Sleep and Breathing at High Altitude

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PREFACE

Some of the sea level sleep studies were conducted at the Peninsula Private Sleep Laboratory, Manly, NSW.

The ventilatory response tests were conducted at the Department of Respiratory Medicine and Sleep Disorders of Royal Prince Alfred Hospital, Camperdown, NSW.

The procedures and protocol of this research were approved by the University of Sydney Human Ethics Department (Nepal research) and by the University of California, San Diego, Human Research Protection Committee (White Mountain research). Informed consent was obtained from all volunteers.

This thesis represents my original work. This work has not been presented previously for the purpose of obtaining a degree.

Pamela Lesley Johnson

March, 2008

DEDICATION

For my mother, Audrey Brown and my children, Evan and Claire Johnson.

I am deeply grateful for your unfailing love and support.

ACKNOWLEDGEMENTS

The Nepal project, which forms the major part of this thesis, would not have been possible without the volunteers who gave up weeks of their time to trek with me into the Nepal Himalaya, as well as many hours for baseline sleep studies and ventilatory response testing at sea level before departure for Nepal. Each volunteer funded their own travel and accommodation and most also performed vital support work during the trek. I would particularly like to thank the volunteers who helped with the sleep studies in the evenings. After trekking for many hours we would arrive at the night's accommodation, and it was shortly afterwards that most of the work was done. I would especially like to thank my friends and colleagues who helped set up for sleep studies every night: Natalie Edwards on the first trek, Sherridon Lysons and Nathan Radford were indispensable on the second trek, David Bolton, Carla Evans, Karina Falland and Claire Johnson on the third trek. Karina also helped enormously in the preparation for the sleep studies before we left Sydney.

Arterial blood gases were collected, often under appalling conditions, by Drs Keith Burgess, Adrian Havrik and Mark Gilbert; there were no failures of the arterial blood sampling due to their skill and expertise. Mark also undertook two extra six hour treks after arriving in Tyangboche from Khunde to find the phone/fax line down and our arterial blood gas analyser needing help only available back at Khunde; Mark returned to Khunde, fixed the analyser and trekked back to Tyangboche the next day.

Some volunteers contributed in surprising ways: Richard Atkin developed a manoeuvre that has proved indispensable in all my subsequent research at high altitude: when administering the Lake Louise questionnaire, if the subject denies headache, they are asked to perform the "Atkin manoeuvre" i.e. a very brisk shake of the head. No one with even mild headache can perform this without wincing.
I would like to thank my friend, Marianne Bennett, who was a volunteer in the second trek and spent each morning of the trek backing up sleep studies, making several copies to ensure that no data was lost. Marianne has also been of invaluable assistance in formatting this thesis.

I would like to thank the two people whose idea it was to trek to high altitudes in order to study sleep and breathing, Dr Buddha Basnyat and Dr Keith Burgess. Buddha has been vitally important to this work; he is well known in the high altitude areas of Nepal and works with the Himalayan Rescue Association as well and conducting vital research work in this area of his country. I highly value his friendship and support.
My colleague, Dr Keith Burgess with whom I travelled to the Himalaya in 1997 in order find out if such a project was possible, was a driving force in the first two treks and continues to conduct ongoing research into high altitude physiology.
I owe a great debt of gratitude to Pemba Sherpa who came with Keith and me on the preliminary and first treks and who taught me how to walk at high altitude (one step one breath) which proved invaluable during all consequent treks.

Professor Colin Sullivan has always been an inspirational supervisor who has guided and encouraged me over the past several years. Colin has an encyclopaedic knowledge of sleep and breathing physiology; I feel privileged to have had the

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The support and encouragement of many friends have sustained me over the years of field work and compilation of this research. I thank you for your friendship, which I value enormously.

Both my children took part in this research, volunteering as subjects for the first trek (Evan) and the third trek (Claire). This has allowed me to discover the purpose of having children: they can be utilised as experimental subjects! Claire has also helped me enormously in formatting this thesis, giving up many hours of her time to do so. I am very grateful for the support of both my children who, fortunately, thoroughly enjoyed their time in Nepal and plan return trips.

The White Mountain research was undertaken in collaboration with Professor Kim Prisk and Dan Popa from the University of California, San Diego. Dan performed vital work in the planning, organisation and conduct of the project before and during the White Mountain project. Dan was also wonderful company and a great team member during our time at the Barcroft laboratory, White Mountain.

Finally I would like to express my appreciation to the Faculty of Medicine at the University of Sydney for assistance in funding part of the projects and, with particular thanks to Dina Bowe whose advice I have benefited from over many years.

Trekking Groups

Group 1

Mark, Evan, Pamela, Natalie, Keith and Adrian

Group 2

Richard, Pamela, Nigel, Alison, Nathan, Dan, Keith, Sherridon, Marianne and Sue

Group 3

Karina, Rishi and Dipendra (guides), Carla, Mathew, Pamela, Claire, David and Louisa

SUMMARY

This thesis describes the work carried out during four treks, each over 10-11 days, from 1400m to 5000m in the Nepal Himalaya and further work performed during several two-night sojourns at the Barcroft Laboratory at 3800m on White Mountain in California, USA. Nineteen volunteers were studied during the treks in Nepal and seven volunteers were studied at White Mountain. All subjects were normal, healthy individuals who had not travelled to altitudes higher than 1000m in the previous twelve months.

The aims of this research were to examine the effects on sleep, and the ventilatory patterns during sleep, of incremental increases in altitude by employing portable polysomnography to measure and record physiological signals. A further aim of this research was to examine the relationship between the ventilatory responses to hypoxia and hypercapnia, measured at sea level, and the development of periodic breathing during sleep at high altitude. In the final part of this thesis the possibility of preventing and treating Acute Mountain Sickness with non-invasive positive pressure ventilation while sleeping at high altitude was tested.

Chapter 1 describes the background information on sleep, and breathing during sleep, at high altitudes. Most of these studies were performed in hypobaric chambers to simulate various high altitudes. One study measured sleep at high altitude after trekking, but there are no studies which systematically measure sleep and breathing throughout the whole trek.

Breathing during sleep at high altitude and the physiological elements of the control of breathing (under normal/sea level conditions and under the hypobaric, hypoxic conditions present at high altitude) are described in this Chapter.

The occurrence of Acute Mountain Sickness (AMS) in subjects who travel form near sea level to altitudes above 3000m is common but its pathophysiology not well understood. The background research into AMS and its treatment and prevention are also covered in Chapter 1.

Chapter 2 describes the equipment and methods used in this research, including the polysomnographic equipment used to record sleep and breathing at sea level and the high altitude locations, the portable blood gas analyser used in Nepal and the equipment and methodology used to measure each individual's ventilatory response to hypoxia and hypercapnia at sea level before ascent to the high altitude locations.

Chapter 3 reports the findings on the changes to sleep at high altitude, with particular focus on changes in the amounts of total sleep, the duration of each sleep stage and its percentage of total sleep, and the number and causes of arousals from sleep that occurred during sleep at increasing altitudes.

The lightest stage of sleep, Stage 1 non-rapid eye movement (NREM) sleep, was increased, as expected with increases in altitude, while the deeper stages of sleep (Stages 3 and 4 NREM sleep, also called slow wave sleep), were decreased. The increase in Stage 1 NREM in this research is in agreement with all previous findings.

However, slow wave sleep, although decreased, was present in most of our subjects at all altitudes in Nepal; this finding is in contrast to most previous work, which has found a very marked reduction, even absence, of slow wave sleep at high altitude. Surprisingly, unlike experimental animal studies of chronic hypoxia, REM sleep was well maintained at all altitudes.

Stage 2 NREM and REM sleep, total sleep time, sleep efficiency and spontaneous arousals were maintained at near sea level values.

The total arousal index was increased with increasing altitude and this was due to the increasing severity of periodic breathing as altitude increased. An interesting finding of this research was that fewer than half the periodic breathing apneas and hypopneas resulted in arousal from sleep. There was a minor degree of upper airway obstruction in some subjects at sea level but this was almost resolved by 3500m.

Chapter 4 reports the findings on the effects on breathing during sleep of the progressive increase of altitude, in particular the occurrence of periodic breathing. This Chapter also reports the results of changes to arterial blood gases as subjects ascended to higher altitudes. As expected, arterial blood gases were markedly altered at even the lowest altitude in Nepal (1400m) and this change became more pronounced at each new, higher altitude. Most subjects developed periodic breathing at high altitude but there was a wide variability between subjects as well as variability in the degree of periodic breathing that individual subjects developed at different altitudes. Some subjects developed periodic breathing at even the lowest altitude

and this increased with increasing altitude; other subjects developed periodic breathing at one or two altitudes, while four subjects did not develop periodic breathing at any altitude.

Ventilatory responses to hypoxia and hypercapnia, measured at sea level before departure to high altitude, was not significantly related to the development of periodic breathing when the group was analysed as a whole. However, when the subjects were grouped according to the steepness of their ventilatory response slopes, there was a pattern of higher amounts of periodic breathing in subjects with steeper ventilatory responses.

Chapter 5 reports the findings of an experimental study carried out in the University of California, San Diego, Barcroft Laboratory on White Mountain in California. Seven subjects drove from sea level to 3800m in one day and stayed at this altitude for two nights. On one of the nights the subjects slept using a non-invasive positive pressure device via a face mask and this was found to significantly improve the sleeping oxyhemoglobin saturation. The use of the device was also found to eliminate the symptoms of Acute Mountain Sickness, as measured by the Lake Louise scoring system. This finding appears to confirm the hypothesis that lower oxygen saturation, particularly during sleep, is strongly correlated to the development of Acute Mountain Sickness and may represent a new treatment and prevention strategy for this very common high altitude disorder.

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Chapter 5. Acute Mountain Sickness and Non-invasive Positive Pressure Ventilation

ABBREVIATIONS

AL	**Acclimatised lowlanders**
AHI	**Apnea hypopnea index**
AI	**Arousal index**
AMS	**Acute Mountain Sickness**
ASL	**Above sea level**
CPS	**Cycles per second**
CSF	**Cerebro-spinal fluid**
cmH_2O	**Centimetres of water pressure**
CO_2	**Carbon dioxide**
CPAP	**Continuous Positive Airway Pressure**
CSA	**Central Sleep Apnea**
CSN	**Carotid Sinus Denervation**
CSR	**Cheyne-Stokes Respiration**
ECG	**Electrocardiogram**
EEG	**Electroencephalogram**
EMG	**Electromyogram**
EOG	**Electro-oculogram**
EPAP	**Expiratory Positive Airway Pressure**
FiO2	**Concentration of Inspired Oxygen**
FSH	**Follicle Stimulating Hormone**

HACE	**High altitude cerebral edema**
HAN	**High altitude native**
HAPE	**High Altitude Pulmonary Edema**
HCVR	**Hypercapnic Ventilatory Response**
HVR	**Hypoxic Ventilatory Response**
IPAP	**Inspiratory Positive Airway Pressure**
LH	**litres**
LOC	**Left outer canthus**
m	**metres**
min	**minutes**
mmHg	**millimetres of mercury**
nCPAP	**Nasal Continuous Positive Airway Pressure**
N_2	**Nitrogen**
NIPPV	**Non-invasive Positive Pressure Ventilation**
NIV	**Non-invasive Ventilation**
NREM	**Non-Rapid Eye Movement**
O_2	**Oxygen**
OSA	**Obstructive Sleep Apnea**
pCO_2	**Partial Pressure of Carbon Dioxide**
pO_2	**Partial Pressure of Oxygen**
PB	**Periodic Breathing**
PEEP	**Positive End Expiratory Pressure**
$P_{ET}CO_2$	**End Tidal CO_2**

RDI	**Respiratory Disturbance Index**
REM	**Rapid Eye Movement**
ROC	**Right outer canthus**
SaO_2	**Oxyhemoglobin saturation**
SD	**Standard Deviation**
SE	**Sleep**
sec	**seconds**
SJ	**Sojourners**
SWS	**Slow Wave Sleep**
Te	**Expiratory Time**
Ti	**Inspiratory Time**
TB	**Tidal breathing**
TIB	**Time in bed**
TST	**Total Sleep Time**
VI	**Minute Ventilation**
VPAP	**Variable Positive Airway Pressure**
VT	**Tidal Volume**

CHAPTER 1

LITERATURE REVIEW

1.1 General Introduction and Historical Perspective

The effects of high altitude on sleep and breathing have been known since man first ventured from low altitude into the mountains for adventure, recreation or travel into mountain areas. Mountaineers noticed that breathing became laboured and that seemed to be due to some lack of quality in the air they breathed, necessitating deeper and more frequent breaths. Exertion caused profound breathlessness and many suffered from headache, nausea and lassitude. Sleep was restless, fragmented and unrefreshing. Observations of breathing during sleep were that there were long pauses in breathing followed by several large, deep breaths.

In the late 19th century Egli-Sinclair, a scientist who was also a keen mountaineer noticed his companion, when asleep during a pause in climbing a mountain, had a breathing pattern similar to "the Stokes character" (Egli-Sinclair 1891). Another Alpinist, Tyndall, who was a physician, was woken from sleep by his companion during a mountain climbing expedition because he was worried about his repeated cessations in breathing (Tyndall 1860).

Breathing during sleep at high altitude was first recorded in 1898 by the Italian scientist, Mosso at 4559 metres in the Italian Alps. This recording of breathing during sleep at high altitude confirmed the reports of Cheyne-Stokes respiration observed by countless high altitude travellers (Mosso 1898).

When advances in technology allowed the electrophysiological recording of sleep, the first to do so at high altitude was Joern in 1970. He studied two men during their sojourn at the South Pole, which has a barometric pressure equal to an altitude of 3000-3800m above sea level. Anecdotal reports of poor sleep quality and highly fragmented sleep at high altitude were confirmed by this study; Joern found that the lightest stage of sleep was markedly increased while the deeper stages were decreased; in one man REM sleep was reduced to only 10% (Joern et al. 1970).

Since this initial study of sleep at high altitude many studies have been performed at geologically high altitude locations and at simulated high altitude in hypobaric chambers. The presence of periodic breathing during sleep has been demonstrated many times and poor quality, fragmented sleep is a common feature of high altitude.

1.2 Normal Human Sleep

Sleep is a behavioural state in which postural recumbence, unresponsiveness, closed eyes and quiescence normally occur. There are two distinct types of sleep: non rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep is comprised of four stages with each being “deeper” than the previous stage i.e. Stage 1 NREM is the lightest and stages 3 and 4 the deepest. The electroencephalogram (EEG), derived from scalp electrodes, demonstrates that the electrical activity of the brain in each of these sleep stages is distinct from the other stages. Stage 1 is a low amplitude, mixed frequency pattern; in Stage 2 spindles and K complexes occur; in Stages 3 and 4 high amplitude, slow EEG signals occur for ≥20% and ≥50% of the 30

second sleep period respectively. REM sleep was discovered in 1953 by Aserinsky and Kleitman; it was found to be as unlike NREM sleep as NREM was to wakefulness. In REM sleep the EEG is similar to the awake EEG but muscle atonia is present and rapid eye movements occur. When subjects were woken during these episodes of rapid eye movements they reported the occurrence of vivid dreams (Aserinsky and Kleitman 1955).

In normal, young adults sleep begins with Stage 1 sleep which persists for a few minutes only; during Stage 1 sleep it is easy to awake from mild stimulus i.e. there is a low arousal threshold in this sleep stage. Stage 2 sleep follows and continues for 10-25 minutes, after which slow wave sleep (Stages 3 and 4) begins; an incrementally larger stimulus is needed to produce an arousal from Stages 2, 3 and 4. REM sleep usually occurs after 60-100 minutes of sleep and this first REM sleep period usually last for less than ten minutes. The stimulus needed to cause arousal during REM sleep varies across the REM period; this variability of the arousal threshold is possibly due to the arousal stimulus being incorporated into a dream rather than causing arousal from sleep. This pattern of NREM sleep alternating with REM sleep occurs across the night with each period of REM sleep becoming longer. Stages 3 and 4 NREM predominate in the first third of the night and REM sleep dominates the last third. Brief episodes of wakefulness are common but are usually too short to be remembered after a night's sleep. Wakefulness constitutes less than 5% of the sleep period. Stage 1 normally constitutes about 2-5%, Stage 2 45-55%, Stage 3 3-8%, Stage 4 10-15% and REM sleep 20-25% of the night's sleep.

Slow wave sleep is maximal in young children and decreases with age in both amplitude and percentage of total sleep. It is very difficult to arouse children from sleep but, with increasing age, the arousal threshold becomes lower and the number of arousals from sleep across the night increases. Thus, with increasing age sleep quality may decrease in some people as periods of wakefulness and the number of arousals from sleep increase.

Sleep onset involves a shift from sympathetic to parasympathetic regulation; muscle tone is reduced, blood pressure and heart rate are decreased, cerebral blood flow decreases in NREM sleep then increases markedly in REM sleep. The muscle activity in NREM sleep is slightly decreased compared to wakefulness but, in REM sleep, there is a dramatic reduction in muscle activity. Upper airway resistance is increased during sleep in association with relaxation of upper airway musculature. Breathing becomes somewhat unstable with sleep onset and the loss of the wakefulness control of breathing (Orem et al. 1985; Longobardo et al. 2002), but in SWS breathing is regular, and slower, compared to wakefulness, with a slightly higher tidal volume. In REM sleep breathing becomes irregular and shallow in association with muscle twitches and rapid eye movements.

With sleep onset cortical input into the control of breathing (wakefulness control) is lost (Orem et al. 1985; Longobardo et al. 2002) and at the same time there are changes to the ventilatory responses to low oxygen and high carbon dioxide which become even more blunted in REM sleep.

These alterations in heart rate, blood pressure, muscle tone and breathing during sleep are all present in normal, healthy humans when sleeping at sea level. Changes to the amount of ambient oxygen, or diseases that affect breathing can cause marked aberrations in oxygen and carbon dioxide levels during sleep.

1.3 Sleep at High Altitude

Sleep disturbance is common after acute ascent to high altitude. Complaints include frequent awakenings with a sense of suffocation and the need to gasp for breath, unrefreshing sleep, and daytime sleepiness with cognitive impairment. Objective findings include the presence of periodic breathing in most people (Reite et al. 1975, Weil et al. 1978) reduced amounts of deeper sleep and increased lighter sleep (Joern et al. 1970, Reite et al. 1975, Miller and Horvath 1977, Nicholson et al. 1988 and many others since) increased wake time and arousals from sleep, but with total sleep time unchanged. Sleep was not recorded electrophysiologically at high altitude until the 1970s but the study of breathing during sleep has a longer history. Descriptions of the poor sleep and altered breathing pattern experienced at high altitude were published in the nineteenth century by several physicians and scientists who were also mountaineers. Tyndall (1860), who was a physicist and keen Alpine mountaineer, on his first ascent of Mont Blanc in 1857 describes falling asleep during a rest from the climb and being woken by his companion who became worried when he noticed that Tyndall was not breathing for long periods of time. Another nineteenth century report by Egli-Sinclair (1891-2) described his breathing during sleep at an altitude of 4400m as being of the “Stokes character, that is it seemed regular during a certain time, after

which a few rapid and profound breaths were drawn, a total suspension for a few seconds then following".

Mosso (1898) was the first to extensively study breathing during sleep at high altitude, at 4559m on Monte Rosa in the Italian Alps. He measured breathing by means of a lever resting on the chest that recorded breathing movements onto a smoked cylinder and found that apneas lasting for about twelve seconds occurred repetitively with hyperpneic episodes of three to four breaths following.

When advancements in technology enabled sleep to be recorded electrophysiologically with surface electrodes and pen and ink polygraphs, the first of many studies into sleep at high altitude was performed. The protocols for each study differed; some were recorded at high altitude locations at various elevations while others utilized hypobaric chambers to simulate high altitude. Some studies recorded sleep after acute exposure to hypobaric hypoxia/high altitude while others recorded sleep days or weeks after ascent. In some studies, particularly those performed in altitude chambers, several nights' sleep were recorded after the subjects had spent each day at sea level. Some studies recorded sleep for one night only while others repeated the measurements on more than one occasion with varying amounts of time between recordings, therefore studying acclimatisation to high altitude. In most studies sleep at high altitude was characterised by the reduction, and in some cases complete loss, of slow wave sleep i.e. Stages 3 & 4 non rapid eye movement (NREM) sleep, increased numbers of arousals or awakenings from sleep and an increase in

light sleep (Stage 1 NREM sleep).

This decrease or loss of slow wave sleep (SWS) with an increased number of arousals from sleep was hypothesised as being an adaptive measure to the hypoxic conditions of high altitude. Sleep is known to be associated with a decrease in minute ventilation

and this decrease was thought to become worse with deeper sleep stages, hence the curtailment of SWS in which ventilation would be at its lowest and hypoxia at its worst. The increased number of arousals at high altitude would act as a stimulus to breathing and thus maintain higher levels of oxygenation during sleep under hypobaric hypoxic conditions.

The first scientific studies into the changes in sleep patterns in humans in environmentally hypobaric hypoxic conditions were by Joern et al in 1970 and Natani et al in 1970 who performed polysomnography on men stationed at Antarctica, which has a barometric pressure of 485 to 525mmHg corresponding to an altitude of 3000 to 3800 metres above sea level. Joern et al studied two men aged 35 and 50 years over three nights in the first week of their sojourn at the South Pole, recording sleep using electro-encephalogram (EEG), electro-oculogram (EOG) and submental electro-myogram (EMG). Measurements of ventilation were made from an impedance pneumograph and arterial blood gases were sampled and analysed.

Joern et al found that compared to sleep data from a normal, healthy, middle-aged population Stage 1 NREM sleep was significantly increased to over 10% of total sleep

in one subject and over 25% in the other subject; Stage 2 NREM was within normal range in one subject but increased to nearly 70% in the other subject. Slow wave sleep (Stages 3 and 4 NREM) was minimal in both subjects. In one subject rapid eye movement (REM) sleep was reduced to 10% of sleep time but, in the other subject it remained within normal limits (23%). The older of the subjects had periodic breathing during sleep in Stage 1 NREM; this consisted of periods of apnea followed by bursts of rapid, deep respiration (hyperpnea) with activation patterns (arousal) occurring in the EEG during hyperpnea. The older subject also had symptoms of Acute Mountain Sickness (headache, malaise, anorexia, nausea and vomiting). Both men rated their sleep as "poor and not restful".

