes of rest before testing. A subject information questionnaire and an AMS questionnaire were completed and physiological variables were measured before and after the summit attempt.

Questionnaires

On the first day the subjects completed a questionnaire (Appendix B) which included questions on age, nationality, gender, smoking status, previous altitude experience, residing altitude, climbing profile over the past 14 days prior to the study, and route to the Gouter Hut. On return to the hut the next day (after the attempted ascent on the summit) the subjects completed a questionnaire, which included ascent and descent information. Documentation was provided in four languages: English, French, Italian, and German.

Physiological measurements

Partial pressure end tidal carbon dioxide, ($PETCO_2$), arterial oxygen saturation (SaO_2), heart rate (HR), and respiratory rate (RR) were measured. All measurements were made using a capnograph (Nellcor Eden NPB75, Puritan-Bennett, Bicester, UK).

Physiological Tests - Procedures

The subjects sat quietly for about 6 minutes, Figure 3A. 2. They were asked to not talk or fidget. They breathed atmospheric air through a mask with a line (Nellcor Eden) attached on the expirate side, which was connected to the capnograph for analysis. The saturation probe was attached on the right index finger. Values were recorded when they were stable (around 4-6 minutes). 'High' and 'low' readings were recorded for all measurements and the averages were subsequently used in the analysis of the results.

Figure 3A.2 Collection of physiological measurements in Gouter Hut (with subject permission).

AMS assessment

AMS scores for Days 1 and 2 were obtained using the self-assessment section of the Lake Louise consensus on AMS scoring (Roach et al, 1993). As suggested, a score of 4 and above was used to define the presence of AMS (Maggiorini et al, 1998).

Statistical Analysis

Logistic regression and Classification Trees (Aitchison et al, 1995) were used to investigate which, if any, variables were predictive of a successful ascent of Mont Blanc. Logistic Regression was also used to investigate which, if any, variables were able to predict the presence of AMS (on reaching the height of the Gouter Hut). The potential predictive variables considered in these analyses were: the pre-summit 'average' values for $PETCO_2$, SaO_2, HR, RR and the subject characteristics obtained from the questionnaires (i.e. smoking status, gender, age, sleeping and climbing profiles over the past 14 days before this ascent). Both the raw AMS score and the presence/absence of AMS were included in the success/failure to climb Mont Blanc analysis.

RESULTS

Eighteen subjects failed to reach the summit. Of these 18, 6 turned back to support their friends who were unable to continue. Thus, only 12 climbers, out of a total of 210, did not reach the summit as a result of altitude problems on the way to the summit. For these 210 subjects, Table 3A.1 presents summary statistics of the physiological variables broken down by the *Ascent Outcome* (i.e. did or did not reach summit). For those categorised as having AMS, only 2 out of 27 (7%) failed to reach the summit as opposed to 10 out of 183 (5%) who failed amongst those without AMS.

	Failed to Reach Summit (n=12)	***Successfully Reached Summit (n=198)***
$PETCO_2$ (mmHg)	34.5 (3.0)	33.0 (5.2)
SaO_2 (%)	86.5 (3.9)	87.3 (5.1)
HR (beats.min^{-1})	99.7 (8.2)	91.1 (12.6)
RR (breaths.min^{-1})	13.7 (5.3)	12.7 (4.6)
AMS Score	2 (0-7)	1 (0-7)

Table 3A.1 Sample means and standard deviations (SD) by summit 'outcome' for 'average values' of physiological variables taken at Gouter Hut before attempt on the summit: end tidal carbon dioxide ($PETCO_2$), arterial oxygen saturation (SaO_2), heart rate (HR), respiratory rate (RR) and acute mountain sickness (AMS) score.

Logistic regression shows that only the *Climbing Profile* over the previous 14 days significantly (p=0.04) affected the Ascent Outcome (i.e. whether or not a subject successfully climbed Mont Blanc from the Gouter Hut) although *Heart Rate* both individually (p=0.06) and having corrected for climbing profile (p=0.07) did get very close to inclusion in the final model. The effect of climbing profile is illustrated in Table 3A.2 where one can see that those who had climbed over 4000m in the previous 14 days had a significant advantage in terms of a successful ascent of Mont Blanc. All subjects who had been to 4000m in the previous 14 days made a successful ascent of Mont Blanc. Although not statistically significant, the slightly higher number of subjects who failed to reach the summit for those who had climbed between 3000 and 4000m in the previous 14 days, as opposed to those who had climbed less than 3000m, is likely to be simply due to sampling variability.

Climbing Profile in Previous 14 Days	***Failed to Reach Summit (n=12)***	***Successfully Reached Summit (n=198)***
Less than 3000m	5	68
Between 3000 and 4000m	7	65
Over 4000m	0	65

Table 3A.2 Climbing Profile in previous 14 days by ascent 'outcome' of Mont Blanc from the Gouter Hut (i.e. maximum altitude reached in previous 14 days).

A Classification Tree for the Ascent Outcome based on these data is provided in Figure 3A.3 and illustrates again the dominating effect of climbing profile. However, Classification Trees allow the investigation of 'high order interactions' not often investigated nor easily identified by Logistic Regression and here this technique highlights the effect of heart rate already suggested by Logistic Regression and indeed uncovers an additional effect of $PETCO_2$. This analysis allows one to deduce that those climbers likely to fail to reach the summit of Mont Blanc from the Gouter Hut are those with a Heart Rate in excess of 85 bpm *and* a $PETCO_2$ of more than 36 mmHg and *who* have not climbed higher than 4000m in the previous 14 days.

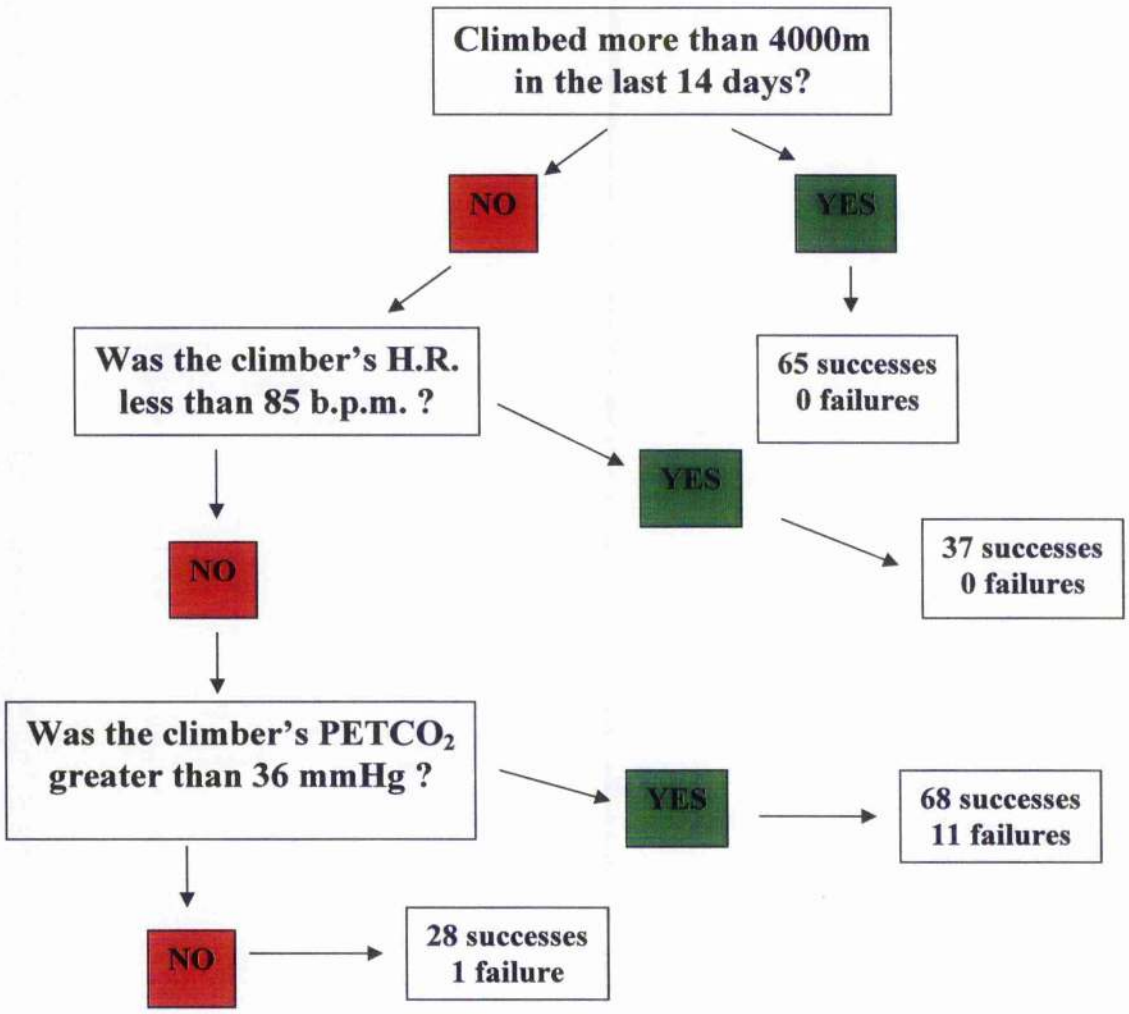


Figure 3A.3 Classification Tree for the Ascent Outcome of Mont Blanc from the Gouter Hut for the 210 subjects.

For the *Ascent Times* (hours) of the 198 successful climbers of Mont Blanc (from the Gouter Hut), various linear model variable selection procedures (such as Forward Stepwise and Best Subsets) indicated that the *Climbing Profile* in the previous 14 days was the key significant ($p<0.01$) factor. The sample mean $\pm$ SD ascent time for those who had been over 4000m in the previous 14 days was 4.03 $\pm$ 0.7 hours, for those between 3000 and 4000m it was 4.27 $\pm$ 0.9 hours and for those below 3000m it was 4.47 $\pm$ 0.8 hours. Further, the *Age* of the (successful) climber appeared to be marginally significant in addition to Climbing Profile ($p=0.08$). However, as can be seen from Figure 3A.4 where 'smooth non-parametric regression' fits of the effect of Age on Ascent Time for the three sub-groups of Climbing Profile (i.e. <3000m, 3000 to 4000m and >4000m in the previous 14 days) are presented, it appears that the relationship of Age and Climbing Profile on Ascent Time is not so straightforward or indeed linear and/or additive! This notion is confirmed and amplified using a Regression Tree approach whose results are illustrated in Figure 3A.5. Here the effects of *Age, Climbing Profile* and *Sex* of the (successful) climber on Ascent Time of Mont Blanc (from the Gouter Hut) and conform to 'conventional wisdom' with older climbers the slowest and younger climbers with recent time spent at altitude the fastest.

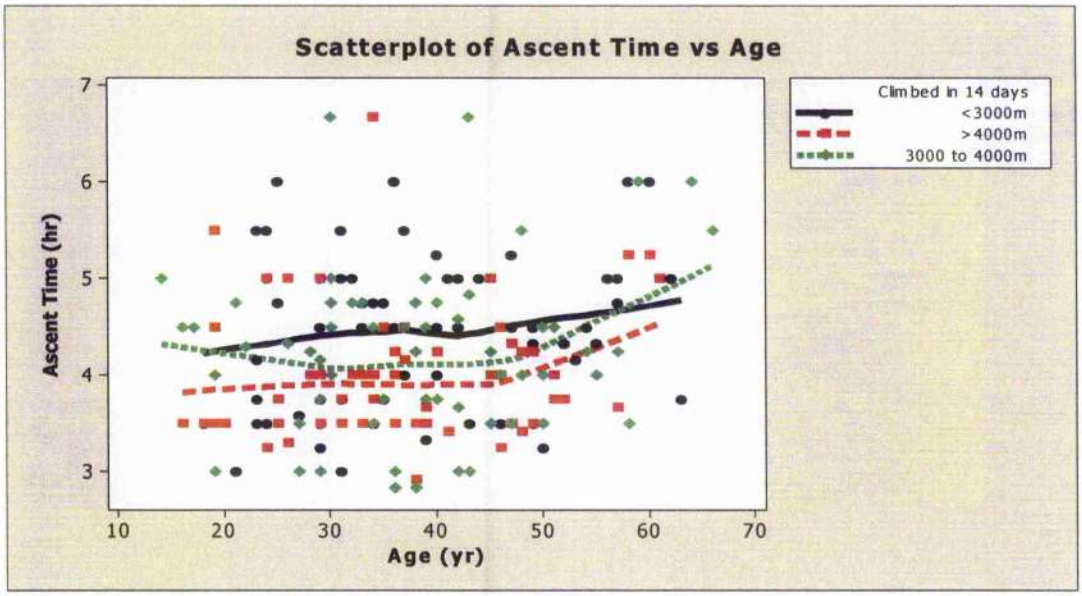


Figure 3A.4 Non-Parametric Regressions on Age for the Ascent Time of Mont Blanc from the Gouter Hut by level of Climbing Profile in the previous 14 days (197 subjects).

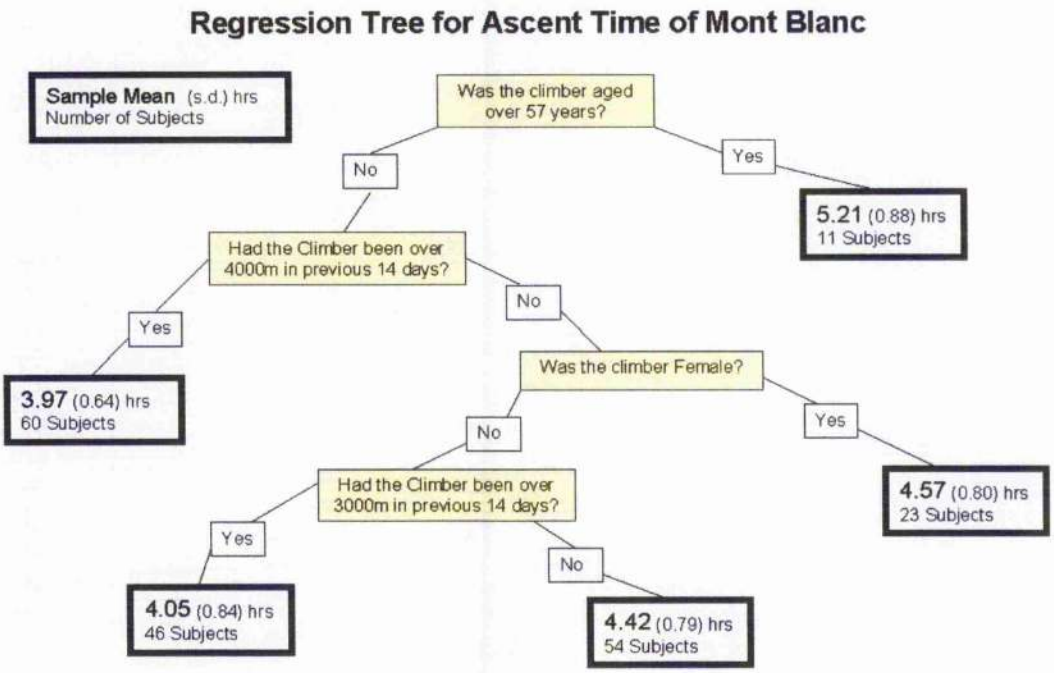


Figure 3A.5 Regression Tree for the Ascent Time of Mont Blanc from the Gouter Hut for the 197 subjects.

Those who had been over 4000m had a higher SaO_2 and lower raw AMS score than those who had not been above 3000m in the previous 14 days (Table 3A.3). Similarly the AMS scores on Day 2 were significantly different between those who had been over 4000m (2.6±2.0 units) compared with those under 3000m (4.7±2.7 units). With respect to presence or absence of AMS (i.e. an AMS score of 4 or more) on ascent to the Gouter Hut, a Logistic Regression showed that the Climbing Profile again proved significant ($p=0.03$) with the Age of the climber verging on being additionally useful ($p=0.07$). The effect of Age was that increasing age decreased the probability of AMS. This analysis was based on the 285 climbers whose physiological measurements were taken at the Gouter Hut of whom 40 had AMS and 245 did not.

	Climbing Profile in previous 14 days		
	Less than 3000m (n=73)	***Between 3000 and 4000m (n=72)***	***Over 4000m (n=65)***
$PETCO_2$ (mmHg)	33.1 (5.2)	32.7 (4.7)	33.5 (5.4)
SaO_2 (%)	**86.0*** (5.9)	87.6 (4.7)	**88.1** (4.1)
HR (beats.min^{-1})	93.3 (11.4)	91.5 (12.6)	89.6 (13.7)
RR (brths.min^{-1})	13.2 (4.2)	12.4 (4.7)	12.6 (5.1)
AMS Score (units)	**2*** (0-7)	1.5 (0-7)	**1** (0-6)

Table 3A.3 Summary statistics of $PETCO_2$, SaO_2, HR, RR, and AMS Score for Day 1 by Climbing Profile in previous 14 days.

Sample mean (SD for all variables apart from AMS.) - sample median (range) for AMS

*Significantly different from over 4000m

There was no strong indication that the presence or absence of AMS (or indeed the raw AMS score) was of any value in predicting the Ascent Outcome of climbers (Table 3A.4) especially if one adjusts for Climbing Profile in the previous 14 days nor indeed that the 75 climbers whose final Ascent Outcome was unknown (or turned back to support fellow climbers) had a significantly higher percentage of AMS than those whose outcome was known (Chi-Square Test, p=0.69).

Ascent Outcome	***AMS*** ***(n=40)***	***No AMS*** ***(n=245)***
Failed to reach summit	2	10
Reached summit	25	173
Unknown etc.	13	62

Table 3A.4 Relationship of presence/absence of AMS (i.e. a raw AMS score of 4 or more corresponds to presence of AMS) to Ascent Outcome.

The relationship between the raw AMS scores before and after the attempted ascent of Mont Blanc from the Gouter Hut is illustrated in the scatter plots of Figure 3A.6 where it appears that there is, at best, a limited relationship between the AMS scores before and after the attempted ascent which hardly differs between those whose ascent was successful and those ascent was not. Indeed, a two-sample t-test of the difference in raw AMS score (after – before) shows no significant difference ($p = 0.13$) between the two ascent outcomes.

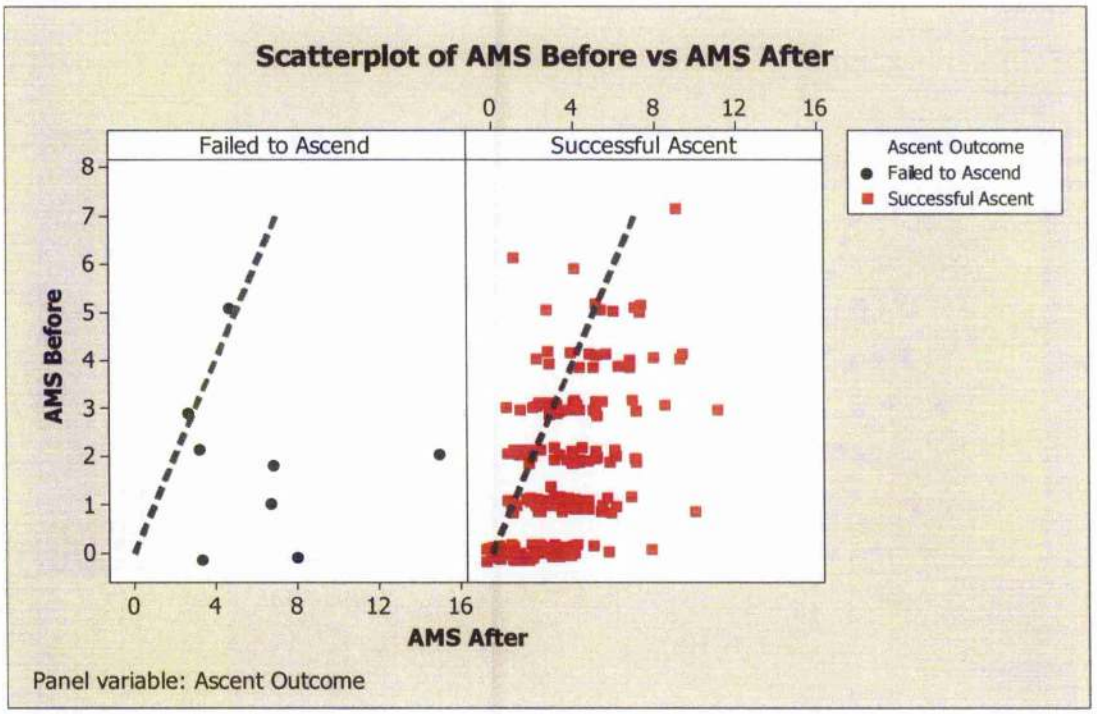


Figure 3A.6 Plots of raw AMS scores before and after attempted ascent of Mont Blanc from the Gouter Hut labelled by Ascent Outcome (plots also include the line of equality of AMS before and after ascent).

As can be seen in Figure 3A.7 there are no meaningful relationships among any of the respiratory variables (viz. $PETCO_2$, SaO_2, HR and RR) – although some have very small sample correlations significantly different from zero - nor indeed of any of these with the raw AMS score taken on arrival at the Gouter Hut. Similarly, there are no worthwhile relationships to be reported after return from the attempted ascent on the summit.

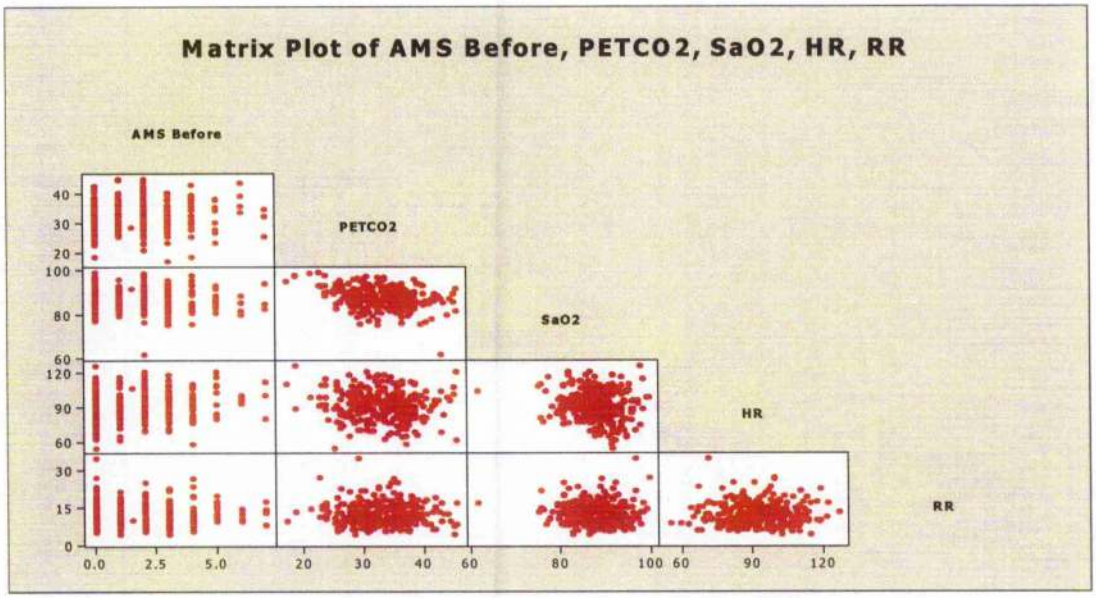


Figure 3A.7 Pair-wise plots of all physiological variables and AMS score taken at arrival at Gouter Hut

DISCUSSION

Climbing Profile over the previous 14 days significantly affected the ascent outcome and ascent times (Table 3A.2). It is not unexpected that recent exposure to over 4000m would confer an advantage for those who wished to ascend a 4800m peak. A recent study by Muza et al (2004) showed that a 12-day period at 4300m resulted in an increase in SaO_2 from 84% on Day 1 to 89% on Day 12. Minute ventilation increased over the same time period from 11.6 to 16.0 $l \cdot min^{-1}$ (Muza et al, 2004). Thus it may have been anticipated that differences in recent exposure to a range of altitudes would have resulted in physiological differences in the subjects in the present study. Table 3A.3 shows that those who had been over 4000m in the previous 14 days had a higher SaO_2 and lower AMS raw score than those who had not been above 3000m. The slightly higher SaO_2 for those who had been over 4000m may have resulted in an advantage during the ascent of Mont Blanc. Those who had been over 4000m in the previous 14 days made the fastest ascent and none of the climbers in this group failed to reach the summit. It may have been expected that the $PETCO_2$ in this group would have been lower (the SaO_2 was higher in this group) than those in the under 3000m group as lower values would indicate an increase in alveolar ventilation resulting from a hypoxic stimulus. However, there were no differences for $PETCO_2$.

For those who had not been to 4000m in the previous 14 days, the classification tree identified two other factors, which had a bearing on ascent outcome, namely heart rate and $PETCO_2$. The higher heart rates (> 85 beats$\cdot min^{-1}$) of those who failed may be may be reflective of an increased sub-maximal cardiac output in an attempt to cope with the hypoxic conditions (Stenberg et al, 1966), but also a reflection of the increased sympathetic activity during high altitude exposure (Malhorta et al, 1976). Altitude acclimatisation is associated with an increase in ventilation. With ventilatory acclimatisation, the increase in alveolar ventilation would result in a decreased $PETCO_2$. Thus, it may not be surprising that the $PETCO_2$ has been included as a factor in the classification tree. In those subjects who had not been to 4000m in the previous 14 days and who had heart rates over 85 beats$\cdot min^{-1}$, 11 out of the 12 failures had a $PETCO_2$ of 32 mmHg or above.