The authors comment that their findings on the altered patterns of sleep in their subjects failed to correspond to any previously described situation. They also postulated that the absence of symptoms associated with these changed sleep patterns (both subjects felt well during the day and were able to engage in quite strenuous physical activity) may be due to the sleep changes being "related to the normal physiological adaptation to reduced pO_2". The authors discussed the well known drop in ventilation that occurs with sleep and its concomitant fall in alveolar pO_2; normally this is insignificant but, at high altitude under hypoxic conditions this drop in ventilation and alveolar pO_2 occurs on the steep part of the oxygen dissociation curve and can produce significant falls in oxygen saturation. They also comment that Bulow (1963) has described a progressive depression of the carbon dioxide drive on respiration during the successive stages of sleep with the highest threshold found in slow wave sleep; thus it is "possible that the elimination of periods of sleep associated

with the greatest diminution of respiration is particularly advantageous in the acute hypoxic state. The hypothesis offered is that decreases in ventilation and alveolar pO_2 is minimised by the curtailment of slow wave sleep as a means of avoiding worsening the hypoxic condition found at high altitude".

Natani et al (1970) studied sleep in four men, using the same methodology as Joern et al (1970), at sea level, four times during a year spent at the South Pole and then again at sea level several months after their return. This study was mainly concerned with the psychological problems that occur during long sojourns at the South Pole, particularly insomnia, depression and anxiety. However, sleep changes were recorded and reported. These authors reported that total sleep time was unaltered but sleep latency was significantly increased during all recordings at the South Pole, slow wave sleep was significantly reduced and remained so several months after return to sea level. REM sleep and Stages 1 & 2 NREM sleep were unaltered. The men were able to physically function well during the days despite the decrements in slow wave sleep. The authors postulate that the well known psychological changes that manifest in men staying at the South Pole (slight depression, insomnia and anxiety) may be associated with the decreased slow wave sleep.

The first study to objectively quantify sleep patterns and associated physiology in humans at a high altitude location was by Reite et al (1975) who studied six normal, healthy young men aged 19-23 years, over twelve days spent at an altitude of 4300 m at the U.S Army Research Facility on the summit of Pikes Peak in Colorado. The mean atmospheric pressure at this altitude is 450 mmHg. The men were studied at sea

level on two non-consecutive nights with polysomnography that recorded sleep onto a Grass Model 6 polygraph using three channels of EEG, three channels of EOG and submental EMG. Breathing was recorded with a mercury strain gauge around the chest and electro-cardiography (ECG) was recorded via one electrode on the sternum. An oxygen cannula was placed in the nares for the purpose of oxygen administration which was given at 4L/minute for five minutes, after increasing the flow rate from 0 to 4L/min over several minutes. The subjects were flown to Denver, Colorado, USA then driven to Pikes Peak. Sleep was recorded on the first night at high altitude and on four more occasions during a twelve day sojourn.

All subjects complained of sleeplessness on their first night at altitude (several subjects thought they had not slept at all) and the objective findings demonstrated significantly reduced Stages 3 & 4 NREM (slow wave) sleep, significantly increased Stage 1 NREM sleep, a trend towards less REM sleep with Stage 2 NREM sleep unchanged. Arousals from sleep were significantly increased with a trend towards more time spent awake. Total sleep time was unchanged. All measurements tended towards a return to baseline values by the last night at altitude and this was accompanied by improved subjective sleep quality.

Five of the six subjects developed periodic breathing during sleep at high altitude. The periodic breathing consisted of four or five rapid breaths (hyperpnea), followed by a 10-20 second period of breathing cessation (apnea). Hyperpneas were occasionally associated with EEG arousal lasting for several seconds. The mean heart rate during sleep at high altitude was higher and during periodic breathing the heart rate was

decreased during the apneic phase and increased during the hyperpneic phase with a difference of up to twenty beats per minute. Periodic breathing ceased within a minute or two of REM sleep commencing.

When oxygen was administered during sleep at high altitude periodic breathing was quickly abolished but there were no effects on sleep state or arousals, nor was there any effect on sleep state or arousals when oxygen was administered during sleep at sea level.

Alveolar P_AO_2 and P_ACO2 values demonstrated marked hypoxia (mean P_AO_2 52mmHg) and hypocapnia (mean P_ACO_2 29mmHg) persisting throughout the eleven days at high altitude with P_AO_2 tending to increase slightly over time at high altitude but P_ACO2 decreasing further.

The authors concluded that the major finding of their study were that subjective and objective sleep quality was dissimilar i.e. all subjects complained of sleeplessness but objective measurement found no decrease in total sleep time and substantial amounts of all sleep stages present. They suspected that the increased arousals and awakenings from sleep contributed to the subjective feelings of poor sleep quality. They postulated that the increased arousals may be due to low barometric pressure influencing the reticular activating system, either directly via the carotid baroreceptors or indirectly via hypoxic or hypocapnic influences on carotid and aortic chemoreceptors but the possible role of these mechanisms' effect on the reticular

activating system and increased arousals from sleep are highly speculative.

It is possible that the number of arousals per hour of sleep was underestimated in this study due to the criteria used to score an arousal i.e. EMG activation, eye movement and alpha activity had to be present for an arousal to be scored; in most studies an arousal is scored in NREM sleep when the EEG abruptly changes, usually to a faster signal e.g. alpha or theta and it is only in REM sleep that EMG activation is also needed to score arousal.

Another finding from this study was the presence of periodic breathing during sleep at high altitude in five of the six subjects and the authors postulate that the hypocapnia of high altitude increases sensitivity to carbon dioxide i.e. the CO_2 sensor gain is increased causing the feedback mechanism that controls ventilation to oscillate, resulting in periodic breathing. However, oxygen administration during sleep eliminated periodic breathing in the subjects, suggesting that hypoxia-dependent disruption of central nervous system function may contribute importantly to the development of periodic breathing at high altitude. During REM sleep periodic breathing was abolished, implying a change of state of respiratory control mechanisms coincident with the onset of REM sleep.

Miller and Horvath (1977) published the finding from their research conducted on four male and four female subjects, aged 18-29 years, in simulated altitude of 3500metres in a hypobaric chamber. The subjects spent only the nights in the hypobaric chamber. They recorded sleep by use of EEG, EOG and ECG over five

nights. The first three nights the subjects slept in the chamber at 747 mmHg/ sea level to accustom them to the experimental conditions. On nights three, four and five the subjects were instrumented with surface scalp electrodes and circumferential Mylar tape electrodes to allow impedance ECG recording. On nights four and five the hypobaric chamber was brought to a simulated altitude of 3500m (493 mmHg) and the subjects slept from about 2300 hours until about 0600 hours.

The authors reported that REM sleep was significantly reduced and Stage 1 NREM increased on night 4 compared to night 3 and Stage 2 NREM percentage was reciprocally smaller; there were no other changes to sleep stage percentage. Night 4 (first night at 3500m) was more disturbed than other nights. They also found that on night 4 male subjects experienced more time awake than female subjects and had less Stage 2 NREM and REM sleep.

The authors concluded from this research that slow wave sleep was not reduced at high altitude as had been reported in previous work. The hypothesis that the loss or reduction of slow wave sleep at high altitude and the increased arousal from sleep protects against sleep hypoventilation that may be more pronounced in deeper, less disrupted sleep allowing greater levels of hypoxia was not supported by the findings from this research.

A study on rats by Pappenheimer (1977) aimed to investigate the physiological basis of insomnia at high altitude that have been reported by mountaineers as well as scientists studying sleep at high altitude; this work on sleep under normobaric hypoxia

specifically looked at changes in slow wave sleep. Rats with implanted EEG electrodes were studied in a chamber in which different gas mixtures were added. Normal sleep in rats occurs in 5-15 minute periods with slow wave sleep (60μV compared to 12.5μV when awake) occupying 50% of sleep time. The rats' sleep was recorded for 5-7 hour periods for five months. When the rats breathed 10% oxygen (equivalent to 5540m altitude) SWS was not sustained for longer than 2-3 minutes, being interrupted by frequent brief returns to a lower voltage EEG closer to the wake value. It appeared that whenever the animal attempted to achieve sustained SWS it woke up. The amount of SWS was reduced in hypoxic rats to 30% of sleep time compared to 50% when breathing 21% oxygen. Behaviourally, the rats appeared restless when sleeping in hypoxic conditions, frequently turning around to curl up again as if to seek a more comfortable position.

The hypoxic rats hyperventilated which resulted in respiratory alkalosis; when 4% CO_2 was added to the hypoxic mixture, respiratory acidosis was prevented but there was no prevention of sleep disturbance; leading the author to conclude that it is reduced oxygen pressure and not respiratory alkalosis that causes the sleep disturbances, possibly from carotid body chemoreceptor feedback to the reticular activating system.

In rats breathing 21% oxygen, minute volume and frequency were reduced in slow wave sleep but in the hypoxic rats frequency was increased; when CO_2 was added during sleep, frequency and minute volume decreased from which the author

concluded that, in hypoxia, the increase of hypoxic sensitivity leading to increased ventilation, is dependent on CO_2.

Pappenheimer comments that this work has quantitatively established that hypoxia interferes with normal sleep, confirming the subjective reports of insomnia at high altitude. However, the techniques used supplied information only about slow wave sleep and the experimental conditions were hypoxia only, not hypobaric hypoxia.

Ryan and Megirian (1982) studied the sleep/wake pattern (SWP) in six male rats under normoxic and hypoxic conditions before and after carotid sinus nerve (CSN) section i.e. ablation of the carotid body. The rats breathing air had a typical and consistent pattern of sleep with proportions of slow wave sleep, REM sleep and wakefulness being characteristic for the rat i.e. REM sleep was almost always preceded by SWS which usually lasted for more than two minutes. After CSN section the SWP parameters remained unchanged when breathing air. On the first day of breathing 10% oxygen dramatic changes to the SWP occurred: REM sleep almost disappeared, SWS was considerably reduced and the duration of the epochs of these sleep states was shortened. The frequency of state changes between wake and SWS was greatly increased. After denervation of the carotid body these changes persisted during hypoxia. On the second day of hypoxia after spending the night having REM sleep suppressed by having the rats sleep on a flower pot (REM paralysis would cause the rats to fall into water) the intact rats were without REM sleep and the changes in SWP were not significantly different from the first day of hypoxia. After CSN section

the SWP was closer to normoxia with REM sleep appearing in increasing amounts and the percentage of SWS the same as intact rats breathing air. The duration of the epochs of REM, SWS and wake were no longer significantly different from those during normoxia. The frequency of state changes also was closer to the normal pattern.

The authors concluded that peripheral denervation i.e. ablation of the CSN, in rats breathing 21% oxygen has no effect on the SWP, the percentage of time in each state of consciousness (wake, SWS, REM) or the frequency of changes between the three states. When the rats breathed 10% oxygen striking disruption of all parameters of the SWP occurred but on the second day of hypoxia the sleep disruption became less striking, largely due to a shift in the pattern of mean duration of epochs towards normoxic conditions. Thus, carotid peripheral chemoreceptors play a more important role in controlling the duration of states than in modifying the frequency of state changes during hypoxic challenge. The authors state that it is evident from this work that hypoxia exerts its affect on the SWP via central mechanisms as well as via the peripheral chemoreceptor. Disconnection of these receptors permits an amelioration of the disrupting effects of hypoxia on the SWP as the exposure to hypoxia is prolonged.

This study confirmed that hypoxia attenuates REM sleep to a greater extent than SWS in the adult rat. The most sensitive parameter of the SWP which is disrupted by hypoxia is the duration of the epochs. About 1.6-2 minutes of SWS are necessary before REM sleep can occur; REM sleep is the last step in the normal sequence of

states of consciousness (wake, SWS, REM); therefore it is the state that is most vulnerable to suppression. It would be misleading however, to believe that the duration of the SWS epoch preceding the onset of REM is not critical.

The same group, in 1983, examined the effects on the sleep wake-pattern (SWP) of adding CO_2 to the hypoxic mixture before and after carotid sinus nerve transection in male rats. During periods spent breathing air (21% oxygen and 4% carbon dioxide) or 10% oxygen and 4% carbon dioxide, the SWP was examined before and after CSN section. When rats breathed air enriched with 4% CO_2 compared to breathing air alone, there was no difference in the pattern of percentage of time spent in each state of consciousness (wake, SWS, REM) and this was true before and after CSN denervation. The mean epoch duration and frequency of state change were also unchanged in both groups with and without CO_2 addition. When breathing 10% O_2 with 4% CO_2 SWP was markedly disrupted, with the greatest change being in the pattern of frequency of changes in state. There was also marked changes in the percentage of time spent in each state and their epoch durations. These changes were present after denervation.

The authors concluded that hypoxia in the presence of hypocapnia caused disruption of the SWP chiefly through a change in the pattern of mean epoch duration. Hypercapnic hypoxia disrupts SWP chiefly through a change in the pattern of frequency of state changes. Carotid denervation partially restored the SWP in hypocapnic hypoxia but had no effect on rats breathing a hypercapnic hypoxic mix.

Thus, in the rat the peripheral chemoreceptor reflex pathway has functional importance in hypocapnic hypoxia but not in hypercapnic hypoxia.

Another study by Pappenheimer (1984) aimed to determine whether hypoxic insomnia is mediated by the peripheral oxygen receptors. Sleep in rats was analysed before and after carbon monoxide was administered in concentrations sufficient to produce moderate cerebral hypoxia without stimulation of breathing via the peripheral oxygen sensors. The rats were also studied after a period of acclimatisation to hypoxia with continued stimulation of peripheral receptors over a period of weeks. The amplitude of cortical slow waves during sleep was measured from recordings of hippocampal EEG. The findings from this study confirmed that hypoxia virtually abolished REM sleep and shifted the amplitude of slow waves towards awake values. Similar disruption of sleep occurred from inhalation of carbon monoxide sufficient to lower the oxyhemoglobin saturation to around 35%. Hypoxia induced by breathing 10.5% oxygen resulted in markedly increased ventilation but was unaffected by carbon monoxide. Pappenheimer concluded from these results that the peripheral chemoreceptors do not mediate sleep disruption in hypoxia. The intense subjective complaints of sleeplessness at high altitude that do not correlate with observation of conventional EEG may be due to this decrease in the amplitude of slow waves during sleep i.e. hypoxia reduces the intensity of NREM sleep without greatly reducing the total duration.

After acclimatisation to hypoxia, sleep gradually returned to near normal values. Ventilation during the two week acclimatisation period decreased slightly but

remained at high levels; presumably due to continued drive from the carotid bodies. Partial recovery of sleep is therefore not attributable to diminished drive from the chemoreceptors controlling ventilation.

Berssenbrugge et al (1983) studied six men at simulated altitude of 3500m (455 mmHg) in order to ascertain the mechanisms of hypoxia-induced periodic breathing during sleep. This study was mainly focused on the mechanism of periodic breathing but the sleep stages were reported in the findings, adding to the small body of knowledge of sleep at high altitude. They found that, compared to baseline sleep studies conducted at sea level, total sleep time was unchanged at 3500m but light sleep (Stages 1 and 2 NREM) was increased significantly from 61% to 83%, slow wave sleep was significantly reduced from 25% to 13% and REM sleep was significantly reduced from 15% to 4%.

In another study by the same group (Berssenbrugge et al.1984) investigating the effect of sleep state on acclimatisation to hypoxia, seven men were studied at sea level and over four nights in a hypobaric chamber at simulated altitude of 3500m. The authors were interested in the ventilatory acclimatisation to hypoxia and the effects that sleep state had on breathing during sleep under hypobaric hypoxic conditions over a four day period; however changes in sleep were reported. They found that compared to sea level total sleep time at 3500m altitude was unchanged, light sleep (Stages 1 and 2 NREM) was significantly increased, slow wave and REM sleep were significantly decreased. They also found that over the four days spent at 455 mmHg sleep stages

returned to near normal amounts.

Finnegan et al (1985) published their work on ambulatory EEG monitoring of high altitude mountaineers. Twelve members of the Army Mountaineering Expedition to Mount Api (7130m) in North West Nepal were studied during the two week ascent from 4115 to 6220m. Ten of the subjects had twenty-channel clinical EEGs at sea level before the climb and three subjects had twenty channel EEG on return from the climb. During the climb three channels of EEG were recorded for 24 hours in nine subjects.

They found that there was a reduction in slow wave sleep at high altitude when compared to two control groups of six soldiers each who were performing similar activities at sea level, and with three soldiers from the control group who were less active at sea level. The overall time spent in Stage 4 NREM sleep at altitude was 30.4 minutes, a 65% reduction compared to the six men active sea level group, who spent an average of 85.5 minutes in Stage 4 NREM sleep and a 74% reduction compared to the three man less active group who spent a mean of 116.3 minutes in Stage 4 NREM sleep. In the three men who had both sea level and high altitude EEG recordings the reduction in Stage 4 NREM was from 68-77%.

REM sleep was also reduced at altitude from between 22% and 39% in the three men who had sea level and altitude EEG recording. They also found that the mean number of arousals per hour of sleep was six.

The authors comment that the reduction in slow wave sleep noted by them was despite the fact that high rates of energy expenditure is known to increase SWS. This reduction in SWS and REM sleep accords with the belief of mountaineers that their sleep is of a poorer quality at high altitude (including members of their own party). However the subjects remained healthy despite hypoxia, perhaps as a result of partial acclimatization and good hydration.

The next published work that reported the findings from a study performed at a high altitude location, rather than in a hypobaric chamber, was by Selvamurthy et al (1986) who studied twenty seven male subjects at 3500m in the Western Himalayas over a two week period. Fifteen subjects were lowlanders taken to 3500m for the first time i.e. sojourners (SJ); six were acclimatized lowlanders (AL) and six were high altitude natives (HAN). Baseline sleep studies were performed at sea level on the SJ group before the subjects were flow to an altitude of 3500m; sleep was recorded every second night on each subject in the three groups over a two week period using EEG, EOG, EMG and ECG. They found in the SJ group that, compared to sea level, total sleep time and sleep efficiency were unaltered at 3500m, slow wave sleep was significantly reduced and arousals increased with acute exposure to high altitude over the two weeks spent at 3500m. This reduction in SWS persisted in the SJ group for two weeks on return to sea level while sleep efficiency improved and latency to all sleep stages shortened even though there had been no significant changes to sleep efficiency or sleep latencies at 3500m. The SJ subjects complained of poor sleep and of tiredness. Four in the SJ group had signs and symptoms of Acute Mountain Sickness (AMS) in the first week at 3500m and these subjects did not have either

frequent arousals or a reduction in SWS.

The authors in this study suggested that the frequent arousals from sleep at high altitude observed in their SJ group was an adaptive feature to prevent the accentuation of hypoxemia known to result from hypoventilation during sleep at high altitude. In their group four subjects who did not have increased arousals or reduced slow wave sleep developed AMS symptoms. The AL and HAN groups also had reduced slow wave sleep compared to the SJ group at sea level but AL and HAN had fewer arousals; the authors state that this further supports the thesis that curtailment of SWS is an adaptive feature of sleep at high altitude. The authors propose that the subjects suffering AMS may have attenuated chemoreceptor sensitivity which fails to sense the increased hypoxemia during sleep; they could also have reticular damping due to hypocapnia and alkalosis, which would reduce the number of arousals from sleep caused by reticular stimulation.

Research performed during a trek in the Himalayas was reported by Nicholson et al (1988) who studied the sleep of six climbers, three of whom ingested a drug known to improve arterial oxygenation and reduce periodic breathing i.e. acetazolamide 500mg daily, and three of whom ingested placebo. Upon reaching an altitude of 4150-4846m each subject ingested temazepam 10mgs on one night and placebo for another night (temazepam is thought to improve sleep at high altitude but may also depress ventilatory response to carbon dioxide thereby worsening hypoxemia). Sleep was recorded by means of two EEG, two EOG and submental EMG. Breathing movement was recorded using a chest impedance method. Sleep was recorded at sea level, one

night at 1100-1400m, one night at 2750-3650m and two nights at 4150-4846m. The study found that, at the lower altitude (1100-1400m) compared to sea level total sleep time and sleep efficiency were reduced and awake time was increased in all subjects; at the medium altitude (2750-3650m) compared to sea level, the only change was reduced sleep efficiency in all subjects; but at the highest altitude (4150-4846m) sleep was markedly disturbed in all subjects with reduced total sleep time and sleep efficiency, less REM sleep, awake time and latency to sleep were increased. When compared to medium altitude the sleep at the highest altitude was also significantly poorer with total sleep time and sleep efficiency reduced, latency to sleep increased and reduced REM sleep. Acetazolamide was shown to increase Stage 2 NREM sleep and reduce wake time. Temazepam decreased latency to sleep and increased REM sleep. The subjects reported better sleep quality when taking temazepam >4000m. There were no differences in the amount of periodic breathing during sleep in those taking acetazolamide or in those taking temazepam and disturbed sleep persisted with and without periodic breathing.

The authors of this study believe that the changes in sleep architecture at 1100-1400m were due to time change between London and Kathmandu; this theory is supported by the finding that sleep was little altered from sea level values at the medium altitude. They conclude that acetazolamide improves sleep at medium altitude but above 4000m marked sleep disturbances persist and temazepam in low doses is beneficial at this altitude. However, it was not known if temazepam depressed ventilation because no measurement of oxygenation was utilized and they suggest further studies are

needed to clarify the relationship between benzodiazepines and sleep hypoxemia.

The findings from a French medical high altitude expedition to the Himalayas were reported by Goldenberg et al (1988). The study was carried out at 4800m. Twelve subjects (three female) had sleep studies recorded at sea level and at 4800m using EEG, EOG and submental EMG to record sleep, and chest and abdominal effort bands to record breathing during sleep. Six subjects were given a benzodiazepine (loprazolam 1mg) and the other six received placebo on the first four nights after arrival at 4800m and again for four nights after twenty days at 4800m. Sleep studies were performed on the fourth night after arrival and again after twenty four days.