Summit times become slower as the age of the climber increased and are slower for females. These findings are not surprising as maximal oxygen uptake (Vo_2 max), a

measure of cardio-respiratory endurance, has been shown to decrease with age with a gradual decline in Vo_2 max from around the age of 20 years. Astrand and Rodahl (1986) give a representative example of this decline when they state that 65 year olds will have a Vo_2 max of ~ 70% of that of a 20 year old. Vo_2 max in females has been found to be, on average around 65 to 75% of that of men (Astrand and Rodahl, 1986).

Although the Classification and Regression Trees are suggestive of significant and interesting effects of various variables, especially Climbing Profile, on the ability to complete the ascent of Mont Blanc and, indeed the time to do so, a further study of performance on this or on a comparable mountain must be carried out to test the predictive capability of these models. One must assess any predictive model, whether simple linear regression or Trees-based models, on a further set of comparable data in order to make justifiable scientific claims.

AMS was significantly lower in those with recent exposure to 4000m+. It is to be expected that recent exposure to altitude would lower the incidence of AMS and enhance performance in a hypoxic environment (Lyons et al, 1995; Schneider et al, 2002). Whether subjects were classified as having AMS or based on the raw AMS score, there was no evidence of any relationship of either of these with summit success or indeed with the ascent time. The incidence of AMS in this study at 3817m was 14% on Day 1 and 46% on Day 2. Another study at a similar altitude to ours, 3650m, in the Swiss Alps (Maggiorini et al, 1990) reported an incidence of AMS of 8%. The incidences seen in this study (14% before the summit attempt and 46% after) almost fall within the range of 12-42% from a number of studies assessed at altitudes below 4000m (Hackett et al, 1979; Houston et al, 1985; Montgomery et al; 1989; Honigman et al, 1993). Even though not all the above studies used the exact same scoring system, they all assessed their subjects using similar guidelines to evaluate their AMS symptoms. Possible reasons for an increase in AMS from Day 1 to Day 2 may be attributed to the increased length of time at a higher altitude as the climbers went to and from the Mont Blanc summit. The onset of AMS symptoms is considered to begin between 6 and 12 hours after arrival at altitude (Ward et al, 2000). Most subjects started to climb to the Gouter Hut from 2300m, with an ascent time of 5-6 hours. Thus, the fact that some subjects were tested fairly soon after they had entered

the Gouter Hut may have been too early to detect AMS symptoms in some of them. Recommendations for the treatment of AMS emphasise that AMS subjects should not climb higher. Thus it is not surprising that the AMS scores increased as climbers went higher and were involved in strenuous exercise (Roach et al, 1998). The great increase in AMS incidence in this study from 14% on Day 1 to 46% on Day 2 is not unexpected as the subjects were at altitude for longer and most of them climbed to 4800m. The finding that AMS incidence is lower in 'older' subjects supports the statement by Roach et al (1995) that the incidence of AMS decreases in 'older' subjects.

There was a poor relationship between the physiological variables and AMS. These findings disagree with studies that have shown that a low SaO_2 is associated with subsequent development of AMS (Roach et al, 2000; Hussain et al, 2001). The link between the severity of mountain illness and hypoxemia has been attributed to hypoventilation (Anholm et al, 1979; Hackett et al, 1982; Moore et al, 1986) and impaired gas exchange (Kronenberg et al, 1971; Sutton et al, 1976). There were no significant differences in $PETCO_2$ between the AMS and non-AMS subjects before the ascent and suggests that hypoventilation is unlikely to be the cause of the AMS.

One subject upon arrival at the Gouter hut on Day 1 had a SaO_2 value of 62%. The subject's $PETCO_2$ was 43mmHg, and he was classified as AMS asymptomatic. The low SaO_2 value was questioned by the experimenters but repeat measurements using another capnograph verified the initial readings. A physician examined the subject and observed central cyanosis. It was speculated that the subject suffered from a cardiac problem. Based on the low SaO_2, the experimenters considered that the subject would be unlikely to reach the summit. However, the subject did reach the summit of Mont Blanc in 5.5 hours. He was advised to seek medical advice as soon as possible.

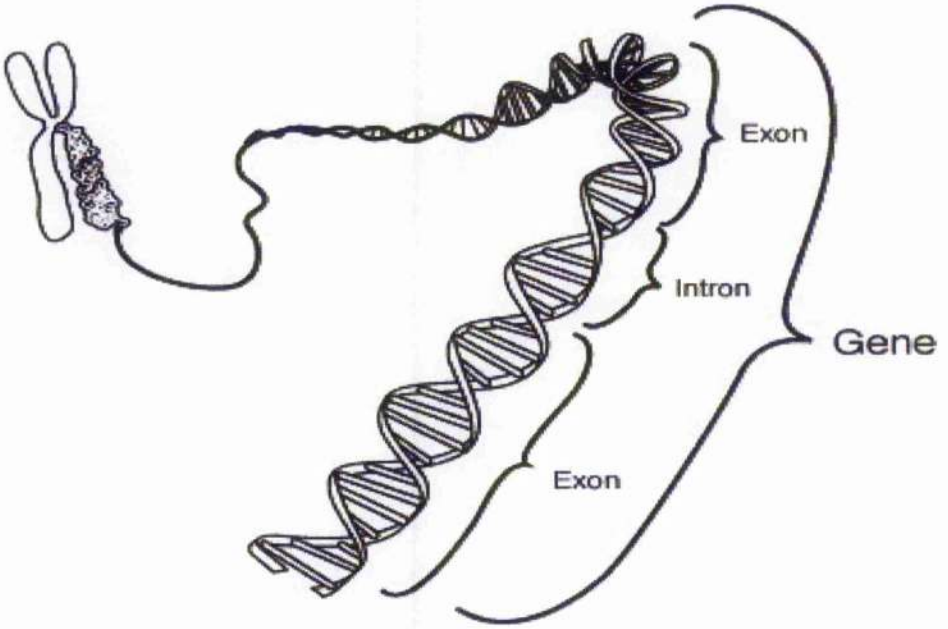
The 6%, n=12 (or 8%, n=18), failure rate is much lower than the estimated 30% failure rate of the Alpine guides' predictions. However, 24% of our tested climbers never reported back to us and these missing data may hide the fact that the failure rate was in fact higher than we recorded. It is possible that the 69 subjects who did not provide summit information failed to do so because they were unsuccessful. This

speculation is unlikely to be valid for some subjects as they descended Mont Blanc by an easterly route and thus did not descend via the Gouter Hut to be tested. There were no differences for any of the measurements tested on Day 1 between those who were tested on both occasions (Days 1 and 2) and the 69 who were not tested on Day 2.

In conclusion, climbing profile over the previous 14 days significantly affected the ascent outcome and ascent times. Previous recent exposure to an altitude of over 4000m resulted in faster ascent times, higher SaO_2 and lower AMS scores than those who had not been above 3000m in the previous 14 days. Recent exposure to over 4000m confers an advantage to those who wish to ascend a 4800m peak.

CHAPTER 3B

Performance at Altitude and Angiotensin Converting Enzyme Genotype



INTRODUCTION

As a component of the circulating (endocrine) renin-angiotensin system (RAS), angiotensin-converting enzyme (ACE) cleaves vasodilator kinins whilst yielding vasoconstrictor angiotensin (which also drives salt and water retention through stimulation of aldosterone release). However, paracrine RAS also exist in human tissues (Yosipiv et al, 1994; Danser et al, 1995; Reneland et al, 1999) where they play diverse roles. A variation of the human ACE gene has been identified, in which the presence (insertion, or I-allele) rather than the absence (deletion, D-allele) of an extra 287-base pair fragment is associated with lower circulating (Rigat et al, 1990) and tissue (Costerousse et al, 1993; Danser et al, 1995) ACE activity.

An excess frequency of the ACE *I* allele has been noted amongst elite endurance athletes (Gayagay et al, 1998; Myerson et al, 1999; Woods et al, 2002, Tsianos et al, 2004) which might be partly explained by a genotype-dependent improvement in skeletal muscle mechanical efficiency with training (Williams et al, 2000). The substantially greater I-allele excess reported amongst high altitude (HA) mountaineers (Montgomery et al, 1998) thus might relate to 'positive' self-selection by success in physical performance (increased metabolic efficiency- the ratio of internal energy consumed per unit energy output) being an especial advantage in the hypoxic environment. Such 'positive' selection might also relate to better-sustained arterial oxygen saturations being associated with the *I*-allele (Woods et al, 2002). Alternatively, this association might relate to 'negative' selection of individuals less prone to the debilitating symptoms of acute mountain sickness (AMS).

To date, no study has 'prospectively' addressed the possible association of ACE genotype with successful HA ascent. Meanwhile, only one (negative) study has so far examined the association of ACE genotype with AMS development (Dehnert et al, 2002). The aims of this study were: to address the relationship between ACE genotype with AMS onset on both, arrival to altitude and consequent return from a higher altitude, to investigate any I allele benefits with altitude performance (assessed by successful or not attempt to the summit of Mont Blanc), and look for any differences in the tested physiological measurements between the ACE genotypes.

METHODS

The study was approved by the Glasgow University Ethics Committee. Written informed consent was obtained from all volunteers.

Subjects

Consecutive caucasian climbers attempting to climb Mont Blanc by the 'normal' route were approached over a nine-day period (Aug 14-22, 2002), and 284 consequently participated. This route entails ascent from the Chamonix valley (1100m) to the Gouter hut (3817m) on Day 1, and thence to the summit (4807m) and back to the hut on Day 2. Subjects taking acetazolamide or steroids (used in AMS prevention/treatment) were excluded from the time of the study. From those who consented to take part, a buccal swab was obtained for future genetic analysis. Physiological measurements ($PETCO_2$, SaO_2, HR, RR) and AMS scores were recorded. Those who chose to descend via the same route were again assessed on day 2, when AMS scores were recorded, and success or failure in summiting was ascertained.

AMS Score Assessment

AMS scores for Days 1 and 2 were obtained using the self-assessment section of the Lake Louise consensus on AMS scoring (Roach et al, 1993). As previously assessed, a score of 4 and above was used to define the presence of AMS (Maggiorini et al, 1998).

Genotyping

Buccal cells were collected using Whatman sterile foam tipped applicators (Whatman Bioscience Ltd, Abington, Cambridge, U.K.) swabbed vigorously against both inner cheeks and dampened under the tongue. The swabs were then pressed firmly onto a Whatman FTA micro-card (Whatman Bioscience Ltd, Abington, Cambridge, U.K). From these, DNA was extracted, and ACE genotype determined at a separate site (UCL), using a three-primer method as previously described (O'Dell et al, 1995).

Statistical Analysis

Differences in physiological parameters between genotypes were assessed by one-way ANOVA, or Kruskal-Wallis where appropriate. Genotype-dependent differences in AMS prevalence and success in reaching the summit were considered via chi-squared tests. Statistical significance was set at $p<0.05$.

RESULTS

Of 1223 eligible subjects on Day 1, 284 agreed to participate. Their genotype distribution (II 56 [19.7%], ID 142 [50%], DD 86 [30.3%], I allele frequency = 0.45) was consistent with Hardy-Weinberg equilibrium. Of these, 210 descended by the same route on Day 2. Their Day 1 physical and physiological characteristics, AMS onset and severity, and genotype distribution (II 43[20.5%], ID 107[51%], DD 60[28.5%]) did not differ significantly (p=0.81) from those unavailable for reassessment. These subjects descended by another route or failed to report back.

Genotype and Success in Reaching Summit

Success in reaching the summit was dependent upon ACE genotype. Of those subjects returning by the same route, I allele frequency for those who reached the summit was 0.47 compared to 0.21 for those who did not reach the summit (p=0.01), with 53 [88.3%] of DD genotype reaching the summit, compared to 102 [95.3%] of those of ID genotype, and *all* 43 [100%] of those of II genotype (p=0.048), Figure 3B.1. Summiting offers a greater variety of descent routes: those who summit are thus more likely to descend by an alternative route than those who fail, who will generally descend by the same route. Even if we assume that *all* the 74 taking an alternative route of descent had successfully summited, the ACE I-allele remains significantly associated with success (I-allele frequency 0.46 that all those taking an alternative route of descent versus 0.21 for success vs. failure groups, p=0.02). Only if one assumes that all those taking and alternative route of descent had failed to summit (an implausible claim, for reasons explained above) does this association weaken (I-allele frequency 0.47 versus 0.40 for success vs. failure groups, p=0.10; for those successful, p=0.25). To consider the possibility whether success to the summit was genotype dependent based on climbing profile (i.e. <3000m, 3000 to 4000m and >4000m in the previous 14 days) the genotype frequency distribution in the most successful group to the summit (>4000m) was 21 II (23%), 48 ID (54%), 21 DD (23%).