In the placebo group the results of the sleep studies were increased wakefulness, decreased SWS and REM sleep. All subjects complained of increased wakefulness during the sleep studies. Periodic breathing occurred in all subjects to varying degrees; the female subjects exhibited less PB than the male subjects. After twenty four days of acclimatisation to 4800m sleep returned to near normal values and PB decreased. Loprazolam tended to decrease Stage 2 latency and did not worsen SWS depression or affect the amount of PB or apnea length; however the benzodiazepine did not improve the complaints of wakefulness.

All the subjects had periodic breathing during sleep at high altitude during Stages 1 and 2 NREM and two subjects had PB in REM sleep. The increased arousals and wake time were not correlated to the amount of PB, with some subjects having almost

no PB but still many awakenings and arousals.

The authors conclude that acclimatisation to high altitude improves sleep and periodic breathing. The presence of periodic breathing at high altitude may be useful for altitude adaptation; sleep modifications such as reduced SWS, increased arousal and wakefulness could also be adaptive, preventing worsening hypoventilation during sleep. Benzodiazepines preserved these adaptive mechanisms.

Another study undertaken at a high altitude location was by Normand et al (1990) who studied six lowlanders (four men, two women) at sea level and then after three weeks spent at 3800m in Bolivia to determine the relationship between sleep state, periodic breathing and oxyhemoglobin saturation. The hypothesis was that periodic breathing during sleep negatively influences arterial oxyhemoglobin saturation. The authors also wanted to determine whether sleep deficits at high altitude are due to cold conditions at night (known to decrease REM sleep) and the vigorous activity of climbing during the days. Sleep studies were performed at sea level and then after three weeks spent at 3800m. Sleep was recorded using EEG, EOG and EMG. Chest and abdominal movement was recorded using strain gauges with nasal airflow monitored with thermistors. ECG and oxyhemoglobin saturation (SaO_2) were also recorded. Arterial blood was analysed for PaO_2, $PaCO_2$ and pH.

These researchers found that total sleep time, all sleep stages and the arousal index were unaltered from sea level measurements. Periodic breathing occurred in NREM sleep in three male subjects but there was no difference in the sleep structure, mean

SaO2, PaO_2, $PaCO_2$ or pH in subjects with or without periodic breathing.

The authors conclude from this study that high altitude does not induce any change in sleep organization and that periodic breathing does not alter sleep or arterial oxygen saturation. They propose that many of the sleep disruptions experienced by climbers and mountaineers may be due in part to the conditions in which they are living – intense muscular activity during the days and uncomfortable and cold conditions at night. However, the sleep studies that these authors have compared their findings to were performed under conditions of acute exposure to high altitude (Reite et al. 1975, Pappenheimer 1977), whereas this work was carried out after three weeks at 3800m.

The highest altitude at which research into sleep in humans has been carried out is the work of Anholm et al (1991) who conducted studies in a hypobaric chamber at simulated altitudes of 4572m, 6100m and 7620m. These studies were called Operation Everest II. Studies were also performed at sea level before and after the high altitude research. Five men were studied over a forty day stay in a hypobaric chamber under increasing reduction in barometric pressure. Sleep was recorded using EEG and EOG; respiratory data was collected by means of chest and abdominal inductance and a close fitting face mask; ECG and oxyhemoglobin saturation were also recorded.

The findings from this study were that all subjects complained of some degree of poor sleep throughout Operation Everest II, with symptoms including difficulty falling asleep, frequent awakening and feeling unrefreshed in the morning. The monitoring equipment worn by the subjects and the uncomfortable sleeping arrangements were

thought to be partially responsible for poor sleep but complaints were also present when sleep was not monitored so hypobaric hypoxia also played an important part in poor subjective sleep quality. There were significant increases in the time spent awake after sleep onset, arousals (2-10 seconds) and amount Stage 1 NREM sleep; there were significant decreases in total sleep time, Stage 2 NREM and in REM sleep. Slow wave sleep was not decreased in these subjects. SWS and REM sleep were also reduced on the first sea level sleep study from what is normal in this age group (around 21% for SWS and 25% for REM sleep) but both increased on the second sleep study at sea level after completion of the high altitude studies i.e. REM sleep approached normal amounts at 21 ± 5% but SWS remained reduced at 10.6 ± 8.6%.

The authors commented that this work has presented new findings in sleep architecture and oxygen desaturation at extreme altitude. Sleep under hypobaric hypoxia was disrupted by frequent arousals and reduced REM sleep; severe oxygen desaturation (<50%) was observed at 282mmHg (7620m) and in one subjects at 6100m. They also suspect that several factors may have altered normal sleep at altitude in this group i.e. noisy equipment, cots or mattresses on the floor, snug-fitting face masks, ear oximeters and inductance bands. The sea level studies were performed only on one occasion so sleep deficits may have been due to "first night effects" of uncomfortable monitoring equipment. However, sleep became more fragmented with increasing altitude which can only be the effects of hypoxia. Nearly all the subjects thought that the discomfort of wearing the monitoring equipment interfered with their sleep with one subjects refusing further sleep studies above 4572m (429mmHg). The reduction in REM sleep and the number of awakenings (10-20 seconds) were nearly

the same at 4572m as they were at 7620m; similarly sleep efficiency did not decrease further after 4572m. This suggests that sleep disturbance does not worsen above 4572m but the authors suspect that the sleep changes could not be detected by the standard sleep scoring paradigm, which is based on 20-30 second periods of EEG to a single sleep stage (20s in this study) with brief 3-5s arousals not reflected in the sleep stages. As a result, changes in the total sleep time and various sleep stages do not fully explain the subjective impressions of sleep loss or deterioration in daytime performance. The number of arousals however, increased progressively as altitude increased and are a more sensitive index of sleep impairment. At 6100m and 7620m the longest uninterrupted period of sleep was less than ten minutes and this is indicative of severe sleep fragmentation.

Mizuno et al (1993) aimed to clarify the relationship between sleep architecture and periodic breathing at high altitude. The study was performed in a hypobaric chamber at simulated altitudes of 1500m, 3000m and 4000m. Five healthy young male subjects were studied at sea level in the chamber and then one night at each of the three altitudes above sea level (ASL). The sleep studies were performed at least three days apart and the order of the ASL studies was randomised. Polysomnographic recordings included EEG, EOG, EMG, ECG, oxyhemoglobin saturation (SaO_2) and breathing from a thermistor and a pressure sensor under the back.

Sleep architecture measurements were similar for sea level, 1500m and 3000m but at 4000m sleep was disturbed and the architecture significantly altered. Sleep latency, sleep efficiency and total sleep time were reduced with time spent awake after sleep

onset increased at 4000m. The nights were divided into three parts: early, middle and late part of the time in bed (TIB); in this way each sleep stage's percentage in each part of the night was calculated. In the early part of the sleep study there were no differences for any altitude but in the middle and late parts the amount of time spent awake after sleep onset was increased, the percentage of Stage 1 NREM was increased, and REM sleep percentage decreased. Periodic breathing occurred in all subjects at 3000m and was increased at 4000m but was highly variable among the subjects with three subjects having 100 apneas or hypopneas per hour and one subject having only 7 per hour. The number of periodic breathing apneas and hypopneas was significantly higher at 4000m. Periodic breathing time for each sleep stage was also calculated. Tendency to PB was significantly higher for Stage 1 NREM than for slow wave sleep (SWS), with only minimal amounts of PB occurring in SWS at 3000m but three subjects had 20% to near 100% appearance of PB in SWS at 4000m.

The authors concluded from this study that because the research was conducted in a hypobaric chamber and the subjects arrived at the chamber about an hour before going to sleep, the brief adaptation time may have caused an increase in the hypoxic effect on sleep. It is necessary to investigate sleep after a longer hypoxic exposure before sleep onset. They note that sleep disturbances definitely occurred above 3000m with definite increases in wake, Stage 1 and decreased REM in the middle and late parts of sleep at 4000m which suggests that the increased hypoventilation of sleep in the early part of sleep resulted in severe hypoxemia and contributed to the increased arousal response in the middle and late parts. The position on the steep part of the oxygen dissociation curve at altitudes above 3000m would ensure that hypoventilation during

sleep would result in a marked reduction in oxyhemoglobin saturation (SaO_2) and decreased SaO_2 has been suggested to cause sleep disturbance. Deep sleep (SWS), in which the most intense stimulus is needed to induce arousal, was observed in the early part of the night at 4000m suggesting that arousal was not caused by lower SaO_2 in deep sleep. Sympathetic stimulation caused by hypoxia in the early part of the night may also have contributed to the increased arousals in the middle and later parts. The shortened latency to sleep that was observed at 4000m suggests that liability to sleep was enhanced by hypoxia.

The effects of periodic breathing on sleep architecture and oxyhemoglobin saturation was investigated by Salvaggio et al (1998). Five subjects were studied (three male, two female). The subjects trekked from 2800m to 5050m over six days and stayed at 5050m for four weeks. Polysomnography was performed during the first and fourth week at 5050m with recordings of EEG, EOG, chin EMG, oxyhemoglobin saturation (SaO_2), airflow using nasal cannula with a pressure transducer, chest and abdominal inductance plethysmography. The changes in sleep architecture found in the first week at 5050m were: decreased slow wave sleep (SWS was absent in four of the subjects) with less SWS in the two subjects who had less periodic breathing; the arousal index was increased with more arousals occurring during periodic breathing than in regular breathing; Stage 1 NREM sleep was increased and REM sleep was unchanged. In the fourth week at 5050m SWS showed a trend towards an increase from the first to fourth week but was still missing in one subject; arousals remained significantly increased in the fourth week; Stage 1 NREM remained increased in three

subjects but had returned to near sea level values in two subjects.

The authors concluded that slow wave sleep tends to disappear at high altitude even in subjects with little periodic breathing; sleep fragmentation was associated with arousals during the hyperpneic phase of periodic breathing. Periodic breathing is associated with only a small increase in SaO_2 with respect to regular breathing but improves over time spent at altitude during wake and sleep regardless of the breathing pattern. The authors note that fragmented sleep occurred in periodic breathing and regular breathing hence the occurrence of PB is not a major determinant of decreased SWS.

Research by Zielinski et al (2000) reported on a group of nine male subjects who were studied at sea level and at 3200m on the first and sixth night. Polysomnography included recordings of EEG, EOG, chin and tibial EMG, airflow by thermistor, chest and abdominal movement, pulse oximetry, ECG and body position. The subjects were driven to the high altitude location at 3200m. Sleep architecture changes at 3200m were few, with a small decrease of 2-4% in slow wave sleep and unchanged percentages of all other sleep stages. There were, on average, twice as many arousals at altitude with large individual variations in the number of arousals and awakenings. Periodic breathing was absent in four subjects but present to varying degrees in the other five subjects in NREM sleep; PB was present to the same degree on the first and fourth nights at 3200m. The number of arousals and time awake did not change from night one to night four at altitude despite a 2% improvement in SaO_2.

The authors comment that their findings are different from previous work by Miller & Horvath (1977) who found, at 3500m that Stage 1 NREM sleep was increased and the work of Selvamurthy (1986) who found that at 3500m sleep was increasingly fragmented and that slow wave sleep was decreased. They suggest that the differences may be due to the slightly higher altitudes at which the above studies were performed. Also less comfortable conditions in the hypobaric chamber may have worsened sleep quality. They conclude that at an altitude of 3200m sleep quality remains satisfactory and the incidence of periodic breathing is rather low compared to that observed at higher altitudes. Large individual variations in the number of awakenings, arousals and intensity of periodic breathing are present.

Mizuno et al (2005) published a study into sleep on Mount Fuji (3776m). Three men were driven from sea level to 2380m then climbed for 4.5hours to reach the summit. Polysomnography was conducted using EEG, EOG, mentalis EMG and ECG In two of the three subjects nasal airflow, chest movement and oxygen saturation were monitored. The sleep studies were performed sea level a month after return form high altitude and on four consecutive nights spent at 3776m. The first night spent at Mt Fuji was considered to be affected by the previous night's short sleep time and the 4.5hour climb to the summit so sleep studies were performed on the second to the fifth night at 3776m. Due to technical problems the results from one subject on night three were lost.

Sleep architecture was altered at 3776m, with two subjects having significantly more time awake after sleep onset on the second night and one subject on the fifth night;

arousals were increased in two subjects on all nights at altitude; longer latency to sleep was observed in one subject on the fourth and fifth nights; slow wave sleep was decreased in one subject on three nights and on two nights in another subject; the amount of REM sleep did not change.

The authors concluded that sleep architecture at 3776m remained unacclimatised over the five nights. In previous work by Normand et al (1990) sleep architecture was normal after three weeks spent at 3800m so the conclusion is that acclimatisation takes longer than five days therefore, when arriving at a high altitude location, schedules of work and rest should be carefully planned during the first week.

High altitude not only induces hypoxia but because of the increased ventilation that the hypoxia causes, hypocapnia is also present. A study that examined the effect on sleep of hypocapnia in cats was carried out by Lovering et al (2003). Four adult cats were instrumented to record EEG, EMG diaphragm and pontogeniculooccipital (PGO) waves and the trachea intubated. Tidal O_2 and CO_2 as well as airflow were also recorded. The cats breathed air (normoxia), hypocapnic and isocapnic hypoxic gas mixtures while sleep and breathing were measured. Compared to normoxia the hypoxic (10% O_2) significantly reduced REM sleep by approximately 80% and increased latency to REM sleep. These changes were caused by reductions in both duration and the number of REM sleep periods. When CO_2 was added to the hypoxic mix to create isocapnic hypoxia, significant increases occurred in both time in REM and the number of REM sleep periods. Nevertheless REM sleep was still reduced by approximately 30% in isocapnic hypoxia compared to normoxia. Other sleep

parameters were not significantly affected by either hypocapnic or isocapnic hypoxia. Sleep disruption was not caused by sleep disordered breathing; ventilation increased (both rate and depth) during hypoxia but no periodic breathing occurred.

Mechanical ventilation was used to induce hypocapnia while maintaining normoxia. REM sleep was significantly decreased with increasing levels of hypocapnia. With extreme hypocapnia wakefulness was increased and there was a trend towards decreased NREM sleep, reduced total sleep time and sleep efficiency. Arousal from sleep was increased in isocapnic hypoxia and also during mechanical ventilation. There was a strong negative correlation between the number of awakenings and the duration of REM sleep.

The authors concluded from this study that, as found in previous work, hypoxia decreases the amount of REM sleep. However, at high altitude, the body must cope with both hypoxia and hypocapnia; this work shows that hypocapnia without hypoxia decreases the amount of REM in cats. Thus hypoxia induced sleep disruption in cats is not only caused by low O_2 conditions but also by low CO_2. This may also be the case with sleep disruption in humans at high altitude.

Each of these studies into sleep at high altitude has a different protocol; some were conducted at actual high altitude locations which were reached either by land or air travel while some were reached after days or weeks of trekking; others studies were conducted in hypobaric chambers to simulate high altitude; some studies were conducted only after acute exposure to high altitude while others were conducted on

more than one occasion over a period of time spent at high altitude thereby obtaining results that are relevant to acclimatisation as well as acute exposure to high altitude. The differing protocols involving different altitudes (simulated or geographical), time before studies were conducted, scoring methods make comparison and accord between the studies difficult.

However, the findings from all these studies demonstrate that subjective sleep quality in humans is worse at altitudes above 3200m, total sleep time is generally unchanged but in many instances the lighter sleep stages are increased and deeper sleep stages (slow wave sleep) are decreased with REM sleep remaining unaltered or decreased. Sleep fragmentation is a feature of all the sleep studies performed and this appears to worsen with increasing altitude. Subjective sleep quality also decreases with increasing altitude with a concomitant deterioration in daytime function. Periodic breathing is almost universal at high altitude but with a wide individual range in severity. Periodic breathing does not disappear after time spent at high altitude and may indeed be a physiological adaptive mechanism.

The increased number of arousals and awakenings during sleep at high altitude may be due to the worsening hypoxia that occurred during sleep at high altitude. The hypoxia may be somewhat alleviated by repetitive arousal; this sleep fragmentation may be the cause of reduced amounts of slow wave sleep, and both increased arousals and slow wave sleep reduction may be adaptive mechanisms to prevent the hypoventilation that normally occurs during sleep but leads to severe oxygen desaturation during sleep at high altitude. Sleep quality improves over time spent at

high altitude; this is most likely due to the improvement in oxygen saturation that occurs with acclimatisation.

1.4 Periodic Breathing

Periodic breathing (also called Cheyne-Stokes respiration after the two physicians who classified it in the mid nineteenth century) is a repeating pattern of apnea, in which respiratory effort is absent, and hyperpnea. Unstable ventilatory control during sleep is the underlying mechanism of periodic breathing (PB) but the pathophysiology of the various forms of PB vary greatly. PB represents instability of the respiratory feedback control system and occurs in congestive heart failure and conditions such as strokes that affect the cerebral cortex of the brain; PB is common in infancy and at high altitude.

In heart failure, PB results in elevated mortality, which may result from the repetitive fluctuations in blood gases, blood pressure and heart rate. The pathophysiology is thought to be related to decreased cardiac output resulting in slowed circulation time, decreased lung volume and increased chemoreflex slope with increased lag time to ventilatory response.

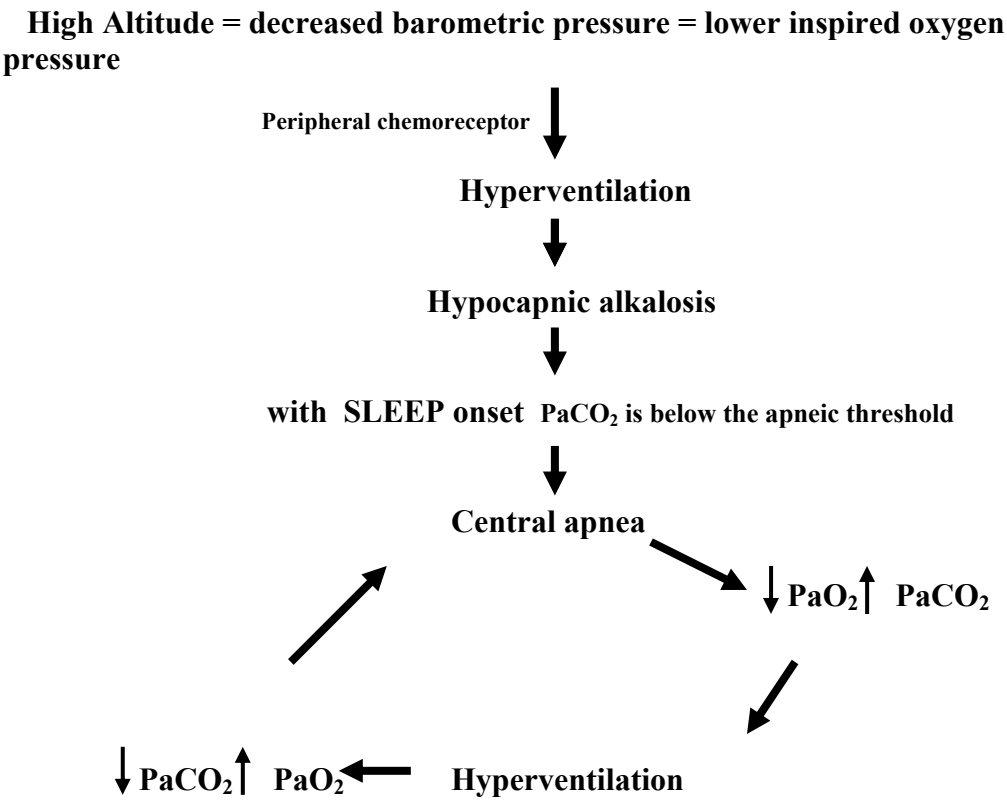
PB at high altitude is common during sleep at high altitude and is secondary to increased ventilation brought about by hypoxia and the hypocapnia that results from increased ventilation.

The dynamics of periodic breathing can be most clearly explained from an understanding of the feedback system that regulates breathing. Neural and circulatory interactions play a major role in the control of breathing during sleep. The feedback system consists of a controller, a plant and a communication channel. In the respiratory control system the chemoreceptors and the brain are the controllers, the lungs, blood and respiratory muscles are the plant and the circulation is the communication channel.

Peripheral chemoreceptors respond to PaO_2 and $PaCO_2$, and the central chemoreceptor in the medulla responds to H^+ concentration. The system operates to keep the arterial partial pressures of oxygen and carbon dioxide within a restricted range by regulating the level of ventilation.

PB occurs in sleep as a consequence of the loss of the input from higher centres of the brain, called the wakefulness drive (Orem et al. 1985; Longobardo et al. 2002) and a change in control of breathing reliant on chemoreceptors alone. Sleep onset results in decreased ventilation and a rise in $PaCO_2$ to a few mmHg above the apnea threshold, making it less likely that central apnea occurs.

Figure 1.4. Schematic representation of changes to ventilation at high altitude



During sleep, the maintenance of regular respiratory rhythm is dependent on chemical stimuli. Sullivan et al (1978) demonstrated that withdrawal of standard stimuli to breathing by administration of oxygen, induction of metabolic alkalosis or interruption to vagal afferents did not lead to changes in respiration during wakefulness but caused apnea during sleep. The unmasking of the apneic threshold in NREM sleep has since been demonstrated by several studies. Using mechanical

ventilation during sleep, Skatrud and Dempsey (1983) elicited a progressive, linear reduction in the diaphragm EMG until apnea occurred. Mechanical ventilation was also used by Simon et al (1993) to demonstrate a sleep induced increase of 2-4mmHg in the set point for $PaCO_2$ independent of sleep induced changes in airway resistance and Meza et al (1998) used assisted ventilation (proportional assist and pressure support ventilation) to identify an apneic threshold that is a few MmHg below eupneic pCO_2.

Mechanical ventilation was also used by Semple et al (1999) to control tidal volume at waking eupneic levels in order to prevent hypoventilation and increased $PaCO_2$ which is normally present upon transition from awake to light sleep. At sleep onset apneas of 15 seconds occurred. These observations demonstrate the marked CO_2 dependence of ventilatory control at sleep onset and the critical importance of the normal sleep induced hypoventilation as a deterrent to apnea and breathing instability.

The major effect of sleep on respiratory control appears to be the unmasking of an extremely sensitive apneic threshold at a $PaCO_2$ close to normal resting values. This causes instability in the ventilatory system during sleep.