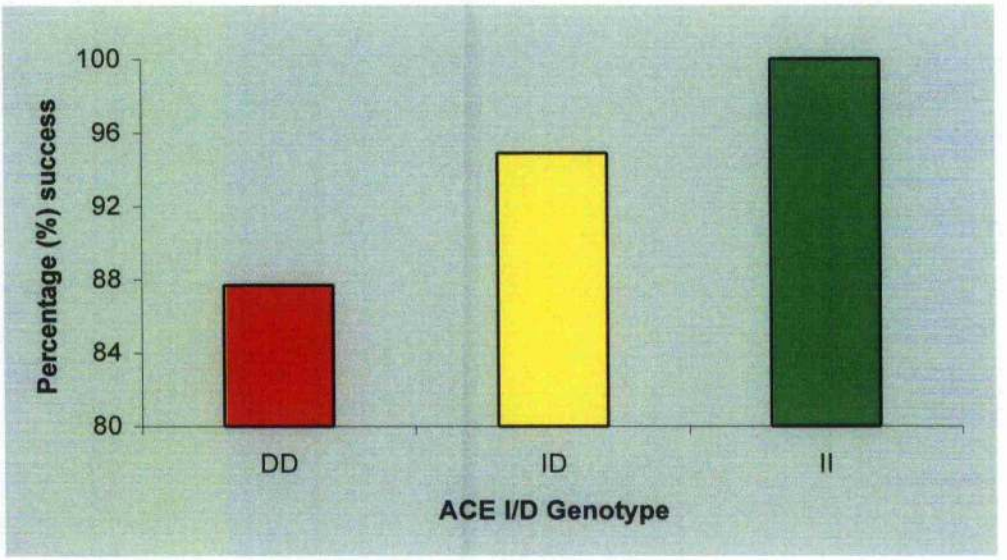


Figure 3B.1 Graph showing percentage of subjects successful in reaching the summit of Mont Blanc for each ACE I/D genotype. Success for those returning by the same route was dependent upon ACE genotype.

AMS incidence and severity

On Day 1, 40 (of 284) individuals were suffering from AMS. The percentage AMS incidence by genotype was 21.4% [12/56] for the II, 7.0% [10/142] for the ID, and 20.9% [18/86] for the DD, (p=0.003) for comparison of genotype distribution between those with and without symptoms the, ID group having a significant lower incidence. On Day 2, 92 (of 200) individuals satisfied the diagnostic criteria for AMS. The percentage AMS incidence by genotype was 48.8% [20/41] for the II, 40.6% [41/101] for the ID and 53.7% [31/58] for the DD group, (p=0.3) for comparison of genotype distribution between those with and without symptoms. Ordered logistic regression showed an association between genotype and AMS severity on Day 1 (p=0.045) in favour of the ID genotype, and no association for Day 2 AMS sufferers (p=0.08). In addition, there was no statistical evidence to suggest that Day 1 AMS sufferers were less likely to be successful in reaching the summit (p=0.25).

Finally, there were no significant differences between the genotypes and the recorded physiological measurements ($PETCO_2$, SaO_2, HR, and RR) on Day 1 or 2, Tables 3B.1 and 3B.2.

	DD	ID	II
SaO_2 (%)	86.9± 5	88.2± 5	87.6± 5
$PETCO_2$ (mmHg)	33.1± 5	32.7± 5	33.3± 6
Heart Rate (beats•min $^{-1}$)	92±13	91.9±13	91.2±12
Respiratory Rate (breaths•min $^{-1}$)	13.1±5	12.4±5	12.9±4

Table 3B.1 Physiological variables data on Day 1 according to ACE genotype.

	DD	ID	II
SaO_2 (%)	88.1± 5	87.8± 8	85.5± 5
$PETCO_2$ (mmHg)	32.7± 5	33.2±55	34.1±5
Heart Rate (beats•min $^{-1}$)	94.5±12	92.6±13	93.7±11
Respiratory Rate (breaths•min $^{-1}$)	15.4±6	14.1±6	14.9±6

Table 3B.2 Physiological variables data on Day 2 according to ACE genotype.

DISCUSSION

The ACE I-allele is associated with success in HA ascent in this, the first prospective study to address this question. Such a finding is consistent with the previously reported excess frequency of the I-allele amongst elite mountaineers (Montgomery et al, 1998). This association however, seems unrelated to AMS incidence or severity. The overall incidence of AMS on Day 1 in this study was 14% and agrees with reports from other studies at similar altitudes in the Alps (Maggiorini et al, 1990; Maggiorini et al, 1998), and such incidence (and severity) were unrelated to ACE genotype. The association of AMS with genotype on Day 1 seemingly relates to a biologically-implausible heterozygote advantage which, itself, cannot account for the genotype-association noted with ascent success.

Thus, the ACE I-allele is associated with a greater likelihood of ascent to a 4800m summit, and this success seems unrelated to a genotype association with AMS development. Such data support those of Dehnert (Dehnert et al, 2002) who similarly found no association of ACE genotype with AMS amongst alpine mountaineers.

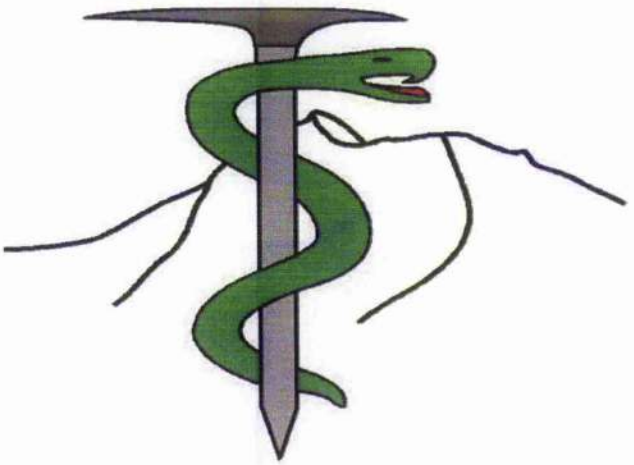
No significant differences were observed between the genotypes and $PETCO_2$, SaO_2, HR, or RR. It was hypothesised that there would be a difference between SaO_2 and genotype in view of the fact that Woods et al, (2002) showed that subjects of the II genotype had higher SaO_2 values, but his results were measured over the span of 12 days at altitude.

Further studies are required to explore the physiological mechanisms underlying this observed association. A genotype-dependence in metabolic/mechanical efficiency of skeletal muscle may partly contribute (Woods et al, 2002). Equally, a better maintained SaO_2 has been previously found amongst I-allele subjects during a rapid ascent to altitude (Woods et al, 2002), a phenomenon which may relate to genotype-dependent differences in hypoxic exertional ventilatory response (Patel et al, 2003), and which may contribute to improved HA performance (Montgomery et al, 1998). Finally, higher ACE activity, as marked by the DD genotype, has been associated with exaggerated hypoxic pulmonary vasoconstriction (Cargill and Lipworth, 1996), and possibly thus with increased ventilation-perfusion mismatch (Hlastala et al, 2004).

In conclusion, it was shown that performance at high altitude is associated with ACE I/D genotype, but this does not appear to be due to an effect on the onset or severity of AMS, or associated with any of the measured physiological variables.

CHAPTER 4

The Effect of ACE Genotype And Hypoxic Ventilatory Response On Daily Arterial Oxygen Saturation And Other Physiological Measurements During a Staged Ascent to 5000m



MEDICAL EXPEDITIONS
2003

INTRODUCTION

A number of factors influence performance at high altitude (HA). Determination of those variables associated with HA problems may help identify those individuals who experience difficulties. Consequently, strategies to prevent HA problems may be used for those susceptible to HA.

The ACE gene's I-allele association with endurance performance (Gayagay et al, 1998, Myerson et al, 1999, Tsianos et al, 2004) and the ability to attain higher altitudes (Montgomery et al, 1998), are both of importance in HA performance. The mechanisms however underlying this benefit of the I-allele are not yet fully understood. A significant genetic influence for increased arterial oxygen saturation (SaO_2) levels exists in HA residents (Beall et al, 1994). A better maintained SaO_2 has been reported amongst II genotype subjects who undertook a rapid ascent to altitude, as opposed to no genotype differences when ascent was gradual (Woods et al, 2002). Furthermore, an excess of the I-allele has been observed in highland natives living over 3000m (Rupert et al, 1999), as well as in HA mountaineers (Montgomery et al, 1988). Despite the positive I-allele associations, Dehnert et al, (2002) and this thesis (Chapter 3B, Tsianos et al, 2004b) reported that no ACE genotype related differences exist for the onset of AMS on ascent to altitude.

The hypoxic ventilatory response (HVR) is also of importance at HA as it aids in the maintenance of increased SaO_2 levels, with a large response resulting in higher oxygen saturations, leading to a better climbing performance (Schoene et al, 1984). Although a brisk HVR may be a factor in predicting onset of Acute Mountain Sickness at altitude (King and Robinson, 1972; Moore et al, 1976), some studies show no such relationship (Milledge et al, 1988; Milledge et al, 1991). Patel et al, (2003) showed the ventilatory response during hypoxic exertion to be genotype related, with those of the II genotype exhibiting a larger increase in minute ventilation. No information is however available on what role the degree of HVR may play on predicting any other physiological measurements.

Previous studies have been characterized by information by small subject numbers. Consequently the findings from those studies may have limitations. There is a need to increase the knowledge base and further explore the current I-allele associations. The

aims of this study were to investigate the role of the ACE genotype on SaO_2, HR and AMS during gradual ascent to altitude (5000m). Furthermore, the degree of HVR, measured during rest at sea level, was used to predict the physiological responses through the daily measurements of SaO_2, HR, and AMS, while any ACE genotype related differences on HVR were also considered.

METHODS

Subjects

The subjects, Caucasian, (n=55, 33 males [36±12 years]; 22 females [32±6 years]), members of a research expedition to Nepal, volunteered for the study. The expedition was organised by Medical Expeditions (MEDEX). All participants where divided into 5 separate trekking groups, and followed the same route, Table 4.1 (page 111) on their way to the research Base Camp (BC) (5000m), Figure 4.1. Ethics permission was granted from the Joint University College London Ethics Committee, and informed consent was obtained from all volunteers.

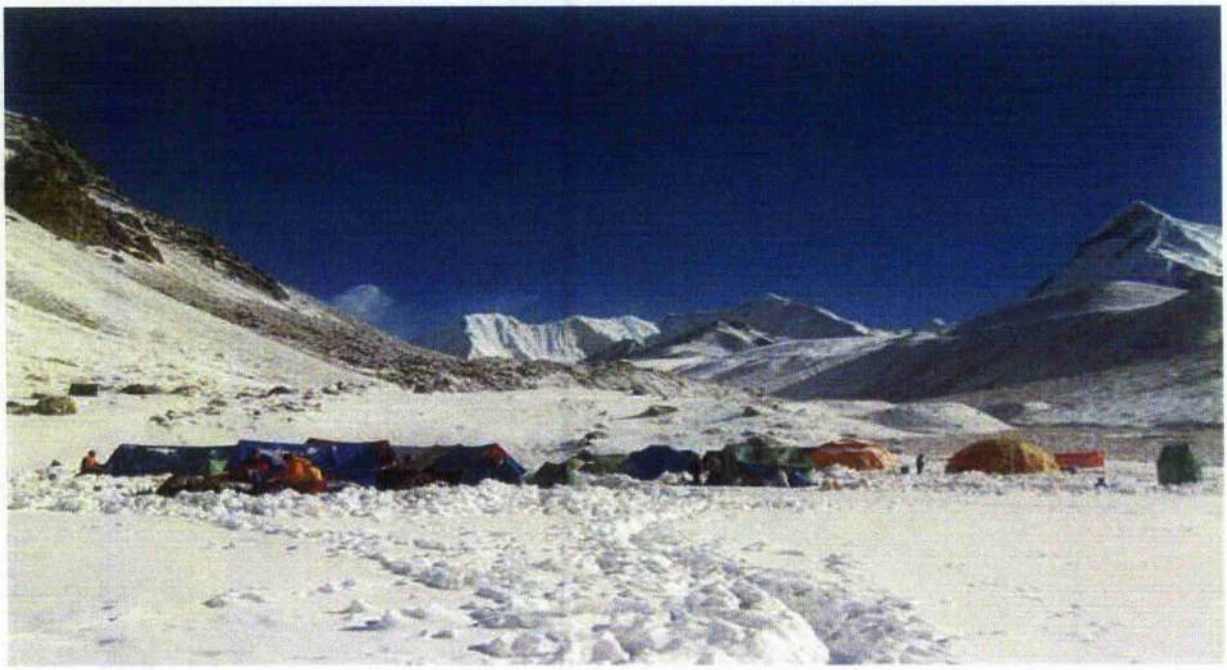


Figure 4.1 Research/Chamlang Base Camp, 5000m.

Design

HVR was measured at sea level during rest, and was assessed 2 months prior to the expedition. Genetic samples were collected and ACE genotype identification was subsequently made at UCL cardiovascular genetics laboratory.

Recording of all physiological measurements (AMS, SaO_2, HR) took place daily in the Nepalese Himalayas during the trek from Tumlingtar (330m) to the Chamlang BC (5000m) in the Hungu valley, as well as for the 3 days after arrival at BC.