Periodic breathing is induced at high altitude when the $PaCO_2$ is driven to below normal levels by the increased ventilation induced by hypoxia. Sleep onset often results in central apnea followed by ventilatory overshoot which drives the $PaCO_2$ below the apneic threshold and perpetuates the periodic breathing cycle.

Loop gain is an engineering term used to describe the stability of a system that is controlled by negative feedback loops. In the case of respiration, loop gain represents the gain or sensitivity of the negative feedback loop that controls ventilation and can be described mathematically as the ratio of a corrective response (e.g. hyperpnea) to a disturbance (e.g. apnea). If the corrective response is greater in magnitude than the disturbance then the loop gain is 1 which leads to self sustaining oscillations in breathing (e.g. periodic breathing); if the loop gain is less than 1, the oscillations decay, but the degree of decay depends on the strength of the disturbance and correction.

Models based on chemical feedback control of ventilation have been proposed to explain respiratory instability at high altitude. Khoo et al (1991) suggest that two factors are needed for self sustaining ventilatory instability; a "disturbance" and a "correction". This would constitute a negative feedback loop. In order to maintain instability the magnitude of the correction must be greater than the disturbance; this ratio is the "loop gain". The other requirement is that the corrective response should occur 180º out of phase with the disturbance; the corrective response then augments the disturbance instead of inhibiting it. The higher the loop gain at a phase of 180º, the more likely it is that periodic breathing will occur, the more marked the pattern of periodic breathing, and the shorter the length of the periodic breathing cycle. Therefore, delays in information transfer, increased controller gain, or decreased system damping will all result in periodic breathing. All these conditions occur at high altitude.

The hypobaria-induced hypoxia of high altitude leads to a low PaO_2; the response to hypoxia is curvilinear so that a low PaO_2 increases the gain in the chemoreceptor system (the controller gain). The CO_2 response is enhanced by hypoxemia, decreased by hypocapnic alkalosis and is linear. Slowed circulation time has been demonstrated at high altitude by Lahiri et al (1983 and 1984) by measuring the lag time from peak ventilation of a periodic breathing cycle and the peak SaO_2 measured at the ear; at 5400m altitude the lag time was found to be 12 seconds compared to 6.8 – 9.4 seconds at sea level. Therefore, the increased gain of the oxygen chemoreflex system and the increased circulation time makes the ventilatory feedback system unstable as predicted by the loop gain model.

Hypoxemia and hypocapnia must both be present for the induction of periodic breathing. Berssenbrugge et al (1983) first induced PB in subjects at simulated high altitude in a hypobaric chamber then administered carbon dioxide to induce normocapnia while maintaining hypoxemia; the periodic breathing was eliminated. Administration of oxygen during hypoxia induced periodic breathing initially caused a lengthening of the apneas then a gradual shortening and elimination of apneas. The stabilization of breathing during oxygen administration resulted in a progressive increase in the end-tidal CO_2. They concluded that in hypoxia induced periodic breathing the ventilatory system behaves in a manner consistent with the presence of CO_2 apneic threshold operating very close to the eupneic CO_2 obtained in NREM sleep.

PB is common in those who travel to high altitude but varies between individuals; the cause of this individual variation is unknown.

1.5 Changes in Ventilation at High Altitude: the Role of the Peripheral Chemoreceptor

As altitude increases, barometric pressure decreases and although the partial pressure of oxygen remains unchanged, its absolute pressure decreases. At sea level inspired oxygen is approximately 150mmHg and approximately 120mmHg at 1600 metres above sea level. The expected arterial partial pressure of oxygen (PaO2) decreases from 100mmHg at sea level to 70mmHg at 1600m. The initial response to the hypoxia caused by ascent to high altitude is an increase in ventilation. This response is mediated by the peripheral chemosensor, the carotid body, which is a tiny organ located at the bifurcation of the carotid artery. The peripheral chemosensor detects the lower partial pressure of oxygen in the arterial blood and sends a signal along the carotid sinus nerve to the respiratory centre in the brainstem. An efferent signal is then sent from the brainstem to the muscles of respiration which causes an increase in ventilation. At any level of PaO_2 the peripheral chemoreceptor also responds to the pH of arterial blood; as hydrogen ion concentration increases (acidosis) ventilation increases. The increased ventilation, which is triggered by the carotid body in response to hypoxia and acidosis, involves increased tidal volume rather than increased breath rate.

The control of breathing was poorly understood until the last hundred years, when some basic discoveries began to throw some light on this area of respiratory

physiology. Studies into the regulation of respiration under acute hypoxia were published by Nielsen and Smith in 1952. Their work in two human subjects showed that there was a linear dependence of ventilation on alveolar PCO_2 and the slope of this relationship was increased by hypoxia. Then work by Dejours et al (1957), demonstrated that ventilatory drive arises from PaO2; this raised questions about the supposed dominance of CO_2 in chemoreflex control. Finally, Cunningham (1973) quantitated the interaction of hypoxic and hypercapnic stimuli in ventilatory control.

These studies were consolidated by the following investigations of the peripheral chemoreceptor of the carotid body.

There have been many studies that have confirmed the importance of the carotid body as the trigger for increased ventilation in response to hypoxia. Studies have demonstrated that integrity of the arterial chemoreceptor drive is essential in determining the level of ventilation and normal acid-base balance of the blood and cerebro-spinal fluid at low altitude and high altitude.

Biscoe et al (1970) studied single afferent chemoreceptor fibres in the sinus nerve in vivo, in cats in intact circulation studies. They studied the effect on a single afferent fibre of changes in arterial pO_2, pCO_2 and hydrogen ion concentration $[H^+]$ with no attempt being made to control blood pressure or measure flow i.e. the carotid sinus was perfused naturally. The authors found that the response curve to decreased arterial pO_2 was similar to a hyperbola i.e. the frequency of nerve impulses increased rapidly at first and then slowed. The discharges of single efferent fibres increased both with

increasing $PaCO_2$ at constant pH and PaO_2, and with increasing $[H^+]$ at constant $PaCO_2$ and PaO_2. The authors concluded that single carotid body afferent fibres of the cat can be activated in vivo by an increase in either arterial $[H^+]$ and increased arterial pCO_2 as well as by a decrease in arterial pO_2.

Bouverot and Bureau (1975) studied three awake dogs at simulated high altitude in a hypobaric chamber at 140m and 3550m. Measurements recorded were resting ventilation, pulmonary gas exchanges, respiratory gases and pH of the arterial blood, acid-base status in the cerebro-spinal fluid (CSF) and ventilatory responses to transient oxygen inhalation. The dogs were studied before and after bilateral carotid body denervation. At low altitude denervation resulted in hypoventilation and respiratory acidosis in arterial blood and CSF. At 3550m hyperventilation and the related alkalosis did not occur in the denervated dogs but did occur in intact animals within thirty minutes of exposure to high altitude. Hyperventilation continued to increase over three hours in the intact animals. In the denervated dogs, hyperventilation was delayed and occurred after 24 hours hypoxic exposure. The authors concluded that the strength of ventilatory acclimatisation to high altitude is dependent on the strength of the arterial chemoreceptor drive. Integrity of this chemoreflex drive of breathing is essential in determining the eupneic level of ventilation and normal acid-base status of the blood and CSF at low altitude and at high altitude.

Forster et al (1976) studied ponies at sea level and simulated altitude before and after chemoreceptor denervation. At sea level after denervation hypoventilation occurred;

at simulated hypobaric hypoxia (PaO2 40-47 mmHg) hyperventilation, which was observed in normal ponies, was prevented. During the second and eighth hour of hypoxia ventilation increased in both groups (intact and denervated), which is a common characteristic of acclimatisation, but it only persisted in the intact ponies; in the denervated ponies hyperventilation was evident only through the 12th and ceased after the 44th hour. The authors concluded that peripheral chemoreceptors are essential for normal ventilatory acclimatisation to hypoxia.

Long et al (1993) investigated both the initial increase in ventilation that occurs with acute exposure to hypoxia and the decrease in ventilation that is known to occur after the first five minutes (called the hypoxic ventilatory roll-off). They studied the ventilatory response to isocapnic hypoxia of cats that had either carotid denervation or a sham operation. The measurements recorded were arterial pO_2 and end-tidal pCO_2 and arterial pCO_2. They were studied first in room air and then at moderate hypoxia (PaO2 40-55 mmHg). Sham/intact animals demonstrated a biphasic response to hypoxia; ventilation rose to 211% of control at 5 minutes then fell to 114% of control at 25 minutes. Denervated cats showed neither the initial nor the subsequent decrease in ventilation. They then added 2% CO_2 to the inspirate and the results were similar: intact cats showed biphasic response to hypoxia but denervated cats showed neither increase nor decrease in ventilation. The authors concluded that both the initial increase and then the decrease in ventilation with acute exposure to hypoxia are dependent on peripheral chemoreceptor output.

Bisgard and Vogel (1971) studied four calves at sea level and five calves at 1600m above sea level after carotid body excision in order to examine the role of the carotid chemoreceptor in ventilation and whether the loss of the carotid body would depress ventilation and result in pulmonary hypertension. They found that ventilation was depressed in all the calves following ablation of the carotid body but there was a wide variation in minute ventilation so the blood gas analysis was found to be a more reliable indicator of ventilation. The $PaCO_2$ increased from 40mmHg to 50mmHg in sea level calves after carotid body ablation indicating a 33% reduction in ventilation. The reduction in 1600m calves was 35%; the authors concluded that the carotid bodies are active in maintaining effective ventilation at sea level and 1600m. There was a reduction but not complete loss of ventilatory response to acute hypoxia after carotid body ablation. This is in contrast to the ventilatory response found in dogs, goats and man. Pulmonary hypertension was the most striking hemodynamic change noted in the 1600m calves; the authors concluded that this was due to hypoxic pulmonary vasoconstriction which was potentiated by hypercapnia and slight acidosis.

Studies in humans of carotid body denervation have examined the effects of glomectomy, a procedure practised widely since 1961 when improvement in asthma symptoms followed removal of the carotid bodies. Wood et al (1965) reported the results of this surgical procedure in three patients. The carotid bifurcation region was exposed and the carotid body excised. Arterial blood gas analysis and lung function tests were performed before and after the surgery. In all three cases, one week after surgery the oxygen saturation (SaO_2) was lower, the $PaCO_2$ was higher, pH lower and bicarbonate higher. Ten to sixteen months after surgery the SaO_2 remained lower,

$PaCO_2$ higher, pH lower and bicarbonate higher. These results indicated that ventilation was suppressed by removal of the carotid bodies. Two patients had no improvement in asthma symptoms while one did have improvement but most likely due to changes in medication. The authors recommend that this procedure not be performed in future.

A study of two subjects who had bilateral carotid body removal and denervation of the carotid sinuses, as a treatment for asthma, was published by Holton and Wood (1965). The two patients were tested before the operation breathing various gas mixtures to measure ventilatory responses: 10% oxygen, with 3% CO_2 and 6% CO_2. The responses for subject A was normal i.e. hyperpnea resulted from breathing the mixtures. There was no cyanosis. Subject B, before operation, responded to 10% oxygen by hyperventilation but there was no change when breathing 3% CO_2. Ventilation was markedly depressed by breathing 38% oxygen. Two weeks after the operation the most obvious change in Subject A was depression of respiration caused by breathing 10% oxygen. At the end of the testing subject A was extremely cyanosed though still conscious. The tests were repeated 10 and 30 weeks after operation in Subject A. On these two occasions mean minute volume was neither depressed nor stimulated by 10% oxygen and the subject became slightly cyanosed. The responses to CO_2 were normal except that on one occasion 3% CO_2 did not stimulate breathing.

In subject B for several days after the operation, breathing was sometimes irregular and slow. Measurement on day 16 after surgery on subject B found breathing to be grossly abnormal i.e. episodes of irregular breathing and small minute volume when

breathing 10% oxygen but the mean ventilation over the 4 minute test was the same as when breathing room air and 100% oxygen and was 45% lower than before the operation. The tests were repeated 10 and 30 weeks after the surgery. In Subject B the arterial oxygen saturation (SaO_2) was 98% before operation and 90% 16 days after operation. Breathing 10% oxygen for 4 minutes decreased the SaO_2 by 37% after which, when breathing room air, the breathing was irregular and the SaO_2 fell often for the next 20 minutes. The patient had many episodes of slow, irregular breathing after this test for many hours. After 6 weeks Subject B was tested again and minute ventilation had returned to near normal whilst breathing room air; the response to breathing 10% oxygen was similar to pre-operatively but the response to 3% CO_2 was now a marked stimulation of breathing. The 10% oxygen test was administered twice; on the first occasion ventilation increased, indicating chemoreceptor activity. In spite of this, 10% oxygen resulted in a period of hypoventilation causing hypoxemia. When 10% oxygen was given for a second time ventilation was decreased. Thirty four weeks after the operation the responses to gas mixtures were similar to those at 6 weeks.

The authors also tested baroreceptor function. The effect of carotid body denervation in both subjects was systemic hypertension accompanied by a rise in heart rate that persisted throughout the period of observation. Tilting the subjects from horizontal to erect elicited normal responses before the operation, i.e. diastolic pressure rise. For a few weeks after the operation tilting the subjects produced no change in blood pressure but then returned to preoperative levels.

The authors suggest that the return of ventilatory responses to near normal may be a function of the aortic chemoreceptors which could either have become more sensitive or increased in number. Alternatively, the central nervous system may have adapted to information from the aortic body receptors.

The response to CO_2 was not decreased by carotid body denervation in either subject, which is in agreement with most previous findings in animals and in man but disagrees with the findings of Nakayama (1961) that CO_2 hyperpnea was abolished by the operation in humans.

Wade et al (1970) published their results on ventilatory responses of fourteen patients who underwent carotid endarterectomy for transient cerebral ischemia. Seven of these patients had unilateral carotid endarterectomy performed and seven had bilateral endarterectomy. Ventilatory response to oxygen and carbon dioxide was performed before and 3-38 days after surgery. Unilateral endarterectomy had little effect on hypoxic responses whereas bilateral endarterectomy always abolished them. Resting $PaCO_2$ increased in all fourteen patients with the mean value before surgery in the unilateral group being 37.5mmHg and after surgery 40.1mmHg ($p<0.05$) and in the bilateral group being 38.9mmHg and after surgery 44.7mmHg ($p<0.001$). There were no significant differences in PaO_2 or pH as a result of surgery. Follow up ventilatory response testing 16 days to 10 months after surgery revealed a sustained loss of ventilatory response to hypoxia and a persistent elevation in resting $PaCO_2$.

Bilateral endarterectomy also affected the blood pressure response to hypoxia. Systolic BP decreased in response to eucapnic hypoxia whereas it had resulted in an increased BP before surgery.

The authors concluded that bilateral endarterectomy abolished the normal ventilatory and blood pressure responses to acute hypoxia and increased the resting $PaCO_2$, indicating a loss of carotid body function as a result of damage to the carotid body or its nerve or blood supply at the time of surgery. The nature of the damage can not be specified but any or all of the structures could be damaged by this surgical technique. The authors also attempted to calculate the percentage of ventilatory response for which the carotid chemoreceptor is responsible; since mean $PaCO_2$ increased from 38.9mmHg to 44.7mmHg, ventilation is 87 per cent (38.9/44.7 X 100%) of normal. Assuming that extra cellular pH at the medullary chemoreceptors is the same in the steady states before and after surgery and, hence, that the contribution of the medullary chemoreceptors to ventilation is unchanged, the 13% decrease in ventilation suggests that the carotid bodies are responsible for 13% of the original respiratory drive.

These studies have demonstrated that when the carotid body was destroyed ventilation decreased and there was loss of increased ventilation upon acute exposure to hypoxia and also the loss of the hypoxic ventilatory roll-off that occurs normally after 5-15 minutes of exposure. These studies confirm that the carotid body is the primary sensor of hypoxia. In the study in which the intact carotid afferent nerve fibres were studied

in vivo it was demonstrated that decreasing PaO_2 as well as increasing $PaCO_2$ and acidosis caused stimulation and increased discharge of the carotid nerve.

1.6 Changes in Ventilation at High Altitude: Ventilatory Responses to Hypoxia and Hypercapnia

Over one hundred years ago it was known that an increase in blood CO_2 or a decrease in O_2 caused ventilation to increase. There is a wide variation in individual responses to high altitude hypoxia. Ventilation increases in all animals that are acutely exposed to hypoxia and these changes have been thoroughly studied in humans and animals. Measurement of the individual's ventilatory response to hypoxia, under both eucapnic and hypercapnic conditions, and the ventilatory response to hypercapnia under hyperoxic, hypoxic and eupneic conditions have been measured in order to discover the differing roles of these ventilatory responses in high altitude conditions.

The peripheral chemoreceptor's action in increasing ventilation in response to hypoxia is brisk because it responds to oxygen and hydrogen ion concentration in the arterial blood that bathes it; whereas the action of the central chemoreceptor is slower to effect change in breathing because it is stimulated by hydrogen ion concentration of the cerebrospinal and brain fluid rather than arterial blood.

There are three independent factors known to determine respiration: a peripheral chemoreflex, a central chemoreflex and a basal (or waking) drive. Studies have been performed that aimed to examine and clarify the action and interaction of these three factors.

To examine the effect of hypoxia on the ventilatory response to carbon dioxide in man, Mohan and Duffin (1997) published their findings from a study in which rebreathing following hyperventilation was used to measure the ventilatory responses to CO_2 at PaO_2 of 100, 80, 60 and 40mmHg.

Seven men were studied using the Read (1967) rebreathing technique in which the subject, wearing a nose clip, breathed through a mouth piece connected to a Y-valve, allowing the experimenter to switch between room air and a breathing bag. Ventilation was monitored via a spirometer that was connected to the bag, which was enclosed in a rigid container. The flow of oxygen into the bag was controlled by a computer to maintain iso-oxia during the testing. Expired air was sampled from a small tube in the mouth piece in order to continuously monitor the partial pressures of expired oxygen and carbon dioxide. Prior to rebreathing, the subjects hyperventilated room air for 5 minutes, following a "slow and deep" breathing pattern. The end tidal CO_2 reached by this method was approximately 25mmHg. At the start of rebreathing the subjects were instructed to take three deep breaths, as an aid to rapid equilibration. The partial pressure of CO_2 in the inspired air was maintained at 40-45mmHg in order that, when rebreathing began alveolar air, rebreathing bag air and arterial blood partial pressure of CO_2 rapidly equilibrated to the decreased venous partial pressure of approximately 35mmHg. A plateau in the end tidal partial pressure of CO_2, where the value remained unchanged over several breaths, indicated equilibration and was a prerequisite for continuing the rebreathing test. The partial pressure of oxygen in the rebreathing bag was chosen so that alveolar and arterial partial pressures of oxygen rapidly equilibrated to the chosen iso-oxic end tidal partial pressure i.e. 100, 80, 60

and 40mmHg. Rebreathing continued until the end tidal CO_2 reached a partial pressure of 60mmHg.

Breath-to-breath ventilation was plotted versus time to determine the first break point above which ventilation increased. Breath-to-breath ventilation versus end tidal partial pressure of CO_2 was plotted to identify the break point above which ventilation increased; this break point was interpreted as the threshold for either the peripheral or the central chemoreflex ventilatory response to CO_2, depending on the subject and the iso-oxic end tidal partial pressure.

The authors found that the ventilatory response to carbon dioxide and the effect of hypoxia varied considerably between subjects. The peripheral chemoreceptor threshold varied between subjects and between iso-oxic end tidal partial pressures; the overall mean declined slightly from 41mmHg at iso-oxic end tidal partial pressures of 80 & 100mmHg to 39mmHg at iso-oxic end tidal partial pressures of 40 & 60mmHg with the overall mean threshold for 100mmHg being significantly greater than at 60 & 40mmHg. The sensitivity of the peripheral chemoreceptor also varied between subjects and between iso-oxic partial pressures but the sensitivity increased in all subjects with hypoxia with most of the increase occurring at an iso-oxic end tidal partial pressure of 40mmHg, being significantly greater than at 60, 80 and 100mmHg.

The central chemoreflex threshold also varied between subjects and between iso-oxic end tidal pressures. The overall mean declined from 48mmHg at iso-oxic end tidal partial pressures of 100 & 80mmHg, to 47mmHg at 60mmHg iso-oxic end tidal

partial pressure and 45mmHg at 40mmHg iso-oxic end tidal partial pressure. The overall central chemoreceptor threshold was significantly less at an iso-oxic end tidal partial pressure of 40mmHg than at 80 & 100mmHg; but the authors point out that the decrease in the overall mean of the central chemoreceptor threshold was attributable to one subject only, who had a mean of only 41mmHg At an iso-oxic end tidal partial pressure of 40mmHg only four of the seven subjects reached their central threshold before reaching their breathing limits.

The central chemoreceptor sensitivity did not vary between iso-oxic end tidal partial pressures but did vary widely between subjects.

The authors commented that in this study they used a modified Read rebreathing method, in which the subjects voluntarily hyperventilated to reduce body stores of carbon dioxide, to test the ventilatory responses to the hypercapnic range with the addition of a flow of oxygen sufficient for metabolism so as to maintain iso-oxia. Holding the oxygen end tidal partial pressure constant during rebreathing, and allowing the CO_2 to slowly increase due to metabolism, ensured that the end tidal partial pressures of CO_2 reflected those of the central and peripheral chemoreceptor environment during rebreathing. The end tidal partial pressures of CO_2 should be the same as at the central and peripheral chemoreceptors at the start of rebreathing, and the rates of change of these partial pressures should be the same during rebreathing; the authors believed that their methodology ensured that these considerations were met. They found that the overall mean peripheral chemoreceptor threshold for CO_2 was 41mmHg, which was similar to the findings from previous studies. This estimate

is near to the normocapnic partial pressure of CO_2. The variation of peripheral chemoreceptor threshold with hypoxia was small (2mmHg) which is smaller than that found by previous studies in dogs (8mmHg) and cats (8-10mmHg). The central chemoreflex threshold for CO_2 during rebreathing varied widely between subjects and the authors are hesitant to suggest that hypoxia may influence the threshold; the overall mean was close to normocapnia.

The implication of this research for the control of breathing in humans is that carbon dioxide must exceed its peripheral chemoreflex threshold before end tidal oxygen partial pressures in the range 40-100mmHg can affect breathing via the peripheral chemoreflex. The authors concluded that it is the degree to which carbon dioxide exceeds the peripheral chemoreceptor threshold and not necessarily its elevation above resting partial pressures that will determine the magnitude of the ventilatory response to hypoxia.

A study that is relevant to conditions at high altitude was published by Corne et al (2003); they studied the hypoxic ventilatory response of eight subjects (four male, four female) during acute stable hypocapnia. Mechanical volume ventilation using a mouth piece was used to create acute stable hypocapnia 6mmHg and 12mmHg below the pre-determined eucapnic level. A t-piece with two unidirectional valves was incorporated into the mouth piece so that subjects were connected to an inspiratory and an expiratory circuit; this allowed control of the proportion of inspiratory gas that passed through a CO_2 absorber thereby permitting adjustment of the concentration of CO_2 in the inspired gas. A pneumotachograph measured flow tidal volume; airway

pressure and end tidal pressure of CO_2 ($P_{ET}CO_2$) were monitored with a pressure transducer and a mass spectrometer; oxygen saturation was monitored with a finger probe. Oxygen was added to the circuit to maintain normoxia then tidal volume was increased with the goal of lowering the $P_{ET}CO_2$ to 12mmHg below baseline. Once the target $P_{ET}CO_2$ was reached the oxygen supply was cut off to induce hypoxia with trial termination occurring when the SaO2 reached 80%. The trial was repeated with $P_{ET}CO2$ at 6mmHg below eucapnia and at eucapnic levels. The authors chose this method because it was possible to control the fall in CO_2; lowering the CO_2 by inducing hypoxia (as in previous research) has limited application because the range of hypocapnia over which hypoxic responses can be studied is limited by the hypoxic response itself i.e. the individual variation in hypoxic ventilatory responses ensures that different levels of hypocapnia are achieved by differing levels of ventilation. Under these conditions stable hypocapnia could be maintained regardless of whether a hypoxic response was present and the hypocapnia was able to be maintained before and during the hypoxic challenge. This methodology obviated behavioural responses while critical measurements were taken. Hypoxia was surreptitiously induced while maintaining spontaneous rhythmic respiratory efforts throughout the trials, allowing accurate measurement of the ventilatory response to hypoxia under stable hypocapnia.

Changes in ventilation were assessed to determine the ventilatory response to hypoxia during hypocapnia. They found that the hypoxic response was attenuated at mild levels of steady hypocapnia and became negligible at moderate levels of steady hypocapnia in normal subjects. The authors state that this is the first study to demonstrate convincingly that hypoxic response disappears below a threshold of

stable end tidal CO_2 i.e. no response to hypoxia was detectable when the CO_2 was reduced by an average of 11mmHg.

The authors concluded that this was the first study to demonstrate convincingly that hypoxic response disappears below a threshold of stable $P_{ET}CO_2$. In all subjects, including those who displayed a vigorous response to hypoxia at eucapnia, no response was detectable when $P_{ET}CO_2$ was reduced by an average of 11mmHg. The authors commented that, because their study involved only eight subjects, they could not exclude the possibility that an occasional individual may retain a hypoxic response when stable $P_{ET}CO_2$ is reduced by more than 11mmHg.

The authors also commented on the issue of the interaction between the central and peripheral chemoreceptor in the ventilatory response to hypoxia; they note that the results of this study provide support for the existence of a central mechanism that contributes to the interaction. The total disappearance of hypoxic response during moderate hypocapnia provides an important clue to the central and peripheral interaction. In this study respiratory motor activity was present throughout; if an excitatory input, associated with hypoxia, was received by the respiratory motor centres of the brainstem, an increase in respiratory activity should result; the lack of such an increase during moderate hypocapnia, therefore suggests that no excitation was received by the respiratory motor centres at this level of CO_2. This lack of input cannot be because peripheral chemoreceptors do not respond to hypoxia at $PaCO_2$ levels used in this study: first, peripheral chemoreceptors have been shown, in animal studies, to retain substantial sensitivity to PaO_2 when the $PaCO_2$ is 30mmHg or even

lower. Second, human studies have shown that even at $PaCO_2$ levels in the mid 20s the peripheral chemoreceptors are not silenced. It seems reasonable, therefore to conclude that central CO_2 determines whether peripheral chemoreceptor input is conveyed to the respiratory motor centres. This may result if central pCO_2 controlled the gain of intermediate neural pathways that process peripheral chemoreceptor input before its arrival at the motor centres. Below a threshold of central pCO_2 the gain is zero. Alternatively, central and peripheral activities are summed and a threshold total amount is required before chemoreceptor activity of either source can influence respiratory motor output. The results from this study cannot distinguish between the two possibilities. The conclusion that the central pCO_2 controls the traffic between peripheral chemoreceptors and respiratory motor centres could help reconcile the two concepts. The relatively slow equilibration with blood of the central pCO_2; thus when the pCO_2 rises during a hypoxic challenge, the increase in central pCO_2 will lag and instantaneous $P_{ET}CO_2$ will thus overestimate central pCO_2, leading to the false conclusion that the hypoxic response disappears with minimal hypocapnia. Conversely, when $P_{ET}CO_2$ progressively falls during a fast hypoxic challenge, instantaneous $P_{ET}CO_2$ underestimates central pCO_2, leading to the conclusion that the hypoxic response may survive severe hypocapnia.

The demonstration that PCO_2 at the central chemoreceptors must exceed a certain value before hypoxia can produce a drive to breathing has important implications. Hyperventilation can produce central apnea and the subject may lose consciousness from hypoxia before experiencing any hypoxic or CO_2 drive to breathe. This scenario is possible because of the differences between the CO_2 and O_2 dissociation curves;

hyperventilation can substantially decrease total CO_2 content while having little effect on total O_2 content, and even in the region of the steepest part of the oxygen dissociation curve its slope is considerably lower than that of the CO_2 dissociation curve. Thus, a given a change in O_2 content produces a much greater change in PaO2 than the change in $PaCO_2$ produced by a similar change in CO_2 content.

The authors commented on some clinical implications from their study. In periodic breathing the cessation of breathing occurs when the $PaCO_2$ decreases below the threshold, but in a matter of seconds it rises again to reinitiate breathing. The deteriorating PaO_2 during the apnea likely does not contribute to the re-initiation of breathing. This scenario explains the periodic breathing that occurs at high altitude.

Increased ventilation when awake lowers the $PaCO_2$ to below the apneic threshold and with sleep onset apnea and hyperpnea occur in a repetitive pattern.

There is positive interaction between CO_2 and hypoxia mediated ventilatory responses such that the slope of the CO_2 response is augmented when the PaO_2 is lower and the response to hypoxia is augmented when $PaCO_2$ is higher.

The role of the central chemoreceptor in the ventilatory response to changes in carbon dioxide has been extensively studied but the interaction between the peripheral (carotid body) chemoreceptor and the central chemoreceptor remains controversial. In an attempt to clarify this relationship, Smith et al (2006) studied unanaesthetised dogs whose carotid sinus was reversibly isolated to maintain normal tonic activity of the

carotid body chemoreceptor while preventing it from sensing systemic changes in CO_2, thereby allowing the determination of the response of the central chemoreceptor alone. The authors aimed to quantify the speed of response of the central and peripheral CO_2 sensors. The authors compared the speed of the increase in ventilation when only the central chemoreceptor was able to sense CO_2 and when both the central and peripheral chemoreceptors were able to sense CO_2. They found that the ventilatory response to abrupt increases in $P_{ET}CO_2$ was delayed by ~11 seconds when only the central chemoreceptors could sense the CO_2 increase while the carotid chemoreceptors were present but maintained at normal blood gas values. They also found that the central chemoreceptors account for ~63% of the steady-state ventilatory sensitivity to hypercapnia, thus the remainder of the steady-state ventilatory sensitivity to hypercapnia, ~37%, was due to the carotid chemoreceptors. They also found a wide variability among dogs.

The authors proposed that the somewhat slower response of the central chemoreceptors versus the peripheral chemoreceptors coupled with the absence of nearly 40% of available CO_2 sensitivity prevents the central chemoreceptors from contributing significantly to ventilatory responses to rapid changes in $PaCO_2$ such as those after periods of hypoventilation and hyperventilation (ventilatory undershoots and overshoots) observed during sleep disordered breathing. Periodic breathing that occurs in congestive heart failure and in hypoxia, consists of ventilatory overshoots secondary to increases in $PaCO_2$ (that occurs during the apneic phase of PB). This overshoot, consisting of 3-4 hyperpneic breaths, normally occurs within 2-3 breaths after an apnea. In the dogs where carotid chemoreceptors were able to sense CO_2, a

much faster onset of the hyperpneic response to CO_2 demonstrated that carotid bodies were the primary receptors and provide a substantial ventilatory overshoot in response to hypoxic stimuli present during apnea.

1.7 Ventilatory Responses to Hypoxia and Hypercapnia: Relationship to Periodic Breathing during Sleep at High Altitude

It has been proposed by several investigators that individuals with a high ventilatory response to hypoxia are more likely to develop periodic breathing (PB) during sleep at high altitude. This concept is best explained by the concept of control theory which has been well explained by Khoo et al (1982). These authors pointed out that two factors are necessary for self-sustaining oscillatory behaviour in a control system: a disturbance and a corrective action. A change in alveolar ventilation can be identified as the disturbance at high altitude i.e. hypoxia induced hyperventilation which results in the corrective action of lowered arterial PCO_2 which tends to reduce ventilation by its action on the central and peripheral chemoreceptors and thus constitute negative feedback. In order for sustained oscillatory behaviour to occur, the corrective action must exceed the disturbance; this ratio is known as loop gain. The second necessary condition is that the corrective action be presented 180º out of phase with the disturbance, so that what would otherwise inhibit the change in ventilation now increases it. Sustained periodic breathing (oscillatory behaviour) occurs when the loop gain exceeds unity at a phase difference of 180º. This theory predicts that the higher the loop gain, the more likely periodic breathing is to occur and the shorter the cycle length. In individuals with a more sensitive hypoxic ventilatory response the loop gain is increased and these individuals would be expected to exhibit more PB at high altitude.

In order to test the theory that a high ventilatory response to hypoxia is related to the development of periodic breathing during sleep at high altitude, Lahiri et al (1983) studied six high altitude-dwelling Sherpas, one low altitude dwelling Sherpa and seven Caucasian lowlanders at 5400m. All the subjects were male and had spent at least 32 days at 5400m before data collection.

Breathing during sleep in high altitude dwelling Sherpas, with low hypoxic ventilatory response (HVR) was compared with seven lowland dwelling Caucasians and the low altitude dwelling Sherpa, all with steep HVR, to determine the relationship between HVR and PB.

Six of the seven lowlanders and the low altitude dwelling Sherpa developed periodic breathing during sleep with cycle times of 19-23 seconds and apneas lasting 10-17 seconds. The PB typically consisted of three or four large breaths in quick succession followed by an absence of breath (and respiratory effort) for about ten seconds. The first breath after apnea was inspiratory. The time delay between peak ventilation and peak oxyhemoglobin saturation, measured at the ear, was 13 seconds. This lag time provided an estimate of lung to carotid body circulatory delay. When these subjects were administered oxygen until SaO_2 reached 100% there were two effects on breathing: inspiratory volumes decreased and apneas increased from 10 to 17 seconds. The apneas became hypopneas, then regular breathing resumed. Lahiri suggested that oxygen administration diminished the arterial chemoreceptor drive and hence respiratory drive. In the absence of respiratory drive, apneas were prolonged, which also means that central CO_2 drive was not an adequate stimulus to breathing. Regular

breathing did not resume until arterial and tissue PCO_2 increased enough to provide adequate stimulus to breathing. The authors assumed from these results that low PaO_2 is critical in the development and maintenance of PB.

Also tested during sleep was the effect of lowered inspired oxygen. The SaO_2 was lowered from 73mmHg to 65mmHg by administering nitrogen. The effect of this was to lower the trough of SaO_2 from 77% to 74% with no change to cycle time or apnea length.

When CO_2 was administered apneas were eliminated, breathing frequency increased and tidal volume decreased. Total ventilation for each cycle increased but PB persisted with a cycle time of 21 seconds. The amplitude of oscillations in SaO_2 decreased and the mean SaO2 increased due to the increased ventilation. When CO_2 was withdrawn, the apneic period returned to 10 seconds after about 135 seconds.

The Sherpas did not develop PB with apnea during sleep at 5400m. When nitrogen was administered to lower the pO_2, PB was still not induced. When a deep breath was taken an apnea occurred then breathing oscillations but this was not sustained. When oxygen was administered and the SaO_2 raised, ventilation decreased momentarily with a few oscillations following. Two of the Sherpas studied occasionally showed striking desaturations during sleep, with SaO_2 as low as 53% which was followed by a large breath, a ten second apnea and 5-6 cycles of PB.

The Sherpa subjects, who showed attenuated sensitivity to hypoxia when awake, also showed least PB during sleep. The lowlanders, who showed high ventilatory response to hypoxia when awake, manifested large amount of PB during sleep. The authors suggest that these results demonstrate that chemoreflex sensitivity and high altitude PB are related.

Another study that examined the relationship between HVR and PB was by Hackett et al (1987). This group was interested in examining the effects of two drugs, almitrine and acetazolamide, on periodic breathing and sleeping oxygen saturation at high altitude. The study was conducted on four male climbers at Mount McKinley (4400m). Hypoxic ventilatory responses were measured when awake at 4400m and again after treatment with each of the drugs. Periodic breathing and sleeping oxygen saturation were measured. They found that both drugs improved the sleeping SaO_2; acetazolamide reduced PB whereas almitrine did not have an effect on PB. Almitrine increased the HVR whereas acetazolamide had no effect on the HVR.

The higher the HVR, the higher the percentage of time spent in PB during sleep ($p < 0.02$). This confirms previous work by Lahiri et al (1983) and Berssenbrugge et al (1983) who also found this relationship between HVR and PB at high altitude.

The relationship between the ventilatory response to hypoxia and the development of periodic breathing at high altitude has been examined by these authors and it appears that the higher the HVR the more periodic breathing occurs during sleep at high altitude.

1.8 Breathing during Sleep at High Altitude

Investigation into breathing during sleep at high altitude has a history reaching back to the 19th century. Mountaineers who were also scientists or physicians wrote articles that commented upon the breathing patterns during sleep at high altitude. One such report is by Egli-Sinclair (1894) who wrote that breathing "had the Stokes character, that is, it seemed regular during a certain time, after which a few rapid and profound breaths were drawn, a total suspension for a few seconds then following". Dr William Stokes, an Irish physician had described, in 1854, the pattern of breathing that "consists in the occurrence of a series of inspirations, increasing to a maximum and then declining in force and length until a state of apparent apnoea is established". Another Irish physician, John Cheyne, had described the same pattern in 1818 and so the breathing pattern is known as Cheyne-Stokes breathing. This pattern of breathing usually was observed in the final stages of heart failure when the patient was very near to death.

In 1898 Mosso published his findings from investigations performed during an ascent of Monte Rosa in the Italian Alps. Mosso took with him an apparatus to measure breathing; this apparatus consisted of "a slender metal bar" that rests on the chest of a supine subject "turning on a pivot that rises and falls as it traces the respiratory movements on a rotating cylinder". During a stay at the Regina Margherita Hut (4559m) Mosso recorded his brother's respiration during sleep in which periodic breathing sometimes persisted for hours and described it thus "three descending movements, of which the first is forcible and the other two or three weak, being

followed by a pause which lasted regularly twelve seconds before the return of another series of three descending respirations. When the thorax is still and the line becomes horizontal, the pulsations of the heart, fourteen or sixteen in number, are clearly noticeable in the latter". He then went on to comment that a "physician seeing these tracings would say that they were from a dying person" as this "interrupted respiration is indeed often observed shortly before death". This form of breathing, first described by Cheyne and Stokes, bears their name.

These findings from Mosso have since been confirmed by many studies carried out at various altitudes from sea level up to 8050m in hypobaric chambers and at actual high altitude locations. Periodic breathing has been shown to be extremely common in lowlanders ascending to high altitude and many studies have been conducted to determine its pathophysiology and each individual's susceptibility.

The causes of periodic breathing were investigated by Douglas and Haldane (1909). In their experiment the subject sat in an arm chair and hyperventilated for two minutes which caused an apnea of about two minutes duration, followed by a few minutes of Cheyne-Stokes (periodic) breathing before a return to normal breathing. This breathing pattern was recorded using a modified Marey stethograph. Samples of alveolar air were taken during this period of abnormal breathing in order to analyse the cause of the periodic breathing. They found that the partial pressure of O_2 (pO_2) rose during hyperventilation from about 100mmHg to a maximum of 141mmHg then fell rapidly during the apnea to 32mmHg at which point the breathing returned and pO_2 rapidly rose to 70mmHg; another apnea followed and the pO_2 again fell, this time

to about 42mmHg. During the few minutes of periodic breathing following the initial apnea the pO_2 rose and fell but with smaller incremental changes, until the oscillations gradually became less and less and breathing became steady after about seven minutes. From these results Douglas and Haldane went on to explain Cheyne-Stokes breathing thus: "the fall in alveolar oxygen-pressure during the primary apnoea, and consequent fall in oxygen pressure in the arterial blood and the respiratory centre, leads to formation of lactic acid in the respiratory centre. As a consequence of this the threshold exciting pressure of CO_2 in the respiratory centre is greatly lowered, so that the centre is excited even though the CO_2-pressure in it is probably more than 10mm. below the normal threshold exciting value. The breathing at once raises the alveolar oxygen-pressure and lowers the CO_2-pressure, with the result that oxygen want is at once removed and the lactic acid previously formed is promptly oxidised or neutralised, leaving the CO_2-pressure in the centre far below the threshold exciting value. Apnoea thus results, and is only terminated when the alveolar oxygen again falls sufficiently to lower the threshold CO_2-pressure to the actual CO_2-pressure in the centre. While this process is repeated again and again, the average CO_2-pressure in the centre is rising, so that there is less and less of the abnormal want of correspondence between the CO_2-pressure in the alveoli and that in the centre." The authors repeated the experiment using different protocols i.e. oxygen instead of air was breathed in the last six breaths of the two minute period of hyperventilation and this caused a very long apnea (>4 minutes) then breathing recommences quietly with no sign of periodic breathing; when oxygen is given in just the last breath of hyperventilation a shorter apnea (3minutes) occurs followed by a short episode of periodic breathing; when the hyperventilation period was reduced so too was the apnea and periodic breathing

episode. When several breaths of a mixture poor in oxygen was taken at the end of the two minutes of hyperventilation the apnea was shortened and the periodic breathing episode increased. They concluded that these experiments confirmed their theory of the cause of periodic breathing. The authors conducted these experiments on each other and noticed that periodic breathing was more easily produced in one of them than in the other; they concluded that there were individual variations in the susceptibility of the respiratory centre to want of oxygen.

They then repeated the experiment using a tube attached to a small tin of soda lime so that the subject re-breathes his own air after it has been deprived of its CO_2. The oxygen content in the air fell rapidly until hyperpnea was produced, which caused fresh air from the distal end of the tube to reach the lungs and the pO_2 to rise; an apnea then occurred because the hyperpnea has reduced the pCO_2 to below the apneic threshold, pO_2 again fell and another hyperpnea resulted; permanent periodic breathing thus resulted. They noted that, if the tube was too long, the subject became cyanosed and this did not disappear with the hyperpnea as it did when a shorter tube was used. They surmised that asphyxia would result if a still longer tube were used. Using the same method with a long tube but with a tin that did not contain soda lime, the authors found that periodic breathing resulted; when the distal end of the tube was attached to oxygen the periodicity disappeared.

Thus by these simple but ingenious methods the authors learned much about the control of breathing, the pathophysiology of periodic breathing and the roles of O_2

and CO_2 in its genesis.

The control of breathing during wake and sleep has been extensively investigated. The control of breathing during hypoxic sleep has been less well studied and many unanswered questions remain. The ventilatory response to hypoxia is thought to be a major factor in the development of periodic breathing (PB) during hypoxic sleep, with a high ventilatory response leading to more PB but this theory has not been resoundingly proved.

Phillipson et al (1977 and 1978) studied sleeping dogs in order to examine hypercapnic and hypoxic ventilatory responses during sleep. In the first study three sleeping dogs were examined; sleep was determined by EEG and behavioural criteria. They used a rebreathing technique to induce hyperoxic hypercapnia and found that arousal from sleep occurred in NREM sleep when the alveolar CO_2 reached 54.2 ± 3.4 mmHg and in REM sleep when the alveolar CO_2 reached 60.3 ± 4.2 mmHg. In REM sleep the arousal response to hypercapnia was between 14% and 33% less than the arousal response in NREM sleep. The authors concluded that centres involved in both waking and ventilatory responses to hypercapnia behave as if they are less aware of or responsive to CO_2 in REM sleep than in NREM sleep.

In the study to examine arousal and ventilatory response to hypoxia (1978) the authors studied four sleeping dogs. Hypoxia was induced by a rebreathing technique in which the CO_2 was maintained at the eucapnic level. Arousal occurred when the oxyhemoglobin saturation reached 87.5 ± 2.6% during slow wave sleep and at 70.5 ±

3.4% during REM sleep ($p<0.005$). The irregular breathing that is typical of REM sleep continued during hypoxia but ventilation was increased. The authors concluded that although arousal responses to CO_2 are delayed in REM sleep, ventilatory responses remain intact and therefore may be of importance in maintaining adequate ventilation during REM sleep.

In humans the respiratory responses to hypoxia and hypercapnia have been shown to be reduced; the behavioural and cognitive influences on control of breathing are eliminated with sleep onset. The result of these changes to ventilation is hypoventilation (decreased tidal volume and respiratory rate) which is most marked in slow wave sleep (Stages 3 and 4 NREM). During slow wave sleep the $PaCO_2$ is increased by about 2-7mmHg with a reciprocal fall in the PaO_2.