ACE Genotyping

5ml single venous blood sample was drawn from each subject and ACE genotype was determined using a three-primer method (O'Dell et al, 1995). All DNA samples were numbered, and not named. No database contains names as well as genotype data. All DNA samples were analysed at a separate site (UCL), blinded to subject data.

Hypoxic Ventilatory Response (HVR)

The hypoxic ventilatory response was assessed through the method of progressive hypoxia and isocapnia, as previously described (Rebuck and Campbell, 1974). A rolling seal spirometer (Morgan Spiroflow, Model #131, PK Morgan, Gillingham, Kent, England) was used with a turbine providing a circulation of gas round a closed circuit. No absorbent was put into the soda lime canister but an external absorber was provided with a tap and bypass so that expired CO_2 could be absorbed or not. This allowed the operator to maintain the $PETCO_2$ constant on the carbon dioxide analyser (Carbon Dioxide, PK Morgan LTD, Rainham, Kent, England). The $PETCO_2$, ventilation, and SaO_2 were monitored via a pulse oxymeter (Pulse Oxymeter 515A, Novametrix, Medical Systems Inc.) and recorded on line using the computer program software "Spike 2". From these measurements, minute ventilation against SaO_2 could be plotted and the $\Delta Vent/\Delta SaO_2$ subsequently calculated ($L \cdot \%SaO_2^{-1}$).

HVR Protocol

The subject was made comfortable in a semi-reclined resting position; a mouthpiece and nose-clip were put on and the subject breathed room air (Figure 4.2). A saturation probe was attached on the subject's right index finger. The spirometer was opened to the air, and when filled with 6L for >70kg subject or 5L for <70kg subject, it was then connected to the breathing apparatus. When the $PETCO_2$ values became steady, the subject was connected to the spirometer at the end of expiration. $PETCO_2$ was kept at starting values by manipulating the bypass tap. As the decreasing SaO_2 values reached 80% the experimental procedure was then terminated by turning the mouthpiece tap to air. Consequent establishment of HVR was made through analysis of traces on the "Spike 2" program, using a breath-by-breath data analysis.

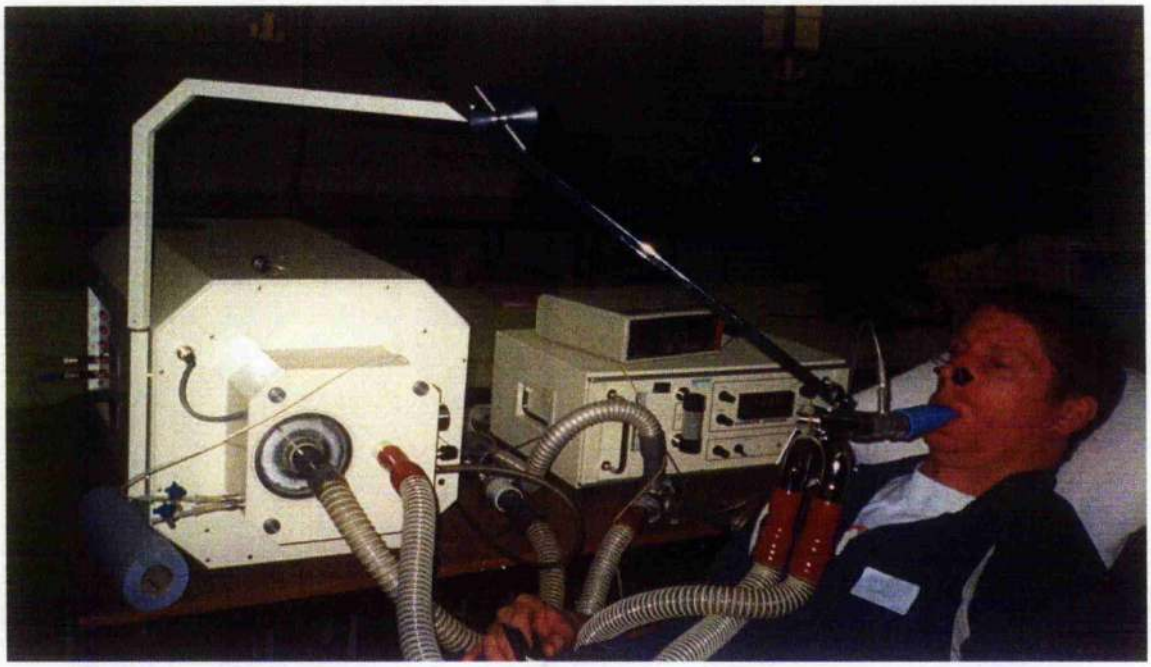


Figure 4.2 HVR assessment (with subject permission).

Measurements in the Himalayas

Physiological Measurements (SaO_2, HR)

The measurements were made daily in the morning, while the subjects were sitting at rest for at least 30 minutes, in a quiet warm environment, and prior to a meal. A pulse oxymeter (Nonin Onyx DE/089) was used for the recording of the data. 'High' and 'low' values were recorded for the measurements of SaO_2 and HR, while the average was used in the data analysis.

Acute Mountain Sickness (AMS)

AMS was measured daily in the morning, using the AMS self-assessment section of the Lake Louise consensus on AMS scoring (Roach et al, 1993). The symptoms tested were: headache, gastrointestinal, tiredness, dizziness, and quality of sleep; the scoring scale for each symptom ranged from 0-3. A combined score of 4 and above denoted AMS, as previously described and recommended (Maggiorini et al, 1998).

Statistical Analysis

Statistical analysis was conducted using STATA (v 8.0, College Station, Texas) unless otherwise stated. SaO_2 and HR are presented as means and standard deviations, whereas AMS was measured on an ordinal scale. Differences in both SaO_2 and HR by ACE genotype over altitude were considered using SAS procedure mixed model, hence considering all repeated measures from all individuals, and a spatial correlation structure was applied to account for the altitudes being unevenly spaced to account for differences in height achieved from day to day. Differences in AMS by ACE genotype over altitude, were considered using generalised estimating equations, in which, AMS was categorized into a binary variable, <4 and >=4, as <4 defined 'no AMS' and >=4 defied 'AMS'; the percentage of individuals with AMS is presented by ACE genotype over altitude. Linear regression analysis was used to examine the effect of HVR on the change in SaO_2 and HR over altitude. To consider whether HVR differed by ACE genotype analysis of variance (ANOVA) was conducted. Statistical significance was set at $p<0.05$.

RESULTS

Hypoxic Ventilatory Response

HVR was assessed in 44 of the subjects. HVR values ranged from 0.14 – 2.38 L/SaO_2. There were no significant differences in HVR by ACE genotype (DD=0.54 ± 0.32 L/SaO_2, ID=0.57 ± 0.39 L/SaO_2, II=0.56 ± 0.12 L/SaO_2), p=0.98.

No significant linear relationship was observed for the HVR effect on daily mean SaO_2, p=0.37, (Figure 4.3) and neither was its effect significant on HR and AMS, p>0.05.

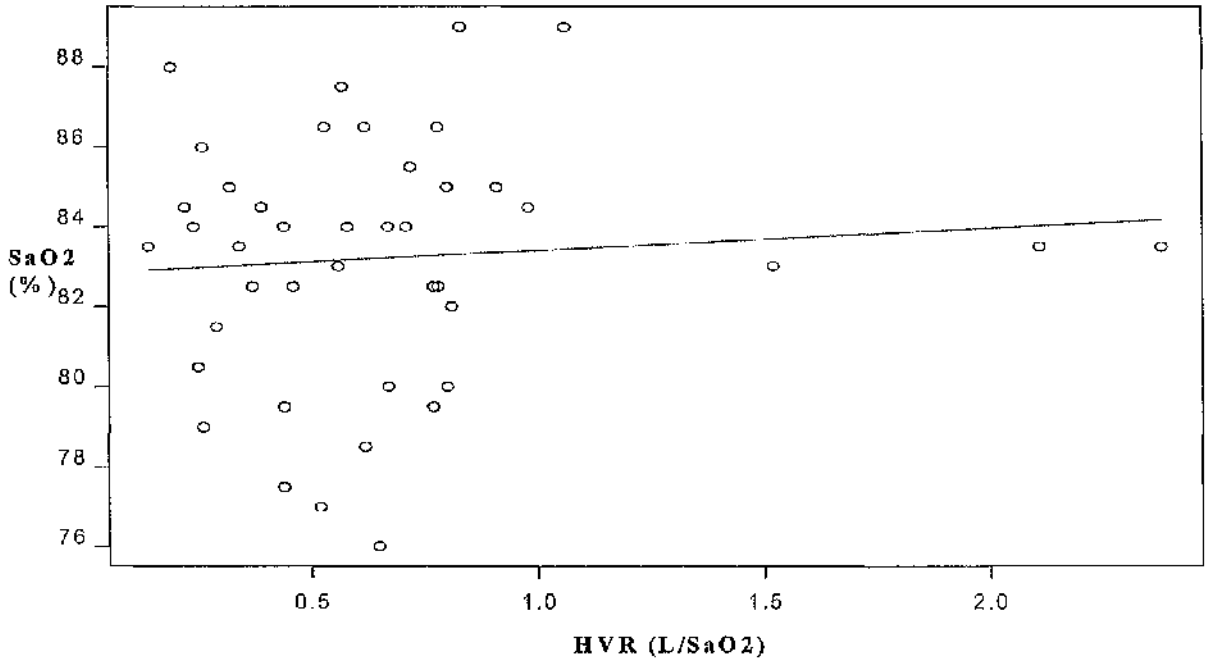


Figure 4.3 Relationship between mean SaO_2 vs. HVR.

Daily Physiological Measurements

Of the participating subjects, 45 subjects agreed to have their genotype information identified. The genotype distribution was: DD=19, ID=21, II=5. Genotype distribution was not in Hardy-Weinberg Equilibrium, DD [42.2 %], ID [46.7 %], II [11.1 %]; I allele frequency is 0.34.

Overall, there is a borderline significance for the differences in SaO_2 changes over altitude according to ACE genotype (p=0.04). Figure 4.4 shows that the II group had relatively lower mean SaO_2 for approximately half of the altitudes. The values were very similar at lower altitudes, and as the altitude increases, the difference between the II group and the two others (DD, ID) broadens, values being lower for the II's. If the 3 days at BC are included in the analysis, then the overall difference becomes a non-significant one, p=0.07.

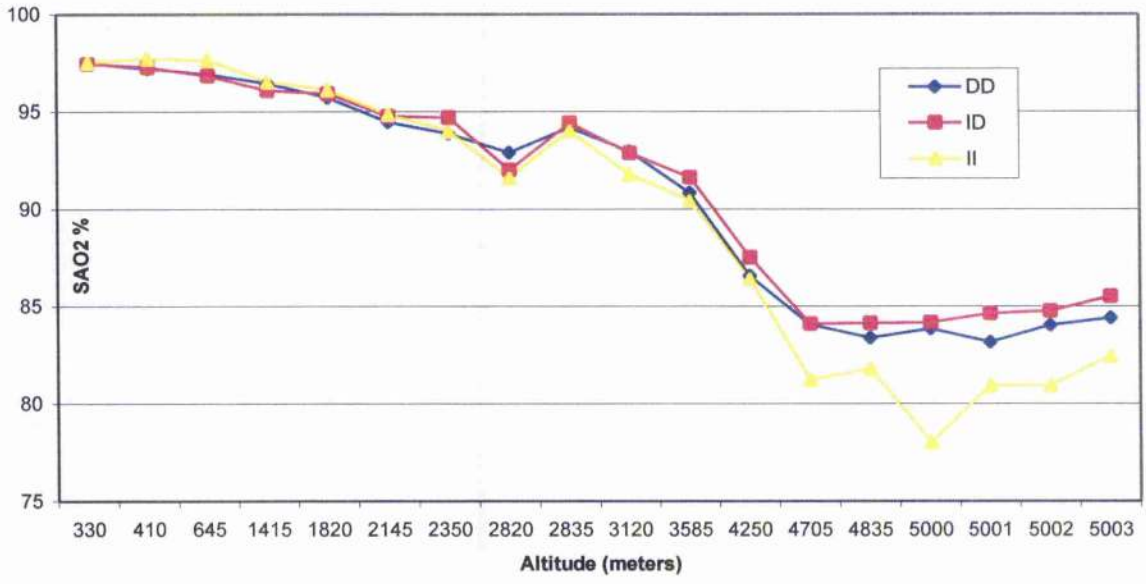


Figure 4.4 Graph showing mean oxygen saturation (SaO_2 %) by altitude according to ACE genotype. (DD n=20, ID n=21, II n=6).

A closer look into the data analysis, and more specifically on the percentage change in the daily SaO_2 from one altitude to the other, revealed that the only significant SaO_2 change between ACE genotypes, was the one between the altitudes of 4835m to 5000m, p=0.44, Figure 4.5.