The changes in ventilatory responses to hypoxia and hypercapnia have been demonstrated in work carried out by Douglas et al (1982 and 1982a) who studied sleeping humans. They aimed to provide evidence for the belief that ventilation during sleep is due to the sum of the hypoxic and hypercapnic drives. In previous work it had been found that hypercapnic ventilatory response (HCVR) was decreased during sleep but the hypoxic ventilatory response (HVR) is maintained at the awake level. HVR was measured awake and asleep; the subjects wore a full face mask that did not leak and hypoxia was induced by the introduction of nitrogen into the inspirate to lower the end tidal pO_2 to 40 mmHg over 3-4 minutes whilst maintaining isocapnia. The authors found that HVR was significantly reduced in all sleep stages compared to awake levels ($p<0.05$), and was lowest in REM sleep. There was no difference in

HVR in Stage 2 NREM sleep and in Stages 3 and 4 NREM (slow wave) sleep. Minute ventilation during sleep was significantly reduced and this was due to shallow breathing that was worst in REM sleep.

Tidal volume awake was 0.71 ± 0.06; in Stage 2, 0.58 ± 0.02; in slow wave sleep, 0.52 ± 0.03 and in REM sleep, 0.43 ± 0.03 litres. They found no difference between phasic and tonic REM sleep.

The authors concluded that HVR is reduced during sleep in men. The degree of depression is related to sleep stage, being most marked during REM sleep with the response reduced to a third of awake levels.

The same group then studied HCVR in sleeping men and women (1982a). Face mask was again used during the tests awake and asleep. The face mask was connected to a bag containing 40% oxygen and 60% nitrogen and the end tidal CO_2 was raised by at least 4% (at least 6mmHg) while the end tidal O_2 was kept at 130mmHg. The mean HCVR was significantly reduced during sleep compared to wakefulness; there was no difference between Stage 2 and slow wave sleep. HCVR then fell further during REM sleep to 28% of awake value. There was no difference between the male and female subjects. The end tidal CO_2 was significantly higher during sleep and, again significantly higher in REM sleep than in Stage 2 and slow wave sleep: awake, 34 ± 0.8; Stage 2, 35.9 ± 0.09; slow wave sleep, 36.4 ± 0.09 and REM sleep, 37 ± 0.8 mmHg.

The authors concluded that the HCVR falls during sleep in adults with a further reduction in REM sleep.

Berssenbrugge et al (1983) examined the effects of sleep state on acclimatisation to hypoxia in seven men in a hypobaric chamber that simulated an altitude of 4300m. The authors attempted to define the role that suprapontine structures of the brain had on acclimatisation to chronic hypoxia. During wakefulness, NREM and REM sleep different structures of the central nervous system are activated and the authors reasoned that these different sleep states may be used as a model for testing the importance of changes in suprapontine influence on the mediation of ventilatory acclimatisation.

Measurements of $PaCO_2$, SaO_2, HCO_3 and pH were measured during wakefulness, NREM sleep and REM sleep, under these conditions of simulated high altitude, on acute exposure, after 10-32 hours and after 72-91 hours. During wakefulness the acute exposure to hypoxia caused the PCO_2 to fall by 5.1±1.2 mmHg, then by a further 3±0.9mmHg after 20 hours and a further 2.6±0.7 mmHg by 83 hours. The mean SaO_2 was lowest at 0.8 hours exposure (75%) then increased by 83 hours to 82% coincident with increased ventilation. Respiratory alkalosis persisted during hypoxia with the arterial pH increased by 0.05 units acutely and remained at this level for the duration of the hypoxic exposure despite additional hyperventilation and compensatory reduction in HCO_3 concentration.

In NREM sleep acute hypoxia (1.9 hours) caused the PCO_2 to fall by 7.2 ± 1.9mmHg; by 21 hours' exposure by a further 4.3 ± 1.3 mmHg with no further fall by 83 hours of hypoxia. Ventilation increased, as in wakefulness, with increasing hypoxic exposure. The mean SaO_2 was lowest at 1.9 hours (64%) and highest at 83 hours (76%) in association with increased ventilation. Respiratory alkalosis prevailed during NREM sleep as in wakefulness, and the arterial pH increased acutely by 0.7± 0.01 units and remained unchanged during the remaining time spent in hypoxia.

In REM sleep, after 21 hours in hypoxia the mean PCO_2 had dropped 10.8 mmHg with little additional change occurring from 21-83 hours. Measurements of SaO_2 and acid-base status were similar to NREM sleep levels.

When the subjects were acutely returned to normoxia after 83 hours hypoxic exposure the main effects in wakefulness and NREM sleep were: 1) SaO_2 increased to 97%; 2) ventilation decreased but still remained 31% and 26% higher than chronic normoxia in each state respectively; and 3) PCO_2 was unchanged or increased but was still 8.9±1.1 and 10.7 ± 1.0 mmHg below chronic normoxia levels in each state. These results demonstrate that the hyperventilation that persisted with acute normoxia was similar in degree during wakefulness and NREM sleep.

The authors concluded from this study that there is no effect of sleep state on the ventilatory acclimatisation to hypoxia. The percentage fall in PCO_2 was remarkably similar in all sleep states (-27 to -31%) with half of this fall occurring during the acute phase of hypoxic exposure. A substantial amount of ventilatory acclimatisation

occurred during the first 24 hours at 4300m with much of this change occurring during sleep. Sleep caused a small but consistent alveolar hypoventilation. The authors concluded that, because they did not see a significant effect of sleep state, the suprapontine influences on ventilatory control which are dependent on wakefulness are not essential to the process of ventilatory acclimatisation.

Under hypoxic conditions of high altitude, ventilation increases during both wakefulness and sleep, this is believed to be mediated by the peripheral chemoreceptor. Studies by White et al (1987), into high altitude periodic breathing during sleep have investigated the role of the hypoxic ventilatory response (HVR) and the hypercapnic ventilatory response (HCVR) and found that those people with a high HVR as well as a high HCVR are more likely to develop PB although the number of subjects was small (6) and only 2 of those developed PB. To investigate the role that acclimatisation to high altitude has on periodic breathing and chemoresponsiveness during sleep, this group studied six men at sea level and an altitude of 4340m when awake and during NREM sleep. The hypoxic ventilatory response (HVR) was measured when the subjects were awake and also in NREM sleep at sea level and at 4340m. During HVR testing at sea level CO2 was added to the mixture breathing to keep the $P_{ET}CO_2$ to within 2 mmHg of the resting level; during sleep HVR testing CO_2 was not added in order to mimic conditions at altitude. As a result the $P_{ET}CO_2$ fell during all studies. Hypercapnic ventilatory response (HCVR) was measured in awake and in NREM and REM sleep, although it was not possible to attain the same degree of hypercapnia (10-15mmHg above resting levels) during sleep, due to arousal so during sleep a $P_{ET}CO_2$ 8mmHg above resting level was considered hypercapnia;

but even this level often led to arousal from sleep at high altitude and 4mmHg above resting levels, in addition to a doubling of ventilation, was considered to be acceptable to measure the HCVR. The HCVR was measured at a constant SaO_2, maintained at the eupneic level, at sea level and at high altitude.

Sleep studies were performed at sea level and on nights 1, 4 and 7 at 4340m. Continuous recordings of EEG, EOG and EMG with respiratory variables recorded intermittently due to equipment limitations. The respiratory pattern during sleep was measured by recording flow and end tidal CO_2 from sampling ports in the full face mask.

The authors found that at sea level and at high altitude the HCVR were reduced by NREM and REM sleep. The NREM HCVR was reduced by about 50% of the awake value and in REM sleep by about 20% of the awake value. When the subjects were initially exposed to altitude the HCVR increased during wakefulness and in NREM sleep; in REM sleep the HCVR did not increase over the sea level values. On subsequent nights at high altitude the HCVR did not increase further but there was a progressive shift leftwards of the HCVR from sea level to day 1 at altitude and from day 1 to day 4 at altitude with no further increase after day 4. This is true for awake, NREM and REM sleep.

Although acute exposure to altitude did not increase hypoxic sensitivity, the slope of the HVR increased steadily and significantly with time spent at altitude. This increase occurred despite the studies being conducted at progressively lower PCO_2 levels.

Periodic breathing occurred in three of the six subjects and varied quantitatively between the three. All periodic breathing occurred in NREM sleep.

The number of periodic breathing pauses per hour at night 1 at altitude correlated best with the HVR measured at sea level in NREM sleep; and was nearly significantly correlated both with awake sea level isocapnic HVR and the NREM sea level HCVR. Periodic breathing was abolished by the addition of either CO_2 or O_2 to the inspired mixture.

The authors state that there are four primary observations from this study: 1) the HVR increased steadily with time at altitude up to 7 days; 2) the slope of the HCVR increased on initial exposure but did not increase further over 7 days, although the position of this response shifted steadily to the left (lower PCO_2 values); 3) the sleep induced decrements in both ventilation and hypercapnic responsiveness to altitude were similar to those observed at sea level with apparently equal acclimatisation during wake & sleep and 4) the quantity of periodic breathing during sleep at altitude was highly variable and tended to occur more frequently in individuals with higher ventilatory response to both hypoxia and hypercapnia. The periodic breathing diminished with time spent at altitude.

The steady increase that the authors found in the HVR over time at altitude may be an important contributor to the gradual increase in ventilation at high altitude, which occurs despite a progressively lower PCO_2 and higher SaO_2. Previous work on carotid denervated goats, ponies and sheep had found an important role for the carotid

chemoreceptor in acclimatisation i.e. ventilatory acclimatisation was diminished or absent in these animals with ablated carotid bodies. The authors state, however that they were unable to show a significant correlation between the individual changes in ventilation and hypoxic responsiveness over the acclimatisation period. As a result the relationship between the VR to acute hypoxia and changes in ventilation during chronic hypoxia (acclimatisation) must remain speculative. The authors did not find an increase in the HCVR over time at altitude but comment that this could be due to the fact that the responses on days 4 and 7 were conducted at higher SaO_2 than on day 1. Had all studies been conducted at a similar SaO_2 the HCVR may have increased over time.

The finding that there was no measure of chemosensitivity measured on the first night at altitude, awake or asleep, that correlated with periodic breathing on that night surprised the authors; they suggested that it may be due to the increased hypocapnia occurring at altitude in subjects with a high HVR. The hypocapnia could have reduced the measured response to isocapnic hypoxia at altitude, thus confusing their measurements. They found that, with acclimatisation, the $P_{ET}CO_2$ level fell before an apnea (apneic threshold) as well as the $P_{ET}CO_2$ level necessary to regularise ventilation during sleep in the two subjects who developed PB. They suggest that this may be due to the shift leftwards (to a lower PCO_2) of the ventilation/PCO_2 relationship that occurs with acclimatisation.

The periodic breathing was abolished by the addition of either oxygen or carbon dioxide and, in both cases, breathing became rhythmic as the PCO_2 increased. The

SaO_2 rises over time spent at altitude and breathing decreases; thus the PCO_2 is not driven as low as in acute exposure to altitude. It appears that hypoxia is necessary to stimulate ventilation and leads to the hypocapnia that produces periodic breathing.

The carotid body may also be an important sensor of CO_2 and play a major role in the development of periodic breathing during sleep at high altitude.

Smith et al (2003) published their findings of the investigation of the role of the carotid body in the development and maintenance of central sleep apnea. This work concentrated on the ventilatory sensitivity to CO_2 below eupnea and specifically on the hypocapnia induced apneic threshold that plays such a major role in periodic breathing development at high altitude. The authors stated that the causes of central sleep apneas are 1) transient ventilatory overshoot, usually attributable to changes in ventilatory drive that are secondary to changes in sleep state and 2) a subsequent hypocapnia combined with a highly sensitive apneic threshold that is unmasked during NREM sleep. In this research the authors attempted to find the chemoreceptors that are primarily responsible for sensing the transient reductions in $P_{ET}CO_2$ and causing apnea during sleep. They studied dogs that were either carotid body denervated or intact and used mechanical assisted ventilation to cause ventilatory overshoot and apnea. They found that apnea occurred within two breaths in the intact dogs (6-10 seconds after the beginning of ventilatory overshoot and reduced $PaCO_2$); while in the denervated animals apneas did not occur until 30-35 seconds after the onset of ventilatory overshoot and reduced $PaCO_2$. The authors concluded that the carotid bodies were required for the apnea that normally occurs following ventilatory

overshoot and for the consequent periodic breathing. Carotid body denervated dogs not only required more time to develop apnea but also required twice as much hypocapnia (-10.1 ± 2.1 vs. -5.1 ± 0.4 mmHg) to develop apnea of the same durations when they were intact. The authors then went on to investigate the role of the carotid chemoreceptor versus that of the medullary chemoreceptor in the development of hypocapnia induced apnea. They used an intact dog in which one carotid body was denervated and the other was perfused via an extracorporeal circuit. When the carotid body was perfused with hypocapnic, normoxic blood in the sleeping dog, ventilation (tidal volume) decreased in a progressive fashion but apnea did not occur. The authors suggested that apnea may only be induced when the ventilatory overshoot preceding hypocapnic apnea causes lung stretch; this mechanism is absent in the hypocapnia induced by the extracorporeal perfusion of the isolated carotid body. When the hypocapnic, extracorporeal perfusion of the carotid body was sustained, the reduced ventilation resulted in hypercapnia (CO_2 4-7mmHg higher than control) and presumably brain extracellular fluid acidosis was also rising, yet the ventilation remained suppressed below control with only a relatively small upward trend in the face of severe acidosis. When the carotid body hypocapnia was suddenly removed, by switching out of the extracorporeal circuit, ventilation suddenly increased to a value greater than control, representing an unmasking of the medullary chemoreceptor CO_2 responsiveness that had been effectively suppressed by the inhibitory effects of carotid body hypocapnia.

The authors proposed that data from these sleeping animal models with either intact perfused or denervated carotid bodies point to a strong and even dominant CO_2

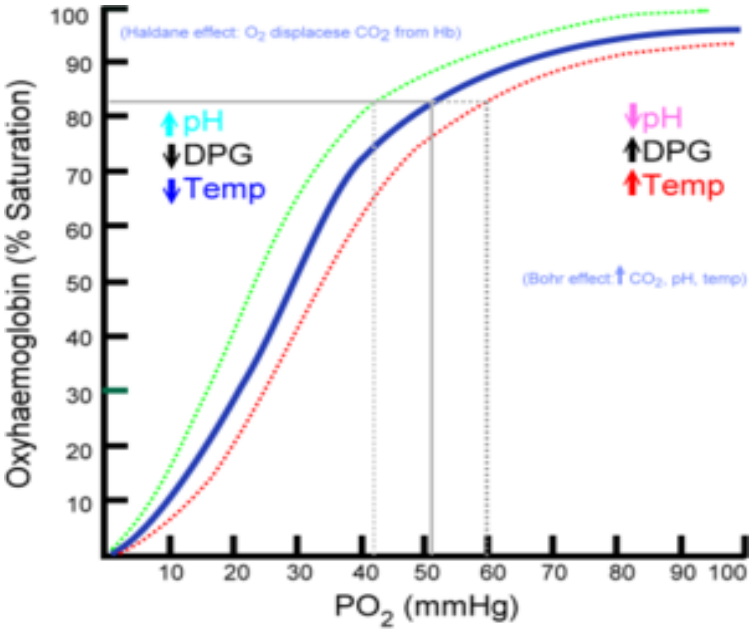
sensing role for the carotid chemoreceptors, especially during dynamic changes in $PaCO_2$. Furthermore, the carotid chemoreceptors were shown to play an essential interactive role in causing apnea in response to transitory ventilatory overshoots.

During sleep, under the hypoxic conditions of high altitude, the decrease in ventilation that occurs leads to further hypoxemia. The reduction in the hypoxic ventilatory drive during sleep contributes to the profound hypoxemia that occurs during sleep at high altitude. Studies of sleep at high altitude have demonstrated marked decrease in oxyhemoglobin levels compared to awake values. During sleep and exercise at high altitude the oxygen levels in the blood are at their lowest level.

1.9 Ventilatory Acclimatisation to High Altitude

Hyperventilation is one of the most important features of acclimatisation to high altitude. Immediately upon exposure to high altitude, ventilation increases in a hyperbolic fashion as partial pressure of oxygen (pO_2) falls and in an inverse linear relationship when plotted against oxyhemoglobin saturation (SaO_2) this increased ventilation slows after about 24 hours but continues to increase. When the PaO2 falls to approximately 60mmHg, which corresponds to SaO2 of approximately 90%, ventilation increases steeply. The PaO2 at which ventilation starts to increase corresponds to the PaO2 at which the oxygen dissociation curve begins to steepen.

Figure 1.9 The oxygen-haemoglobin dissociation curve.



The O_2-Hb dissociation curve is a sigmoidal curve that represents the relationship between O_2 concentration and the percentage saturation of haemoglobin. As the concentration increases from about 90% there is a significant plateau in the curve.

This increased ventilation results in respiratory alkalosis as CO_2 is removed. Humans undergo a progressive increase in ventilation upon exposure to high altitude/hypoxia and this response occurs despite the development of respiratory alkalosis and an improved arterial oxygen level i.e. acclimatisation. This response implies either a gradually increasing sensitivity of the carotid body or of the central respiratory controller in the brainstem. Acclimatisation to high altitude occurs over a period of days or weeks; each individual will acclimatise at a different rate and this is thought to be dependent on the individual's ventilatory response to hypoxia (HVR). Research has demonstrated that HVR increases with time spent at high altitude but respiratory alkalosis persists; it is not known why ventilation continues to increase with time at

high altitude even though oxygenation is improved and blood has become more alkaline – the alkalosis should blunt ventilation but the hypoxic chemosensors continue to operate at a higher degree of sensitivity as acclimatisation proceeds. The ventilatory response to hypercapnia (HCVR) also changes with time spent at high altitude: there is a shift to the left as $PaCO_2$ falls and a steepening of the carbon dioxide response line which results in the person being more sensitive to CO_2 after time spent at high altitude. These changes to ventilation start immediately upon exposure to high altitude and continue over a period of days, resulting in a higher PaO_2 and lower $PaCO_2$.

Several studies have investigated the effects of prolonged exposure to high altitude and the ventilatory acclimatisation that occurs.

In 1953 Astrand published his work on acclimatisation to high altitude. In order to clarify the effects on ventilation of prolonged exposure to high altitude two male subjects were studied under conditions of simulated altitudes of 3000m for 3 days, and then 4000m for 5 days in a hypobaric chamber. Expired air was analysed, and breath rate and tidal volume were measured to assess ventilation. Acute exposure was compared to chronic exposure and to sea level values during rest and at various levels of exercise; the subjects exercised on a bicycle for 8-10 minutes at various intensities. The subjects breathed either air or oxygen, with or without the addition of 3.9% CO_2.

At high altitude, during exercise and at rest, ventilation was increased, with the highest ventilation occurring during the most vigorous exercise. When oxygen instead

of air was breathed ventilation decreased. At sea level during exercise, but not during rest, ventilation was decreased by the addition of oxygen to the inspirate. The higher the work load at sea level and at high altitude, the more pronounced was the increase in ventilation.

Ventilation increased over time spent at high altitude. After five days at 4000m ventilation was increased by around 20% with any given workload compared to acute exposure to high altitude.

The end tidal CO_2 was lower at rest or any exercise level with prolonged exposure compared to acute exposure, confirming that ventilation was increasing over time. When oxygen was breathed on days four and five the end tidal CO_2 rose from 25mmHg to 31mmHg (decreased ventilation); however, the alveolar CO_2 reached after five days exposure when breathing oxygen was markedly lower than the CO_2 when breathing air or oxygen at sea level during rest or any level of exercise. The authors therefore concluded that, in an acclimatised person given oxygen to remove the hypoxic drive, ventilation is driven by CO_2 which suggests an increased sensitivity in the respiratory centre to CO_2.

On return to sea level after five days at 4000m ventilation was around 17% higher when breathing air and 23% higher when breathing oxygen that it was before ascent. Five days later ventilation returned to pre-exposure levels. When 3.9% CO_2 was added to the inspirate before exposure to altitude, ventilation increased from 10 L/minute to 22 L/minute. After five days high altitude exposure ventilation increased

from 11 L/minute to 47 L/minute when CO_2 3.9% was added to the inspirate. After acute exposure to high altitude there was no difference in the ventilation in response to added CO_2 when it was re-tested at sea level.

The authors concluded that respiratory drive after acclimatisation to high altitude is more sensitive to CO_2 than is normally the case. Within seven days return to sea level the respiratory drive is back to normal. Hypoxic drive dominates control of ventilation over time spent at high altitude and is most evident during exercise. Residual hyperventilation after acclimatisation, which persists for several days after return to sea level, has been ascribed in the past to greater sensitivity of the respiratory centre to the $CO_2/NaHCO_3$ ratio i.e. changes in ventilation were much more sensitive to CO_2 than it was prior to high altitude exposure; $NaHCO_3$ is decreased during high altitude exposure and is restored five days after return to sea level.

In order to study the ventilatory response over a period of time spent at high altitude, Forster et al (1971) studied three different groups of people: ten sea level residents before during and after a 45 day sojourn at 3100m; nine first and second generation natives of 3100m and nine adolescents born at sea level who had resided at 3100m for the past 2-16 years.

Ventilatory response to hypoxia and CO_2 was tested in the sea level residents before ascent, and after 4 days, 7 days and 45 days sojourn at 3100m then again after return to sea level. There was a 53% increase in ventilatory response to CO2 in seven of the ten lowlanders after 4 days at altitude and, from the 4^{th} to the 45^{th} day six of the ten

demonstrated 47% increase. After 45 days eight of the ten showed a definite increase with the mean being 120%.

Highlanders were tested only at 3100m. In the highlanders ventilatory response to CO_2 was similar to lowlanders at sea level but none of the individual indexes of the highlanders were as high as the mean index of the 45 day-acclimatised lowlanders.
The ventilatory response to hypoxia increased in the lowlanders during their sojourn at 3100m with the greatest increase occurring after 2-3 weeks at high altitude. After the third week the response began to decrease in eight of the ten lowlanders and by the 45^{th} day, in three subjects it had almost returned to sea level values. In the post-altitude period the lowlanders were hyper-responsive to hypoxia with a mean increase of 150% on day 7 post altitude. After 45 days post altitude none of the lowlanders had returned to their pre-altitude levels.

The highlanders were less responsive to hypoxia than the sojourning lowlanders (approximately 200% difference). Of the highlanders only two natives and two residing lowlanders were as responsive to hypoxia as the sojourning lowlanders. The ventilatory response to hypoxia was also lower in the highlanders than it was in the pre-altitude lowlanders.

The authors concluded that with chronic exposure to high altitude the ventilatory response to hypoxia and CO_2 change in the following ways: the response to both stimuli is increased from sea level during the first weeks of chronic exposure; the response to both stimuli is gradually reduced toward normal sea level values with the

hypoxic response decrease preceding the CO_2 response decrease; if initial exposure was during childhood, the response to hypoxia decreases over months to below sea level values; the ultimate degree of desensitisation to hypoxia might be genetically determined and/or influenced by duration and intensity of chronic exposure.

The role of the carotid body chemoreceptor in ventilatory response to chronic hypoxia in goats and sheep was studied by Lahiri et al (1981). The time-course changes in ventilation, pCO_2, pH and pO_2 of arterial blood and cisternal fluid were measured before and following surgical ablation of the carotid body and exposure to simulated altitude of 3660-5000m. The authors found that at sea level the animals hypoventilated chronically after ablation of the carotid bodies and developed mild hypoxemia and hypercapnia. When exposed to acute hypoxia before chemodenervation, the animals hyperventilated and developed alkalosis with decreases in pCO_2, which reached a peak in two days. After denervation, in acute hypoxia, the increase in ventilation was small and delayed and the pH decreased from 7.3 to 7.1 while the pCO_2 rose. In the intact animals in hypoxia hyperventilation, with a fall in pCO_2 and rise pH, reached its peak in two days then subsided over the next few days. Several denervated animals died during chronic hypoxia and the survivors showed either a small decrease or an increase in arterial pCO_2. The authors concluded that in hypoxia an intact peripheral chemoreceptor (carotid body) is necessary for ventilatory acclimatisation which raises the arterial pO_2 in spite of alkalosis. The authors also proposed that a central tissue metabolic acidosis resulting from a direct affect of acute hypoxia is partly compensated as hypoxia is prolonged and it decreases

ventilatory drive hence opposing the ventilatory acclimatisation during chronic hypoxia initiated by the peripheral chemoreceptors.

A study of ventilatory acclimatisation in seven cats was conducted by Vizek et al (1987). The authors investigated the role of the peripheral chemoreceptors and mechanisms of ventilatory acclimatisation to hypoxia. The authors aimed to further investigate the ventilatory acclimatisation to hypoxia, defined as a gradual increase in ventilation with a decrease in arterial PCO_2; persisting hyperventilation despite improving oxygenation; and the fact that acclimatisation occurs even when hypoxia is limited to the carotid bodies and without systemic or brain hypoxia occurring.

The study examined ventilatory and carotid body responses over a prolonged period of time i.e.48 hours in fourteen cats in a hypobaric chamber at simulated altitude of 4600m. Ventilatory responses to hypoxia could be measured in each cat before and after hypoxic exposure but the invasive technique of carotid sinus nerve recording could only be done once in each animal. The authors therefore compared carotid body hypoxic responses of cats exposed to hypoxia with measurements made on a separate group maintained in room air. The two groups were matched according to their hypoxic ventilatory response (HVR). HVR was measured before and after 48 hours of hypoxic exposure of simulated altitude 4600m.

After 48 hours at 4600m the pH rose to 7.43 ± 0.02 compared to 7.36 ± 0.02 in controls. The end tidal (ET) CO_2 fell from 34.5 ± 0.9 to 28.9 ± 1.2 mmHg in room air and from 28.1±1.8 to 21.8±1.9mmHg in hypoxia. The HVR increased following hypoxic exposure to an average 50% higher than pre-exposure levels. The carotid sinus nerve hypoxic response was 80% higher than the control group after hypoxic exposure.

The authors also calculated a "translation index" to describe the central nervous system (CNS) translation or conversion of the peripheral chemoreceptor activity into ventilation during acclimatisation. This index was calculated by dividing ventilation by the increase in carotid sinus nerve activity produced by a decrease in $P_{ET}O_2$ from 150 to 40mmHg. They found that this index was unchanged by acclimatisation, averaging 0.76 ± 0.09 for acclimatised cats and 0.82 ± 0.07 for controls.

The 48 hours of simulated altitude produced acclimatisation manifested as decreased $P_{ET}CO_2$ and was accompanied by an increase in ventilation. This was associated with an increased carotid body response to hypoxia despite lower $P_{ET}CO_2$. The response of the carotid body was larger in acclimatised cats during an isocapnic hypoxic challenge; that this response was larger despite a lower $P_{ET}CO_2$, which typically depresses carotid response, suggests an impressive augmentation of carotid body function during acclimatisation. This is additional evidence that supports the suggestion that the change in peripheral chemoreceptor function may be a feature of acclimatisation.

On return to normoxia the $P_{ET}CO_2$ was lower in the acclimatised cats which prompted the authors to ask whether basal carotid body activity increases with acclimatisation or is there increased translation of the peripheral chemoreceptor activity on ventilation. They compared the translation index in the two groups and found that it was not increased in acclimatised cats, suggesting that enhanced CNS translation of chemoreceptor activity into ventilation is not a major contributor to increased HVR in acclimatisation; by exclusion, the peripheral chemoreceptors are a more important source of the increased HVR with acclimatisation. This is further supported by the finding that output from both carotid bodies is necessary to maintain the increased level of ventilation and HVR in acclimatised cats. Unilateral section of the carotid sinus nerve resulted in increased $P_{ET}CO_2$ and decreased HVR in acclimatised but not in control cats. The authors suggested that this indicates an increased dependency of ventilation and HVR on output from the carotid body during acclimatisation.

The authors state that CNS involvement in acclimatisation remains unclear; the unchanged translation index suggests only a small role for the CNS during acclimatisation; perhaps CNS is responsible for maintaining increased ventilation as it persisted in acclimatised cats even after bilateral carotid sinus nerve section. They suggested that changes in secondary modulatory effects such as decreased activity of the inhibitory, possibly dopaminergic, influences.

The authors concluded that enhanced peripheral chemoreceptor responsiveness accompanies acclimatisation to hypoxia and may contribute to the attendant rise in ventilation.

A study that aimed to further investigate the role of the carotid chemoreceptor in acute and prolonged hypoxia was published by Nielsen et al (1988). The authors conducted the research on goats because of its well documented and rapid acclimatisation to hypoxia. Forty six anaesthetised goats were studied; the carotid sinus was isolated and small strands teased out from the desheathed nerve in order for impulses to be recorded. The goats either inspired a gas mixture that achieved about arterial 40mmHg PaO_2 within ten minutes with $PaCO_2$ maintained at about 40mmHg. Acute hypoxia was studied then prolonged steady-state isocapnic hypoxia was maintained for up to four hours while ten minute samples of arterial blood was analysed for PaO_2, $PaCO_2$ and pH.

The authors found that in acute isocapnic hypoxia the discharge frequency of the carotid chemoreceptor fibres was a brisk on/off response to hypoxia and restoration of normoxia. The response curve was hyperbolic. In prolonged hypoxia (longer than 60 minutes duration) there was a time-dependent increase in chemoreceptor discharge frequency after the first hour of hypoxia increasing at an average rate of 1.3 ± 0.02 impulses per hour.

After return to normoxia the discharge frequency was higher when compared to the pre-hypoxic period. However, the inability to restore blood gases in all cases made it impossible to conclude that the discharge frequency was different between pre and post measurements.

The authors used sodium cyanide (NaCN) to identify the carotid fibres in the preparation and also to test the integrity of the preparation during the study. Injection of NaCN into the carotid fibres resulted in an increase in impulse frequency from 1.7 ± 0.1/hour to 17.9 ± 0.7/hour. If the preparation did not exhibit a brisk response to NaCN the data were discarded.

The authors concluded from this work that the responses of the goat to NaCN and to hypoxia are similar to other species. The carotid body chemoreceptor activity progressively increases in a time-dependent manner during isocapnic hypoxic exposure of more than one hour in anesthetised goats which agrees with work carried out on cats which demonstrated increased hypoxic sensitivity of the carotid chemoreceptor after two days and after four weeks exposure to hypoxia. When comparing the time course of the development of acclimatisation, it appears that acclimatisation to hypoxia is faster in the goat than the cat. The carotid body may play a direct role in providing ventilatory drive during acclimatisation to hypoxia. A characteristic of ventilatory acclimatisation to hypoxia is the persistent hyperventilation on first returning to normoxic conditions but the actual role of the carotid chemoreceptor is unknown; the authors suggest that exposure to prolonged hypoxia may cause a time-dependent depletion of the putative inhibitory carotid body neurotransmitter, dopamine which would result in increased carotid body activity as the inhibitory effects of dopamine is progressively withdrawn.

The authors summarised their findings thus: the carotid body afferent discharge progressively increases during the course of sustained isocapnic hypoxia of more than

one hour in the anesthetised goat and, this increased activity contributes to the progressive hyperventilation characteristic of the initiation of ventilatory acclimatisation to hypoxia.

These studies have examined ventilatory response to acute and prolonged hypoxia, and acclimatisation to high altitude. The carotid bodies sense both hypoxia and hydrogen ion concentration, exhibiting a multiplicative effect to the combined stimuli of hypoxia and changes in hydrogen ion concentration. Both the carbon dioxide partial pressure and the hydrogen ion concentration of arterial blood can affect the hydrogen ion concentration in the carotid body and thereby ventilation. The ventilatory response to hypoxia in the presence of increased hydrogen ion concentration will be greater than the response to hypoxia alone. The existence of a threshold for the hydrogen ion concentration, below which no stimulation occurs, complicates the peripheral chemoresponse to hypoxia. The strength of hypoxia needed to elicit a response is greater at lower partial pressures of CO_2 because of the existence of the threshold. However, at high altitude the arterial partial pressure of carbon dioxide is rapidly lowered due to increased ventilation and there is little doubt that this increase in ventilation is driven by lower barometric pressure leading to lowered alveolar oxygen pressure, stimulating the peripheral chemoreceptor.

1.10 Periodic Breathing, Arousal from Sleep and Oxyhemoglobin Saturation

During periodic breathing at high altitude only about half the periodic breathing (central) apneas result in arousal from sleep. Despite this failure to arouse, ventilation

increases after a period of 8-20 seconds of apnea and the oxyhemoglobin saturation rises, before another apnea begins.

It has been known for some time that sleep results in decreased hypoxic and hypercapnic ventilatory responses. It seems that the most likely cause for the decrease in ventilatory responses during NREM sleep is the loss of the wakefulness drive to breathe (Orem et al. 1985; Longobardo et al. 2002), a decreased metabolic rate and an increase in airflow resistance. The further reduction of VR in REM sleep may be due to altered central nervous system function. This blunted VR allows the development of hypoventilation during sleep and of sleep-related hypoxemia and hypercapnia which is more marked in REM sleep.

During sojourn at high altitude, in response to the hypoxic conditions, ventilation increases up to four fold with the result that after 12-24 hours the SaO_2 rises and the PCO_2 falls. At high altitude sleep onset hypoventilation leads to increased hypoxemia but this occurs in the presence of hypocapnia. The finding that arousal does not always occur with the apneas of periodic breathing may be explained by the fact that although marked hypoxemia occurs during the apneic phases of PB, PCO_2 remains below the apneic threshold and there is no increase in intrathoracic pressure, no stretching of the lung nor increased resistance in the upper airway, all of which contribute to arousal from sleep.

Arousal from sleep in humans in response to hypoxia has been shown to occur in only about half of hypoxic episodes. Berthon-Jones and Sullivan (1982) demonstrated this

poor hypoxic arousal response in nine normal, healthy human subjects (four female). During NREM and REM sleep the subjects were subjected to hypoxemia as low as 70% saturation while maintaining eucapnia by using a rebreathing method. They found that there was a marked variability in arousal levels both in NREM and REM sleep, with subjects failing to awaken by 70% SaO_2 (their safety level) in 12 out of 26 (46%) NREM tests and in 7 of 15 (47%) REM sleep tests. The authors concluded that, in humans, at normal alveolar CO_2 tension, hypoxia is a poor arousal stimulus for NREM and REM sleep. The authors also measured the hypoxic ventilatory response (HVR) awake and asleep and found that, in NREM sleep the HVR was reduced from 0.68 ± 0.07 L/min/% SaO_2 during wakefulness to 0.42 ± 0.6 L/min/% SaO_2 and in REM sleep was further reduced to 0.33 ± 0.06 L/min/% SaO_2. The reduced HVR was significant for wake to NREM and REM ($p<0.01$) but not for NREM to REM sleep. This confirms previous findings of reduced HVR in sleeping humans.

It has been proposed that periodic breathing (PB) during sleep is advantageous i.e. the repetitive hyperventilation acts to maintain higher sleeping oxyhemoglobin saturation than sleep without PB. Alternatively, it has been proposed that PB and the increased cardiac output that may be present during the part of the PB cycle in which hypoxia is at its worst (hyperpneic phase), would result in enhanced delivery of this poorly oxygenated blood.

West et al (1986) studied breathing in six male subjects who were acclimatised to 6300m i.e. members of an Everest expedition residing at Camp 2 (6300m) for at least 17 days prior to being studied. The subjects were found to have PB for an average of

72% of recording time and the mean oxyhemoglobin saturation (SaO_2) was 73% and minimum 63%. Two subjects had a mean SaO_2 <60%. The authors had previously performed arterial blood gas analysis and extrapolated the PaO_2 to be in the order of 33mmHg. Because all six subjects developed PB it was not possible to compare the SaO_2 of subjects with and without PB but the authors hypothesized that PB would result in more severe oxygen desaturation and circulation of poorly oxygenated blood. The rationale for this assumption was that increased chemoreceptor gain occurs with time spent at high altitude and this increased chemoreceptor gain makes the respiratory control system more unstable, predisposing towards periodic breathing during sleep. This increase in the hypoxic ventilatory response has been linked to the success of mountain climbers who can tolerate extreme altitudes (Schoene et al, 1984). The paradox presented by the presence of PB in those with a high HVR, and the profound hypoxemia that occurs during PB, with the success at high altitude of those with a high HVR has puzzled researchers for some years. There may be some physiological advantage that has not yet been understood, to PB during sleep at high altitude.

Given the high incidence of periodic breathing at high altitude, Ghazanshahi & Khoo (1993) examined the effects of PB on blood gases and aimed to discover if the repetitive falls in oxygen that occur during PB impose physiological penalties. The muscular effort of breathing at high altitude is known to account for an increased proportion of oxygen uptake and the authors aimed to determine if the pauses in breathing effort during apneas were beneficial in the savings in muscular effort that may occur in PB.

The authors used computer modeling of gas exchange to examine whether ventilating with a PB pattern offered any advantage over uniform tidal breathing (TB). They found that, contrary to the general belief that PB and episodic apnea present detrimental effects, PB patterns can actually lead to more efficient gas transport. The SaO_2 in TB was below the PB SaO_2 minimum.

There has been no definitive answer to the question of whether PB is advantageous during sleep at high altitude but it appears that the success at high altitude of lowlanders with high HVR may provide some evidence that, at least, PB is not detrimental to the tolerance for high altitude in those acutely exposed and those who are acclimatised. The lack of both a high HVR and the absence of PB in high altitude-dwelling Sherpas further confuses the matter.

1.11 Prevention and Treatment of Acute Mountain Sickness

Acute Mountain Sickness (AMS) affects some people who ascend from sea level to altitudes above about 3000metres; but can affect some people at altitude as low as 2000m.The symptoms are assumed to be due to mild cerebral edema from hypoxic brain injury and include headache, nausea, loss of appetite, ataxia, dizziness, weakness and poor sleep. The reported frequency of AMS varies widely from 9% to over 60% depending on the altitude.

Acute mountain sickness has been described since at least 1531, the year the Moguls invaded Ladakh and Western Tibet. The Moguls called AMS “yas” and the Tibetans called it “damgiri” & “dam” (breath seizing) or “dugri” (poison of the mountain).

They described it as vomiting, exhaustion, difficulty sleeping, aphasia and swelling of the hands and feet. Death often eventuated if rapid descent was not undertaken; in fact, the Mogul sultan, Said Khan died of damgiri on the Suget Pass on his way from Ladakh to Kashgar. The cold, ever present at these high altitudes, worsened the condition and horses were also severely affected.

Christian missionaries who travelled into central Asia and established missions in Tibet were among the first Europeans to bring back descriptions of AMS. One missionary, Father Andrade, crossed the Himalayas in 1624 and described part of the journey thus: “many people die on account of the noxious vapours that arise, for it is a fact that people in good health are suddenly taken ill and die within a quarter of an hour, but I think it is rather owing to the intense cold and want of heat, which reduces the heat of the body”. Other missionaries also believed that the illness was caused by noxious vapours that were extruded by poisonous weeds. Another missionary, Father Desidrei, in 1716 commented that he thought the symptoms of AMS were due to “sharp, thin air” and he suffered from severe headaches. This theory was supported by Father Belligatti who, in 1739, wrote that he believed that the illness resulted from the “rarefaction of the atmosphere”. Many years later the Russian traveler, Prejavalski, in1876, attributed the illness to “the enormous elevation and rarefaction of the air”. (Quotes from High Altitude Medicine and Physiology, 3rd Edition, 2000; eds. Ward, Milledge, West)

The first modern description of AMS was by Ravenhill (1913) who described the condition as it affected miners in Chile who worked at 4700m. Ravenhill was serving

as a medical officer for the mining company and observed that the miners, who ascended to the mine by rail, were suffering the uncomplicated effects of altitude alone. AMS was called “puna” by the local Bolivians and Ravenhill used this term to describe AMS thus “It is a curious fact that the symptoms of puna do not evince themselves at once. The majority of newcomers have expressed themselves as being quite well on first arrival. As a rule, towards the evening, the patient begins to feel rather slack and disinclined for exertion. He goes to bed but has a restless and troubled night and wakes up the next morning with a severe frontal headache. There may be vomiting, frequently there is a sense of oppression in the chest but there is rarely any respiratory distress or alteration in the normal rate of breathing so long as the patient is at rest. The patient may feel slightly giddy on rising from bed and any attempt at exertion increases the headache, which is nearly always confined to the frontal region”.

Prevention of AMS involves ascending slowly, resting for two days at each new altitude above 3000m before ascending further and prophylactic acetazolamide. Treatment of AMS depends on the severity: headache can be treated with paracetamol and caffeine if not severe; rest will often alleviate AMS symptoms. It is important to understand that AMS can lead to the more serious high altitude disorders: High Altitude Cerebral Edema (HACE) and High Altitude Pulmonary Edema (HAPE), both of which can be fatal. Rapid descent is recommended when AMS symptoms do not abate after rest, or if symptoms of cerebral edema (confusion, ataxia, coma) or pulmonary edema (pink frothy sputum, difficulty breathing) develop; it may be necessary to carry the AMS sufferer to lower altitude but, in mountain trekking and

climbing situations, it is often necessary for the sufferer to walk to lower altitudes. If oxygen is available it can be administered until descent is possible. Rapid recovery occurs with the use of a portable fabric hyperbaric chambers (Gamow bag made by Portable Hyperbarics Inc; Illion, NY, USA and Certec bag made by Certec, Sourcieux le Mines, France)) into which the patient is sealed; the pressure inside is increased by use of a foot pump. These devices imitate rapid descent by 1500-2500 metres. These bags are available in some areas of high altitude trekking and climbing. Recovery is usually rapid with either oxygen administration or use of the hyperbaric bags but the pressure must be maintained, and operation of the foot pump quickly becomes exhausting at high altitude.

Treatments for AMS under field conditions are few. In some trekking and climbing areas there are no medical facilities, while in others there are aid stations or field hospitals that can provide oxygen and/or hyperbaric bag treatments.

Positive end expiratory pressure (PEEP) is known to improve gas exchange in various forms of pulmonary edema, presumably by recruitment of microatelectatic alveoli and improvement of gas exchange. Wayne (1976) reviewed the mechanisms and actions of PEEP in the treatment of acute respiratory failure. Proposed mechanisms of the action of PEEP include the following: shift in interstitial pulmonary water into the capillaries; increased lung volumes by the prevention of expiratory airway collapse; increased diameter of the large and small airways, which thereby decreases airway resistance and improves the distribution of ventilation; decreased alveolar capillary

blood flow coupled with augmented alveolar ventilation, that results in an improved ventilation to perfusion ratio and PaO_2.

Research by two groups, Demling et al (1975) and Caldini et al (1975), found that PEEP did not have a drying effect on the lung; in fact it was found to favour accumulation of liquid in the extravascular space.

In cases where airway collapse due to a surfactant defect and elevated minimal surface tension, PEEP may keep the airways open and maintain alveolar patency with an attendant increase in functional residual capacity.

Several studies have examined the effect of PEEP at high altitude. Each of the following studies used a face mask and valve that applied pressure only during expiration i.e. expiratory positive airways pressure (EPAP), allowing inspiration to occur ambient pressure.

PEEP/EPAP was used on Mount McKinley in Alaska to treat high altitude pulmonary edema (HAPE) by Larson (1985). Nine climbers were studied at an altitude of 4400m at the Mount McKinley medical aid station. Three of the climbers had HAPE (cough, cyanosis, dyspnoea, tachycardia, tachypnoea and râles) and six had no symptoms. PEEP of 5cms and 10cms was used via a spring loaded expiratory valve and face mask (Down's). There was no change to oxygen saturation, respiratory rate or heart rate in the controls but, in the three patients the SaO_2 rose from a mean of 53.3±10.1%

to 63±10.2 % with 5cms PEEP and to 72±5.7% with 10cms PEEP. The respiratory rate in the patients fell from a mean of 22±0 to 16.7±1.8 on 5cms PEEP and to 15.7±3.1 on 10cms PEEP. The symptoms of HAPE improved while using PEEP but returned when the mask was removed. Two of the climbers returned to their tent and used PEEP 10cms for 6 hours as they awaited safe conditions before descending.

The author concluded that PEEP is a useful tool in the treatment of HAPE in field conditions and, because the system exerts positive pressure only during expiration, the risk of barotrauma is small in individuals with no underlying lung disease. Venous return is presumably adequate because the system allows normal negative intrathoracic pressure during inspiration. They recommend PEEP as a first aid in HAPE in field conditions.