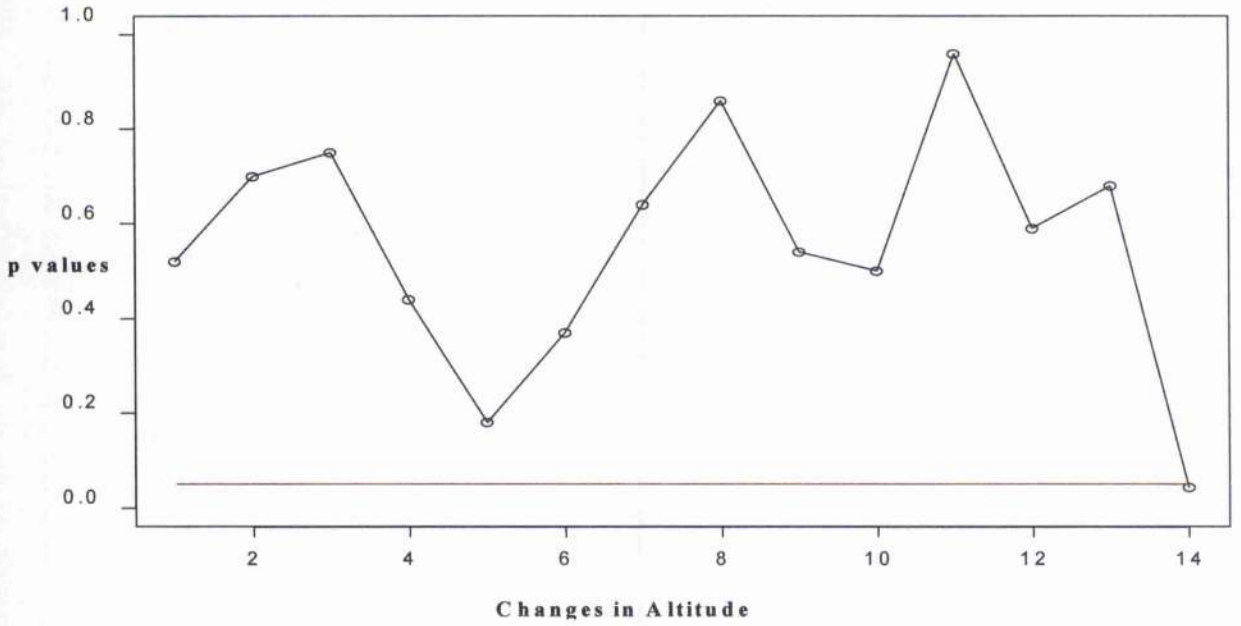


Figure 4.5 p values for differences in percentage change in daily SaO_2 by ACE genotype between Changes in altitude.

X axis values: 1=change between 1st and 2nd altitude change, 2=change between 2nd and 3rd altitude change, ...14=change between 14th and 15th altitude change.

Red line denotes the p= 0.05 significance level.

Figure 4.6 shows the mean HR by altitude and ACE genotype. Although mean values in the II group were higher, there were no significant HR differences by altitude and ACE genotype, p-value 0.99. The same was true for the daily AMS onset, with altitude change. There were no differences in AMS incidence by altitude and ACE genotype, $p>0.05$, Figure 4.7.

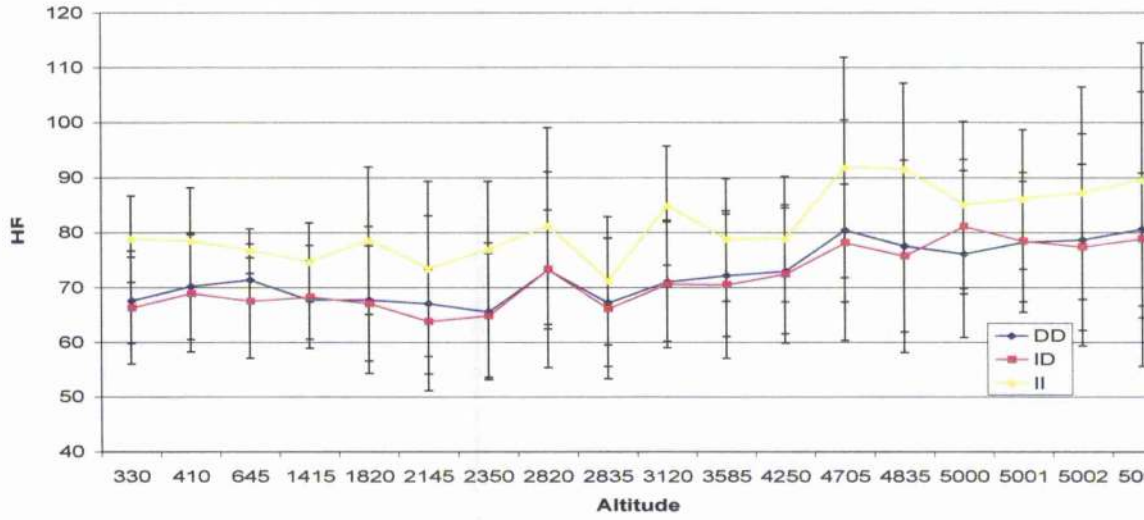


Figure 4.6 Graph of mean (and SD) HR (beats•min^{-1}) by altitude (m) and ACE genotype.

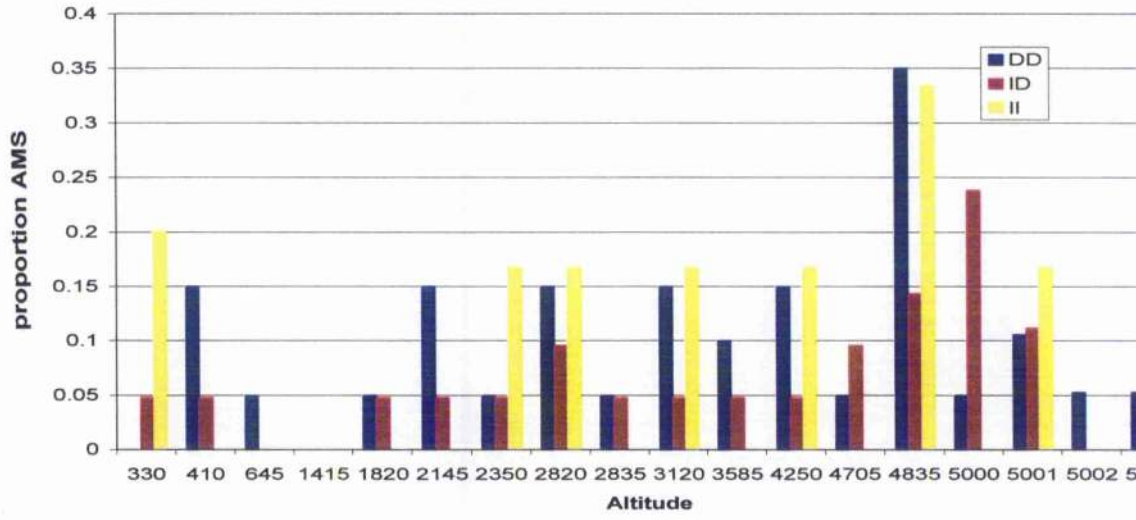


Figure 4.7 Graph of percentage of those having AMS, split by ACE genotype, over the 18 changes in altitude (m) (including the days at BC).

DISCUSSION

The finding that the II genotype may be associated with a lower SaO_2 during a trek from 330 to 5000m is contrary to a previous study (Woods et al, 2002), which reported genotype-dependent alterations in SaO_2 in which the II genotype resulted in higher SaO_2. The finding in the present study however, is questioned. While a statistical significant difference was found, there is some doubt as to the physiological significance of this finding. In the Woods et al (2002) study, a 'rapid' and a 'slow' group ascended to approximately 5000m, in an average of 12 and 18.5 days respectively. SaO_2 values were independent of the ACE genotype and remained so for the slow ascent group, in whom the fall in SaO_2 with ascent did not differ amongst genotypes. However, SaO_2 in the rapid ascent group was significantly higher for those subjects with a II genotype ($p=0.01$). The present study investigated a group whose ascent profile to 5000m was 'slow', requiring an average of 19-21 days to arrive at BC. There were no differences between any of the genotypes for the daily SaO_2, except for the last change in altitude before arrival to BC, a change of less than 150m, 4835m to 5000m, although, the overall statistical significance suggests that the II's have lower SaO_2 values. Although, there is an overall significance in the particular results, the physiological meaning of the magnitude of this difference is very small. The most likely explanatory reason for such an observation in the last change in altitude, is speculated be have arisen from the very small number of II subjects in the present study, 5 II vs. 19 DD vs. 21 ID. The small number of II's in the group may not have been truly representative for what actually happens at altitude in II genotype subjects, during this particular ascent profile. Furthermore, the ascent rate is of importance in the ways certain physiological changes will occur. Woods et al (2002) showed a better maintained SaO_2 for the II subjects whose ascent profile was rapid (12 days). The lack of an effect of the ACE genotype on SaO_2 during a slower ascent, an average of 18.5 days in the Woods et al (2002) study and 19-20 in the present one, is probably a reflection of the reduced influence of ACE activity. This difference between rapid and slow ascents is likely to be due to the short-lived (as low as 12 days) beneficial effects of the RAS at altitude associated with the I-allele (Milledge et al, 1983).

HR at HA increases as a reflection of an increased sympathetic drive and also due to a higher cardiac output (during the first week) in response to the reduced oxygen

content in arterial blood (Stenberg et al, 1966), as well as due to dehydration resulting in a reduced stroke volume (SV) (Ward et al, 2000). In the present study a HR increase in the group is indeed observed with altitude, but this difference is not significant between ACE genotypes. Wood's HR and ACE genotype unpublished data on the same groups from his work on ACE genotype and SaO_2 (Woods et al, 2002) also showed no genotype differences in both slow and fast ascent groups (Woods, personal communication).

As the I-allele is associated with decreased levels of ACE, this allows for natriuresis and diuresis, both beneficial adaptations to altitude, aiding in reduced formation of edemas, whose increased fluid retention for the D-allele could contribute to Acute Mountain Sickness (Bartsch et al, 1991). However, an ACE genotype dependence for AMS onset with daily changes in altitude was not observed, in agreement with a previous report (Dehnert et al, 2002), as well as with the results obtained in Chapter 3B of this thesis. Although the ascent profiles in the Dehnert et al, (2002) and Chapter 3B studies were very rapid ones (an average of 3 days to reach 4559m and 3817m respectively), it is unlikely that a slower ascent, an average of 19-21 days in this study, would have changed the findings. During a slower ascent profile, individuals acclimatize more efficiently and are less likely to succumb to AMS symptoms (Ward et al, 2000).

The reflexive increase in ventilation induced by hypoxia, the hypoxic ventilatory response, may aid in an improved performance at altitude. The finding that HVR cannot predict AMS susceptibility at high altitude agrees with previous such reports (Milledge et al 1988; Milledge et al, 1991; Bartsch et al, 2002). However, an enhanced ability to respond faster to the hypoxic condition would allow for better-maintained SaO_2 levels (Schoene et al, 1984). This was not was confirmed here in that those subjects with a brisk HVR did not have higher SaO_2 values during the trek compared to those with a slow HVR. Patel et al. (2003) on the other hand, showed an ACE genotype related advantage during acute exertional hypoxia in which those subjects with the II genotype exhibited a larger increase in minute ventilation, which may account for the increased SaO_2 levels found in the fast ascent profile subjects by Woods et al (2002). In both latter studies exposure to hypoxia, was either acute or fast. The present study did not show a genotype selective benefit on HVR. The HVR

measurements in this study were made at rest, whereas in the Patel et al, (2003) study measurements were made during sub-maximal exercise, which may have instigated a greater hypoxic response accounting for the observed genotype differences. It is likely that the slow ascent profile in this study may have acclimatized the subjects sufficiently, and why no relationship was observed between HVR and SaO_2.

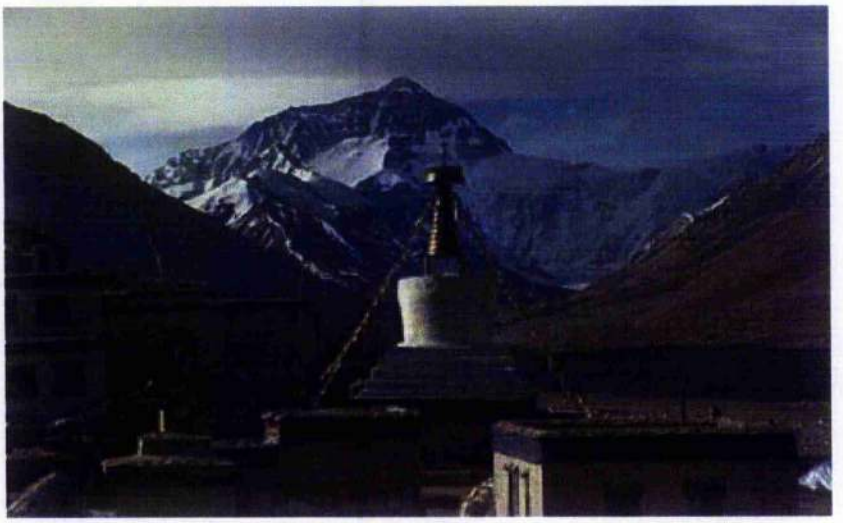
In conclusion, although a borderline significant result was obtained suggesting overall lower SaO_2 values for the II genotype, its true physiological significance is questioned. Further, no genotype related differences were seen for either HR or AMS. There were no differences in HVR by ACE genotype, and no association effects for the speed of the HVR response were observed on daily SaO_2, HR or AMS values. ACE genotype appears to have a greater influence on performance when acclimatisation time has been limited or when hypoxic exposure is acute, and as the present group underwent a 'slow' ascent profile, the non-significant genotype related results are likely to have been due to this, and also possibly the very low number of II's in the group.

Place	Altitude (m)
Tumlingtar	330
Kartighat	410
Ghote	645
Phedi	1415
Guranse	2820
Gadel	1820
Kiraunle	2610
Basmir	2750
Nusa	2910
Zetra Kola	3160
Kothe	3560
Tagnay	4290
Khare	4895
Triffin	4770
Base Camp	5000
Base Camp Day1	5000
Base Camp Day2	5000
Base Camp Day3	5000

Table 4.1. Trekking Schedule by Altitude

CHAPTER 5

ACE Genotype and Mount Everest Climbers, 8850m



INTRODUCTION

Mountaineers aspire to climb to the highest mountain on earth, Mount Everest, at 8850m. However, there is no existing systematic investigation on why some fail or succeed. Since the first recorded expedition to Mount Everest in 1922 until 2002, there have been 175 deaths, and at least 1655 summit successes; a ratio of 1:10, the worst year in 1996 had a ratio of 1:6.5. A number of possible factors that may influence summit success in climbing are acclimatization, weather conditions, use of supplementary oxygen, physical endurance, or even one's individual physiology to name a few. One variable, which may have a bearing in performance on Everest, is the ACE genotype.

The I-allele version of the ACE gene is well known for its associations with beneficial physiological responses in hypoxic conditions (Montgomery et al, 1998; Woods et al, 2002; Patel et al, 2003; Tsianos et al, 2005). To date, no other study has investigated summit success and a possible association with genotype. This study set out to describe the ACE genotype in a number of climbers who attempted to climb Mount Everest and to relate ACE genotype in those successful summiteers.

METHODS

The study had institutional ethics committee approval (UCL), and written informed consent was obtained from all volunteers.

Subjects: High altitude mountaineers (n=64, 58 males [36± 8.8 years] 6 females [33.1± 4.6 years]) were recruited from both Mt Everest base camps (5200m) North side-Tibet and South side-Nepal, prior to an attempted ascent to the summit (8850m), in the spring of 2004.

Genotyping: Buccal cells were collected using Whatman sterile foam tipped applicators (Whatman Bioscience Ltd, Abington, Cambridge, U.K.) swabbed vigorously against both inner cheeks and dampened under the tongue. The swabs were then pressed firmly onto a Whatman FTA micro-card (Whatman Bioscience Ltd, Abington, Cambridge, U.K). From these, DNA was extracted, and ACE genotype determined using a three-primer method as previously described (O'Dell et al, 1995).

Statistical analysis:

Descriptive analysis was performed for the group as a whole, those who succeeded, and those who failed. Chi-squared analysis was used to determine any differences in genotype distribution between the two groups.

RESULTS

Genotype distribution for the entire group (n=64) was: 14 DD [22%], 32 ID [50 %], 18 II [28%]; I allele frequency 0.53, and was consistent with Hardy-Weinberg Equilibrium. Genotype distribution in those who succeeded (n=42) was: 10 DD [24%], 22 ID [52%], 10 II [24%]; I allele frequency 0.50 (Figure 5.1), and in those who failed (n=22) was 4 DD [22 %], 10 ID [53%], 8 II [25%]; I allele frequency 0.59. There were no genotype differences between successful and failed climbers, p=0.56. For Caucasians alone (n=53), genotype distribution in those successful (n=36) was: 8 DD [22 %], 19 ID [53%], 9 II [25%]; I allele frequency 0.51, and in those who failed (n=17) was: 4 DD [24 %], 7 ID [41%], 6 II [35%]; allele frequency 0.56. There were no genotype differences between successful and failed climbers, p=0.69.

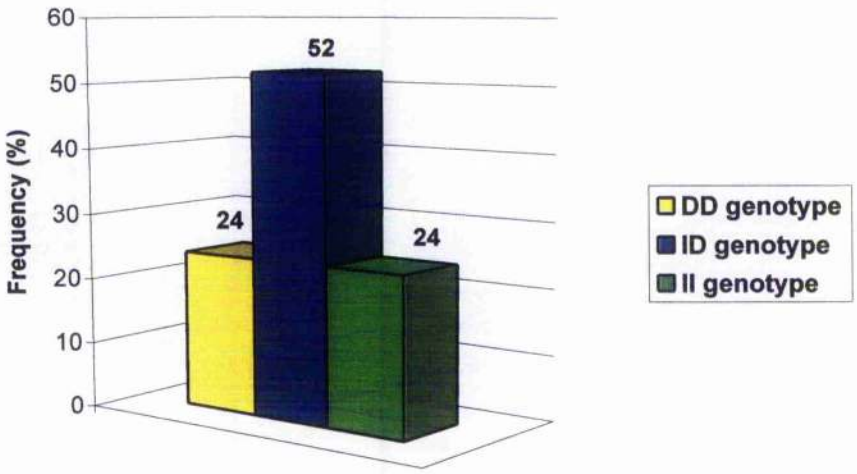


Figure 5.1 ACE genotype distribution amongst successful summiteers (n=42), I-allele frequency 0.50, p=0.56.

DISCUSSION

Previous studies have suggested a selective advantage for those with the II genotype at HA. The results of the present study do not support such findings. Instead, an exactly equal allele frequency was found in those who reached the most hypoxic point on the surface of this earth. There are a few speculations for this observation. Montgomery et al, (1998) reported that amongst 25 British mountaineers who had ascended beyond 7000m without the use of supplementary oxygen, a significant excess of the I allele and II genotype was demonstrated. Amongst the 15 climbers who had ascended beyond 8000m without supplementary oxygen, none was of the DD genotype (6 II and 9 ID), and when ranked by the number of such ascents, the top performer was of the II genotype. This is a very small group for a genotype-performance association, nevertheless, an allele skew amongst high altitude mountaineers was demonstrated. The possibility that Montgomery's et al, (1998) findings are a coincidence in favour of the I-allele and II genotype could be attractive, but may not be realistic.

The successful climbers in the present study, indeed, successfully ascended Everest at 8850m, but all used supplementary oxygen. All of Montgomery's climbers had ascents without the use of supplementary oxygen above 7000m, and more than half above 8000m. The use of supplementary oxygen at extreme altitudes is of physiological (West et al, 1983a) as well as psychological assistance (Everest summiteers personal communication). It is possible that a genotype selective disadvantage at extreme altitudes may have been masked through the use of such ergogenic aid, as this enhances performance. The use of oxygen in essence eliminated to a degree the severe hypoxia, which may otherwise induce genotype related effects such as pulmonary vasoconstriction and its subsequent maladies.

Acute versus chronic exposure to altitude is a likely explanatory reason for the present findings and the differences between Montgomery's study. A characteristic in the mountaineers studied by Montgomery et al, (1998) was their ability for rapid ascends on high mountains (Montgomery personal communication). It was previously shown in this thesis (Chapter 3B) that those climbers with an II genotype were significantly more successful (none failed) during a rapid ascent to the summit of Mont Blanc (4807m); an altitude not as extreme to the ones being discussed here, but nevertheless

high enough to cause many of hypoxia's ill effects on the body if attained rapidly. Patel et al, (2003) showed an II advantage for minute ventilation, in which those subjects with the II genotype had higher ventilations during acute experimental exposure to hypoxia; a response beneficial for maintaining SaO_2 levels a high as possible. Increased arterial oxygen saturations have been shown to be crucial for high altitude performance (Schoene et al, 1984), and Woods et al, (2002) demonstrated an II advantage for higher daily SaO_2 in those climbers undertaking a rapid ascent schedule to altitude. Milledge et al, (1983) however, clearly showed that any RAS benefits at altitude are rather short lived (12-20days), and as time progresses any advantages from the effects of a particular ACE genotype (II in this case) disappear. Woods et al, (2002) and this thesis (Chapter 4) both confirm the latter suggestions and showed that physiological responses during staged and slow ascents to HA do not differ amongst subjects of the 3 ACE genotypes. On the other hand though, exposure to altitude in those climbers who attempt to summit Mount Everest is chronic. Three to four weeks are required to arrive at BC (5200m) in order to successfully acclimatize, and another three to four weeks at higher elevations for preparatory climbing, establishing high altitude camps, and resting, before a potential summit attempt.

It could be suggested that the II genotype is of benefit for mountaineers during rapid and acute exposure to hypoxia, whereas when exposure is slower and chronic, all genotypes appear to behave similarly. For the purposes of attempting the summit of Mount Everest, it would seem rather doubtful that ACE genotype plays a major role during such slow ascent profile to HA. However, it is likely that once at extreme altitudes, comparable to ones in the 'death zone' (above 8000m), the ability of the human body to utilize more efficiently the scarce amounts of oxygen, which most likely includes genotype-dependent differences in substrate selection, metabolic efficiency, and muscle fibre type (Jones and Woods, 2003), may well be depended on ACE genotype. It is probable that slow and chronic exposure to hypoxia, along with use of supplementary oxygen, could both compensate for any disadvantages that the most likely D-allele carriers would otherwise experience. The predominant factor in many studies showing an II genotype advantage during acute exposure to hypoxia, rapid ascent profiles, or ascents to very high altitudes, appears to be the hypoxic response. Thus, removing to a large extent the stressor of severe hypoxia via the use

of supplementary oxygen, any beneficial effects of the II genotype under hypoxic conditions may indeed be masked. However, in order to strongly suggest this hypothesis, those summiteers who have ascended Mount Everest without the use of supplementary oxygen *must* be tested for ACE genotype identification in a future study, in hope to show the advantages of the II genotype, if indeed any exist at all.

In conclusion, a self-selective advantage of the II genotype in climbers successfully ascending Mount Everest was not observed, but instead, an equal allele frequency was found; all summited however, using supplementary oxygen.

CHAPTER 6

General Conclusions

This thesis explored physiology and genetic predisposition of humans during performance in mountainous environments. Firstly, the physiological responses (objective and subjective) of individuals exposed in a laboratory simulated mountainous environment were investigated in order to assess a particular mountain rescue equipment. Secondly, the physiological responses during rapid and slow ascents of mountaineers to altitude were examined. Finally, the possibility that a genetic variance may influence performance at altitude was investigated.

The focus of the first study was on the means by which, after an accident occurs, the rescue party can prevent hypothermia in a casualty. Mountain rescue teams can achieve this through the use of the casualty rescue bag, by placing the casualty inside the casualty bag (CB). Previous work by Grant et al, (2002) assessed casualty rescue bags currently used across Scotland by rescue teams, for effectiveness in protecting a victim from already established or a potential hypothermic state. The objective was to assess a rescue equipment in the form of a casualty rescue bag, but entirely composed of a 1 layer bubble-wrap (BW) and used amongst the Norwegian mountain rescue teams. The CB that performed best in the Grant et al, (2002) study was compared against this mountain rescue innovation. 12 volunteer subjects were exposed in an environmental chamber, under cold (-10°C) and windy (wind speed 2.7 $m \cdot sec^{-1}$) conditions. During equal timed intervals, subjects had their Vo_2, T_{skin}, T_{core}, and HR measurements recorded, as well as an assessment of their subjective responses to shivering and cold perception. The results showed that under the tested experimental conditions the BW bag did not protect the subjects as efficiently as the CB. Though there were no differences in T_{core} drop, T_{skin} was lower in the BW, and moreover, the subjects felt colder and shivered more in the BW. It is not unusual to encounter the environmental conditions imposed during this study in the Scottish Highlands or a number of mountain ranges worldwide (Alps or Himalayas). However, the specific environmental conditions, 'cold' and 'windy', are not generally representative of many mountain conditions, as 'wetness' is present in places such as Scotland and Norway. Testing in a wet environment would be rather difficult to standardise, as it would be difficult to maintain the same amount of wetness at the same sites in all of the subjects. Nonetheless, it was demonstrated that the CB offers higher protection in

comparison to the already used BW protective equipment. A future study on BW efficiency could include 2, or even 3 layers of BW. This would still have a lower weight and bulk than a standard CB.

Then a field study was undertaken in the French Alps. The research took place in a refuge hut at an altitude of 3817m. 285 volunteer climbers who aspired to ascend Western Europe's highest mountain, Mont Blanc, 4807m, were investigated during a rapid ascent profile (2-3 days) starting from the Chamonix valley (1100m). The aim was to determine the factors affecting a climber's ability to ascend Mont Blanc, and to investigate what influence genetics would have in their performance. The volunteers had their physiological responses of SaO_2, $ETCO_2$, HR, and RR measured, while they subjectively assessed, through the use of a questionnaire, how they felt in order to determine whether they had established AMS. Their climbing history and other demographic variables were also documented. The data was recorded before and after their attempted ascent to the summit, and their performance on the mountain (success or failure to reach the summit) was documented. Furthermore, considering it may have an influence on performance, a genetic sample was obtained to identify their angiotensin converting enzyme (ACE) genotype. It was shown that climbing profile over the past 14 days prior to an attempted ascent significantly affected ascent outcome and time to the summit. Those with recent exposure to >4000 meters had an advantage in attempting this peak, while their AMS incidence was lower and SaO_2 levels higher. Older climbers (>57 years) and females had slower ascent times than those of younger males. Reports from some subjects indicated that their companions did not want to be tested, as they felt unwell. Thus, the small number of subjects who failed to reach the summit may be unrepresentative and consequently the results regarding the failure rate may be misleading. In an attempt to recruit a less biased sample, a future study could include testing climbers in a staged and progressive manner. In order to recruit a more representative sample, testing would start at low altitudes as it is presumed that all climbers would be well at low altitudes. Then, it would be important to follow up on all climbers at all testing altitudes.

On the genetics front, the first prospective reports were provided in assessing ACE genotype and its influence on AMS status after arrival to altitude, and return from a subsequent attempt to attain a higher altitude, in this case the Mont Blanc summit. No homozygote genotype advantages were observed on AMS onset or severity on either Day 1 or 2. However, it was shown that the I-allele of the ACE gene was associated with greater success at high altitude. I-allele frequency in those successfully reaching the summit was more than twice higher compared to the one for those who failed. Of those climbers who failed to make the summit, none were of the II genotype. As with any such study, replication and extension are to be recommended. A limitation was the low follow-up, almost 25% of individuals never reported back on Day 2 and were unavailable for reassessment. Nevertheless, it is thought that this was not a source of bias for the genetics analysis; genotype distribution amongst this group was no different from those who used the same route of descent as ascent.

Research was continued at similar altitudes, however, this time during a slow and staged ascent; a trek from Tumlingtar (330m) to Chamlang Base Camp (5000m) in the Hungu valley of the Nepalese Himalayas over 19-21 days. 55 volunteers had their physiological responses (SaO_2, and HR) and AMS status recorded, daily. The variables were subsequently correlated to their ACE genotype, while assessment of their hypoxic ventilatory response (HVR) was used in an attempt to predict their daily physiological responses as altitude changed over time. As this was a particularly slow ascent profile, no major physiological differences between genotypes were anticipated. It was found that the II's had lower daily SaO_2 values than the DD's and ID's. Day-to-day analysis however, showed that the overall lower significance in SaO_2 in the II's might may not be physiologically meaningful after-all, while the low number of II's in the group is speculated to have negatively affected the results. Daily HR and AMS did not differ between genotypes either. A predicative ability for daily AMS, HR and SaO_2, via the use of the HVR measurement was not observed. It is recommended that future studies of this kind have genotype groups as similar as possible, while investigation of the effects of HVR on daily measurements during a fast ascent profile to similar altitudes would be of valuable information.

Finally, this thesis ended with an investigation on human performance and genetic predisposition in climbers attempting to summit Mount Everest. While Everest stands at 8850m, its summit is the highest and most hypoxic point man can encounter on the surface of this earth. The ACE genotype of 64 climbers was assessed in order to determine any relationships between summit success and genotype. It was found that there were no genotype differences in those who successfully reached the summit. Instead, an equal allele frequency was observed. It is believed that the beneficial effects of ACE activity may be limited to acute hypoxic exposure, and thus the most probable reason why no genotype self-selection was observed. Furthermore, the use of supplementary oxygen at extreme altitudes, is likely to have further masked the probable I-allele and II genotype advantage.

During all field studies, such as the ones described in this thesis, there are many unpredictable factors. It is not easy to control for the 'willingness' of the participating subjects to perform all suggested and planned testing. In particular it was noted that as subjects became unwell they were reluctant to continue with the testing, or even be tested in the first place. This was unfortunate as those subjects would have been of distinct interest in the studies. In future studies, data collection from such subjects would be recommended in order to gain a better physiological insight in those not able to perform optimally at altitude, although, and as observed in this thesis, such attempts may not always prove fruitful.

In closing, one should consider if the incentives in undertaking this kind of genetic research, hoping to identify the polymorphic loci implicated in the inter-individual variations in performance, are worth the time, money, and effort invested. In this thesis the ACE gene was presented as an example of many genes whose one or more multi-functioning polymorphisms could only contribute to altering performance ability, which could also account for the observed inter-individual performance variation. As Payne and Montgomery (2004) explain, such research would identify the root of these variations in performance ability, the genes responsible can be known, the mechanisms that highlight the observed phenotypes will be uncovered, and finally information from all these physiological processes can be applicable to

human pathological states. A common question arising from the exercise and sporting community is whether or not selection of ultimate performers could be based on genetic testing alone. The conservative answer is probably 'no', although, it is possible that individuals possessing the most complimentary combinations of gene variants could be identified in the future. However, identification of the genes regulating physical performance is still in the early stages of research. A 'single gene for performance' is unlikely to be identified, as elite performance depends on a number of variations in a number of genes, and finally being influenced by a number of environmental factors (Payne and Montgomery, 2004). Therefore, in the future, one would have to be genotyped for numerous polymorphisms, provided all involved in physical performance have been identified; in the meanwhile, a much straightforward way is to simply observe one's performance under the discipline of interest. Finally, it should be *emphasized* that 'optimal' genetics alone cannot guarantee success. The psychological factors involved are also decisive for success during performance, as is keeping focused during competition or under a stressful situation, such as in extreme hypoxia, whilst, in the 'death zone'.

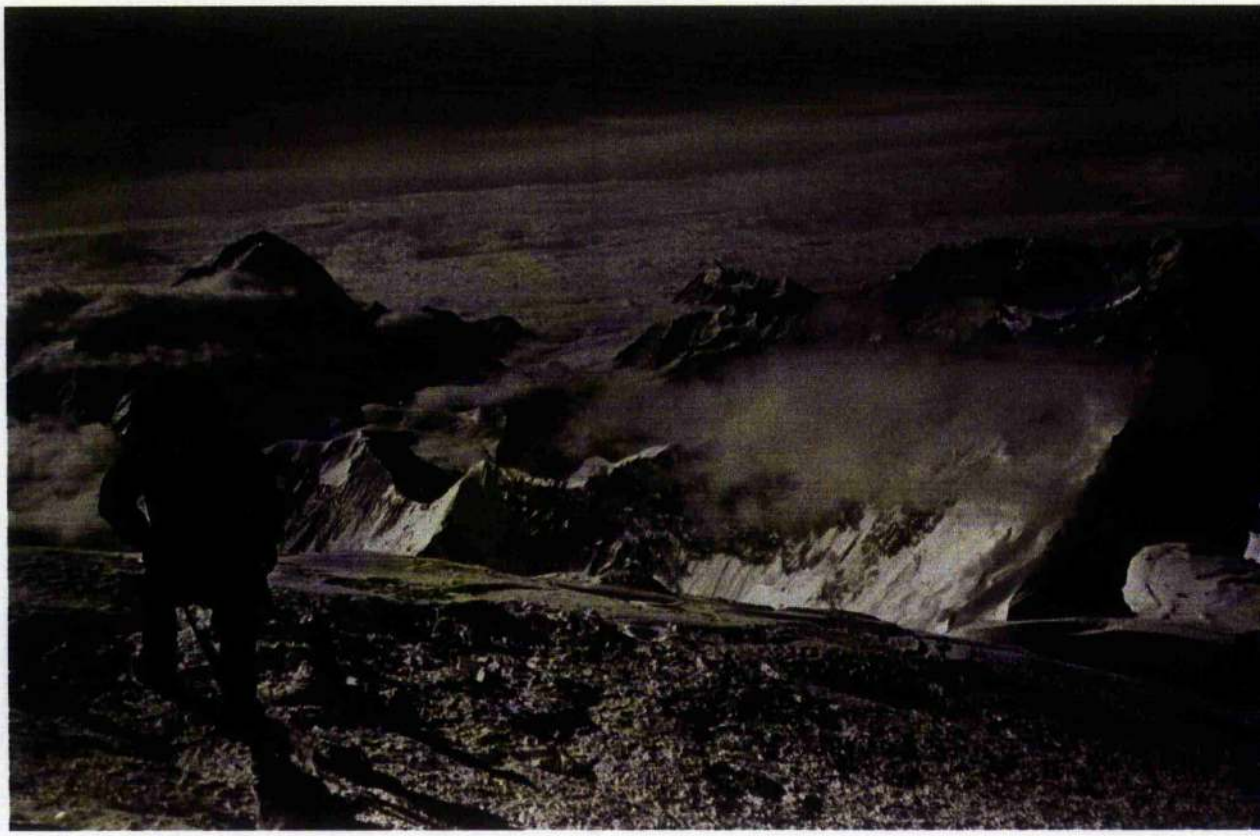


Figure 6.1

On the summit of Mount Everest. Photo taken by author on May 18th 2004, the first Greek climber to ascend fr 'classic' North Side route attempted by Mallory and Irvine in the 1920's, successfully ascended first by the Chinese in and last, but not least, the first solo ascent without the use of supplementary oxygen by Reinhold Messner in August of To this day, author still chooses not to be tested for ACE genotype identification.

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APPENDIX

Appendix A

Lake Louise Acute Mountain Sickness Scoring Scale

(Roach et al, 1993)

Self-Assessment Section

HEADACHE
0 none at all
1 mild headache
2 moderate headache
3 severe/incapacitating headache

GASTROINTESTINAL SYMPROMS
0 good appetite
1 poor appetite
2 moderate nausea or vomiting
3 severe/incapacitating nausea and vomiting

FATIGUE AND/OR WEAKNESS
0 not tired or weak
1 mild fatigue/weakness
2 moderate fatigue/weakness
3 severe fatigue/weakness

DIZZINESS/LIGHTHEADEDNESS
0 none
1 mild
2 moderate
3 severs/incapacitating

DIFFICUTLY SLEEPING (last night)
0 slept as well as usual
1 did not sleep as well as usual
2 woke many times, poor night's sleep
3 could not sleep at all

Appendix B

Studies 3A and 3B, Subject Questionnaire

BEFORE Ascent to Mont Blanc

Name (Print)..... **Male/Female** **Age**.....

e-mail address: ..... ***Country***..... ***Date***.....
Time.....

1. Are you taking medication to prevent altitude problems? **YES** **NO**
   if YES please state?.....
   for how long?.....
2. Have you had altitude sickness in the past? **YES** **NO**
3. At what altitude do you normally reside?.....
4. At which altitudes have you been over the past 14days (residing and climbing)?
   .....
5. What was your route to the Gouter Hut, and how long did it take you to get here?
   .....
6. Have you climbed Mont Blanc before? **YES** **NO**
7. What is the highest altitude you have ever achieved?
   .....

FOR RESEARCHER USE ONLY

E_TCO_2	**upper**	.....
	lower	.....
SaO_2	**upper**	.....
	lower	.....
H.R.	**upper**	.....
	lower	.....
R.R.	**upper**	.....
	lower	.....

A.M.S. .....

Gene sample
YES / NO

AFTER Descent

Name (Print).....

Date..... ***Time.....*** ***Time of return to hut.....***

1. Did you make the summit? **YES** **NO**

if YES how long did it take to go up from the Gouter Hut? Hrs.....Mins.....
how long did it take to come down from the summit to the Gouter Hut? Hrs.....Mins.....

if NO where did you turn back? .....

what was the reason? (please circle)

- fatigue
- breathlessness
- headache
- bad weather
- you injured yourself
- another member of the group was injured or could not continue

2. How many climbers were there in your climbing group?.....

3. Did you have a professional guide with you? **YES** **NO**

FOR RESEARCHER USE ONLY

$ET CO_2$	**upper**	.....
	lower	.....
SaO_2	**upper**	.....
	lower	.....
H.R.	**upper**	.....
	lower	.....
R.R.	**upper**	.....
	lower	.....

A.M.S. .....

Ethnicity: Please circle what is most appropriate

1. White	2. Mixed
Country_____	D White and Black Caribbean E White and Black African F White and Asian G Any other mixed background
3. Asian	**4. Black**
H Indian J Pakistani K Bangladeshi L Any other Asian background	M Caribbean N African P Any other Black background
5. Other Ethnic Groups	**6. Not Stated**
R Chinese S Hispanic T Any other ethnic group _____	Z Not stated

Are you a smoker? Yes / No

if YES, how many cigarettes/how much pipe tobacco per day? _____

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