Schoene et al (1985) evaluated the use of expiratory positive airways pressure (EPAP) on four climbers with HAPE and thirteen healthy climbers during exercise on a bicycle ergometer at Mount McKinley (4400m). The healthy volunteers (12 men, 1 woman) had climbed to 4400m without developing altitude illness; resting SaO_2 in this group was 85±3%. The four male patients with HAPE had dyspnoea, tachycardia, dry cough, râles and resting SaO_2 of 54 ± 11%. The SaO_2 increased significantly in the HAPE subjects with increasing EPAP of 5cms and 10cms, while the respiratory rate fell and tidal volume increased. There were no adverse effects from using EPAP. In the healthy volunteers, EPAP 5cms and 10cms at rest and during exercise increased SaO_2.

The authors stated that EPAP works in this setting by improving V/Q match and gas exchange by the recruitment of microatelectatic alveoli, similar to the way in which PEEP is presumed to improve gas exchange in patients on mechanical ventilation. The heart rate did not increase in HAPE subjects when using EPAP and this supports the concept that using only expiratory pressure allows normal negative inspiratory pressures to occur and normal venous return. The authors recommend further studies to test the reliability of EPAP as treatment for HAPE in the field.

The use of PEEP/EPAP to prevent the occurrence of AMS was tested by Savourey et al (1998). A group of 22 subjects who trained regularly as endurance runners were exposed to two sessions of 8 hours simulated altitude in a hypobaric chamber of 4500m. The order was randomized and 2 weeks separated each 8 hour session in the chamber. The subjects were studied with or without PEEP of 5cms H_2O during the hypobaric exposure. The 5cms H_2O PEEP was applied using a face mask with a bi-directional valve that allowed 0cms H_2O inspiratory pressure. Oxygen saturation was measured and an AMS score was derived from the Lake Louise Acute Mountain Sickness questionnaire plus clinical assessment. Arterial oxygen, pH, carbon dioxide and sodium bicarbonate were measured from an arterial blood sample taken at 1700 hours.

The authors found that in the subjects without PEEP, 53% of subjects developed AMS with a Lake Louise Score (LLS) of 3 or higher (up to 12). In subjects with PEEP the prevalence of AMS was 23% ($p < 0.01$) with a LLS score below 3. The SaO_2 was not significantly different with and without PEEP; PaO2 was slightly increased (+ 0.74%,

p = 0.06), $PaCO_2$ was also slightly increased (+ 0.76%, p = 0.07) and pH was increased from 7.47 to 7.50, p = 0.04 with PEEP which the authors conclude attest to a lesser arterial alkalosis, probably related to the higher level of CO_2. These changes may be due to PEEP's ventilatory effects such as the recruitment of microatelectatic alveoli.

Launay et al (2004) tested the use of PEEP at high altitude under field conditions in order to determine its effect in preventing the occurrence of AMS. The research was carried out during ascent of Mont Blanc (4810m). Eight healthy male subjects were studied. The PEEP consisted of a bi-directional valve that allowed 0cmsH_2O inspiratory pressure and 5cmsH_2O expiratory pressure; the valve was used with a face mask (Hans Rudolph). The eight subjects climbed Mont Blanc twice: once with PEEP of 5cms and once without PEEP. The presence of AMS was determined using the Lake Louise scoring method [(72)]. Heart rate and pulse oximetry were measured using a finger probe and oximeter and blood pressure was taken at the same time; the Lake Louise score was also derived this time, using questionnaire and clinical assessment.

The authors found that without PEEP 6 of the eight subjects developed AMS (75% prevalence) with Lake Louise scores of 3, 3, 3, 4, 4 and 6. When PEEP was used only one subject had a Lake Louise score of 3 (12.5% AMS prevalence). Heart rate and blood pressure were unchanged by PEEP. The oxygen saturation decreased during both ascents but tended to be higher with PEEP (p = 0.07). The authors concluded that low PEEP is an efficient method for preventing AMS under field conditions at high

altitude without any adverse medical side effects. They suggest that larger studies are needed and to better clarify the physiological mechanisms involved.

It is clear from these studies that the use of expiratory positive airways pressure is a useful tool in the prevention and treatment of AMS and for the treatment of HAPE. The physiological mechanisms are not clear but recruitment of microatelectatic alveoli is proposed by most of the authors. Improvement in the oxygen saturation suggests that arterial blood oxygenation is improved with EPAP and this may be related to an increase in alveolar ventilation.

In order to further examine the physiological mechanism by which PEEP improves ventilation Savourey et al (1999) studied 22 normal, healthy subjects during 4 hours of exercise and 4 hours at rest in hypobaric hypoxic conditions (4500m). The subjects were studied at 0m altitude and at 4500m one week apart, using 5cmsH_2O of PEEP via face mask and a bi-directional valve (EPAP) during rest and exercising on cycle ergometer. Ventilatory parameters and breathing pattern were calculated from: tidal volume, minute volume, duration of inspiration, duration of expiration, total breathing cycle, respiratory frequency (f), duty cycle (inspiratory time/total breathing cycle time) and mean inspiratory flow which were all calculated by computer from the flowmeter data. End tidal partial pressure of oxygen and carbon dioxide ($P_{ET}O_2$ and $P_{ET}CO_2$) were measured; heart rate and oxygen saturation were monitored.

The results demonstrated that using PEEP under hypoxic conditions at rest and during exercise does not modify the breathing pattern. The absence of significant effects of

PEEP on the $P_{ET}O_2$, although PEEP is used to improve gas exchange in high altitude illness, could indirectly suggest that in healthy subjects exposed to hypoxia impaired gas exchange is not present. The authors concluded that hypoxia modifies the drive component of the breathing pattern but not the inspiratory duty cycle and that, secondly those ventilatory parameters are affected by 5cms PEEP without changes in the breathing pattern, SaO_2 or heart rate. Therefore PEEP does not alter ventilatory performance during short hypoxia at rest or during exercise.

Although the mechanisms of PEEP/EPAP in preventing the occurrence of AMS and improving the symptoms when it does occur, as well as being beneficial in the treatment of HAPE, are not definite, it is an extremely useful tool to add to the limited methods available in field conditions at high altitude to treat high altitude illness.

CHAPTER 2

GENERAL METHODS

This Chapter describes the general methodology used for all experimentation in human subjects described in this thesis. Specific details relevant to each experimental protocol are described separately in the relevant chapters.

Each volunteer gave informed consent and the study protocol was approved by the University of Sydney Human Research Ethics Committee (Nepal Study) or by the University of California, Human Research Protection Program (White Mountain Study).

2.1 Subjects

The nineteen subjects who were studied in the Nepal Himalaya were recruited from colleagues and associates. Each subject paid for his or her travel and accommodation expenses during the time in Bangkok and Nepal. Nineteen healthy, non smoking, sea level-dwelling volunteers were studied in Nepal and at sea level, and seven healthy, non-smoking, sea-level dwelling volunteers were studied at White Mountain and sea level. In the Nepal group there were ten male and nine female age matched subjects between twenty and fifty-two years of age (mean 34.1 ± 9.3 years); the mean body mass index (BMI) was 23.4 ± 2.8 kgs/m^2 (range 17.5-27.4kgs/m^2). The White Mountain group consisted of students recruited from the University of California, San Diego. There were three female and four male volunteers aged 21-25 years (mean 23.6±1.5); the BMI was 22.7 ± 1.8kgs/m^2.

The specific demographic details of each volunteer are provided in the relevant chapter.

The female subjects were not taking oral contraceptives during the time at high altitude nor for the month before the high altitude data collection. Subject #5 in the Nepal group was taking Flixotide bd and Ventolin prn but her asthma had been stable for several months before the trek and remained so during the trek. Subject #18 in the Nepal group took Ventolin prn for his asthma but had been stable for several months before the trek and remained so during the trek. No subject ingested alcohol on the day of their sleep study; no subject took respiratory stimulant or depressant medication 24 hours before their sleep study. Paracetamol, ibuprofen, codeine and caffeine were used for headache when required but none of these medications was ingested 12 hours before sleep studies.

None had traveled to high altitude in the twelve months before the study.

2.2 Sleep and Breathing during Sleep

Each volunteer underwent an overnight polysomnography study at sea level before departing for the high altitude location. The White Mountain group had sleep studies performed in their homes and the Nepal group had sleep studies either in their own homes or in the Peninsula Private Sleep Laboratory, Manly, NSW, Australia.

Sleep studies were conducted in the evenings when the subjects retired for the night. The Nepal group had nineteen usable sleep studies at sea level, 1400m and 3900m; two sleep studies were unusable at 3500m and one at 4200m; five sleep studies were unusable at 5000m. One sleep study had no SaO_2 data at 3500m and four had no SaO_2

data at 4200m. Therefore eighty seven sleep studies were analysed at high altitude and nineteen at sea level.

All seven sleep studies in the White Mountain group, at sea level and two nights at 3800m were usable for analysing breathing during sleep but only four had full EEG data for the purposes of analysing sleep architecture i.e. twenty one sleep studies were analysed.

Fourteen of the Nepal subjects had arterial blood gas analysis within an hour of waking from the overnight sleep study at sea level and at each altitude during the trek, before ingesting food or caffeine.

The Lake Louise Acute Mountain Sickness Questionnaire (Roach et al.1993) was administered to each subject within an hour of waking from the sleep studies, before ingesting food or caffeinated beverages. The score derived from this questionnaire was used to quantify the presence and severity of Acute Mountain Sickness.

Sleep state was recorded using two channels of electroencephalogram (EEG; C3/A2, O2/A1), two channels of electro-oculogram (EOG), and one channel of submental electromyogram (EMG). Each 30 second epoch of recording was sleep staged visually according to the standard criteria of Rechtschaffen and Kales (1968). Each epoch was classified as either wakefulness (W), Stage 1 non rapid eye movement (NREM) sleep, Stage 2 NREM sleep, Stage 3 NREM sleep, Stage 4 NREM sleep (these last two stages were pooled and called slow wave sleep) and rapid eye movement (REM) sleep. Also calculated were: total sleep time in minutes, sleep latency (time from start of recording/lights out to sleep onset), REM latency (time from sleep onset to the first

epoch of REM sleep), sleep efficiency (percentage of recording time spent asleep) and minutes and percentage of total sleep of each sleep stage.

An arousal from sleep was defined as an abrupt change in the EEG frequency lasting for 3-15 seconds; in REM sleep submental EMG tone also was present in order to score an arousal. Each arousal from sleep was attributed to either: obstructive apnea/hypopnea, central apnea/hypopnea according to the relationship of the start of the change in the EEG signal to the termination of the respiratory event. Arousals that were not related to any event detectable on the airflow or Respiratory Inductive Plethysmography (RIP) signals were deemed spontaneous arousals. An arousal index (AI) was calculated for the total AI which consisted of the obstructive apnea/hypopnea AI, central apnea/hypopnea AI and the spontaneous AI combined.

Airflow was measured using nasal oxygen cannula and pressure transducer. Thoracic and abdominal movement were recorded using respiratory inductive plethysmography (RIP).

Sleep channels, airflow, thoracic and abdominal movement were recorded by the Compumedics Portable polysomnography (PS1 or PS2) in the subjects' homes and at high altitude, or by the Compumedics S series in the sleep laboratory.

Oxygen saturation was measured by a finger oximeter (Biox 3700e; Ohmeda, Boulder, CO, USA, in the sleep laboratory and built-in oximeter in the Compumedics PS1/2 system in the home and at high altitude).

The respiratory parameters measured included the apnea/hypopnea index (AHI) which was made up of obstructive and central apneas and hypopneas. The AHI was defined as the number of apneas and hypopneas occurring per hour of sleep. Obstructive apneas were defined as a cessation of airflow lasting ≥ 10 seconds with continuing respiratory effort (measured on the thoracic and abdominal RIP). Obstructive hypopneas were defined as a reduction of airflow ≥ 20% lasting ≥ 10 seconds, with continuing respiratory effort, and terminating with EEG arousal and/or oxygen desaturation ≥ 3%. Central apneas were defined as the cessation of breathing and respiratory effort lasting ≥ 10 seconds. Central hypopneas were defined as a reduction in airflow and respiratory effort ≥ 20% lasting ≥ 10 seconds and terminating with EEG arousal and/or oxygen desaturation ≥ 3%.

Figure 2.2.1 Portable Polysomnographic Equipment and Transportation

Transportation of the Equipment used in the Research in the Himalaya

Portable Polysomnographic and other research equipment being loaded and carried by Sherpa porters and Yaks at Pheriche (4200m). Above the tree line, porters also carried sticks to make a fire to heat food and water during the trek.

2.3 Ventilatory Response Testing

Each subject had ventilatory response (VR) tests for eucapnic hypoxia, hypercapnic hypoxia and hyperoxic hypercapnia before departure to Nepal or White Mountain. These tests were performed during the afternoon two to three hours before or after 2pm. The female subjects had VR testing performed in both the follicular and luteal phases of their menstrual cycles; these phases were determined by daily measurement and recording of the morning oral temperature and confirmed by analysis of venous blood taken at the time of the VR testing; follicle stimulating hormone, luteinising hormone, oestradiol and progesterone levels were tested to determine the phase of the menstrual cycle. The luteal phase was determined by increased temperature and the VR testing was performed within forty eight hours of the temperature spike; the testing was repeated within forty eight hours of menses (follicular phase).

The Nepal subjects came to the VR testing facility in Royal Prince Alfred Hospital, Department of Sleep and Respiratory Medicine, Sydney, Australia.

The slope of the change in minute ventilation was calculated by linear regression using the Microsoft program, Excel. Minute ventilation was calculated from computer recordings of inspiratory time, expiratory time, respiratory rate (frequency) and tidal volume. The slope of the change in minute ventilation against SaO_2 and CO_2 was calculated; the number derived for each test is used as the subject's hypoxic and hypercapnic ventilatory response.

2.3.1 Ventilatory Response Testing Equipment

The ventilatory response equipment was originally developed by Dr Michael Berthon-Jones [Berthon-Jones and Sullivan 1982; Berthon-Jones and Sullivan 1984] and is illustrated in Figure 2.3.1. The subject breathed via a mouthpiece which was connected via light, flexible polyethylene hoses to a completely closed, biased flow circuit comprising a four litre flow-through polyethylene bag, by-passable soda lime absorber and a fixed speed blower (12 volts, 50 litres/minute recirculation). Total circuit volume (bag full) was 8.3 litres. An adjustable outward bleed of 0-8 litres/minutes with high dynamic resistance on the blower allowed circuit gas concentrations to be adjusted by injecting gases (air, oxygen, nitrogen or carbon dioxide) from a cylinder downstream from the bag. The bag was encased in a box connected to a No. 3 Fleisch pneumotach with 450 mm of smooth tubing each side to ensure laminar flow. Flow was measured with a differential pressure transducer (Validyne DP-45 and amplifier; Validyne Corp; Northbridge, CA, USA), with a Grass 7P122B amplifier (Grass Instruments, Quincy, MA, USA). Resistance at the mouthpiece, at a flow rate of 1 litre/second, was 1.4cmH_2O/litre/second. The total dead space of the mouthpiece and connecting tubing was 56 millilitres. The entire apparatus was in turn encased in a cabinet that could be pressurized. Circuit materials were acrylic, polyethylene, silicone rubber and food-grade PVC in order to minimise chemical odours.

Arterial oxyhemoglobin saturation (SaO_2) was measured continuously during testing via a finger probe and oximeter (Biox 3700e, Ohmeda, Boulder, CO, USA) set on fast sampling mode (5Hz). Heart rate data was also obtained from the oximeter. End tidal carbon dioxide tension ($P_{ET}CO_2$) was measured using an infrared carbon dioxide

analyser (Hewlett-Packard HP 47210A Capnometer; Hewlett-Packard Inc; Waltham, MA, USA) connected to the mouthpiece. All signals were calibrated at the beginning and end of each test. The concentration of inspired oxygen (FiO_2) was measured at the mouthpiece by a fast response paramagnetic oxygen analyser (Datex Multicap CNO-103-21-01, Datex Instrumentation Corp; Helsinki, Finland) and displayed continuously to the operator.

During each test the filtered flow signal, the $P_{ET}CO_2$ and SaO_2 signals and the heart rate were digitised and processed on an IBM compatible AT computer with a 12-bit A/D converter sampling at 125 Hz. From the flow signal, the inspiratory and expiratory time and tidal volume were measured and minute ventilation was calculated.

The subjects were allowed to adjust to breathing via the mouthpiece attached to the circuit before testing commenced. This 5-10 minutes adjustment time, breathing room air, allowed the subject's $P_{ET}CO_2$ to settle to resting levels.

The circuit is operated by a series of two sets of solenoid valves. The first set consists of low pressure valves which control the flow of gas in the breathing circuit. The valves allow for the adjustment of flow through the soda-lime absorber and allow the subject to be turned into or out of the breathing circuit.

The second set of solenoid valves are high pressure reduction valves which allow the injection of short pulses of air, oxygen, carbon dioxide or nitrogen into the breathing circuit. By adjusting the number of pulses of each gas, this system allows for the

accurate and rapid control of the breathing circuit's gas composition. Importantly, the injection of gas into the circuit occurred close to the return from the subject side of the circuit, thus a high level of mixing occurred before any changed gas composition appeared in the inspired line.

The opening and closing of each of the solenoid valves within the circuit, and thus the gas composition of the circuit, is controlled by computer software (Laboratory Software, Leonay, NSW, Australia), which precisely maintains the subject's SaO_2 and $P_{ET}CO_2$ at targets that have been set by the operator. The model for predicting the gas composition on-line to allow control of both oxygen saturation and end-tidal CO_2 during progressive hypoxia includes an index of metabolic rate to predict the fall in the SaO_2. Controlling the $P_{ET}CO_2$ depended on observation of the capnograph read-out to direct air through the soda-lime absorber or not; each individual's ventilatory response to hypoxia differed, with a brisk response causing a more rapid lowering of the $P_{ET}CO_2$ and therefore required a greater adjustment and control of end-tidal CO_2.

Hyperoxic Progressive Hypercapnic Ventilatory Response Testing: the technique used in this research was described by Read (1967) *i.e.* hyperoxic rebreathing from a small bag initially containing carbon dioxide in concentration similar to that of oxygenated mixed venous blood.

2.3.2 Ventilatory Response Testing Methods

Calibration of the equipment used to monitor oxygen saturation, heart rate and end tidal carbon dioxide (SaO2, HR and CO2) was performed immediately prior to VR testing. Gas cylinders (oxygen, carbon dioxide and nitrogen), VR apparatus and the

computer are turned on and appropriate voltages generated by each piece of equipment to correspond to physiological outputs; the voltages are acquired by the computer and used to calculate and record SaO_2, CO_2 and HR. The equipment is prepared by filling and emptying the breathing bag several times to ensure room air is used during the initial part of the VR testing.

The oxygen probe was applied to a finger. The subject breathed through the mouth piece of the VR equipment, with a nose peg used to prevent nasal breathing. The first five minutes was used to acclimatise the subject to the equipment and measure and record baseline oxygen saturation (SaO2) and end tidal carbon dioxide ($P_{ET}CO_2$) while breathing room air.

2.3.3 Control of Oxygen Saturation

The rate of addition of oxygen is based on the following equation:

$$VO_2 = \text{metabolic rate } (0.3L/min) + K/T \ln (100 - Sa0_2)/(100 - \text{target})$$

where K = 1.25L/min

T = 0.5 min

Target – target set by the operator

The metabolic rate was chosen as an arbitrary value base on an average value from a number of normal subjects. Additionally, if the SaO_2 was greater than the target value, and the SaO_2 was above or equal to 84%, the circuit content was exchanged with N_2 at a rate of 12L/min.

2.3.4 Control of End-tidal Carbon Dioxide

The $P_{ET}CO_2$ was controlled by the use of the soda-lime absorber. The flow through the soda-lime was switched in and out of the circuit with a variable fraction of a 5 second cycle. Each breath, the duty cycle is adjusted by:

adjustment per breath = T_{tot} * ($P_{ET}CO_2$ – target)(0.00125 + 0.05 * current fraction)

where T_{tot} – total time of a breath (in seconds)

Target = target $P_{ET}CO_2$ set by the operator.

The amount of adjustment depends on the current absorption and any error in the $P_{ET}CO_2$. For example, if the absorber is completely bypassed, the adjustment will be 0.125 %/sec/mmHg. If the absorber is on fully, adjustment will be by 0.51 %/sec/mmHg.

Each study consisted of three stages. Initially a five minute control period was recorded, where the subject breathed air via a mouth piece with CO_2 extracted from the circuit by soda lime absorption and O_2 added to maintain 21%. The subject's mean $P_{ET}CO_2$ mmHg was noted during that time.

2.3.5 Eucapnic Hypoxic Ventilatory Response Test

In the second (eucapnic hypoxic) stage of the study, the subject's SaO_2 percentage was lowered to 80% over 90-120 seconds by the addition to the circuit of nitrogen at 8% per minute; $P_{ET}CO_2$ was maintained at the control value throughout this stage. Recording was started and allowed to proceed for 30-60 seconds before selecting 80%

target saturation; when SaO_2 reached 80% the test was ended. In the third stage of the study the subject removed the mouthpiece and nose clip and breathed room air for ten minutes while SaO_2 was continually monitored.

2.3.6 Hypercapnic Hypoxic Ventilatory Response Test

The next study (hypercapnic hypoxia) was conducted in a similar manner to the hypoxic study; with the mouthpiece being inserted and the subject breathing room air for five minutes. The subject's mean $P_{ET}CO_2$ was noted and the target was set on the computer for the $P_{ET}CO_2$ to reach 8mmHg above this control value. The subject's $P_{ET}CO_2$ was increased (by injecting a bolus of CO_2 into the circuit) until it was 8-9mmHg above the control value. The subject breathes via the mouth piece until the CO_2 reaches the target; the subject continues to breathe on the apparatus for 5-7 minutes, allowing the equilibration of the cerebrospinal fluid to that of arterial CO_2. Recording is not started until after the equilibration period. When this $P_{ET}CO_2$ value was reached the subject's SaO_2 was lowered to 80% over 90-120 seconds in the same method as the hypoxic study. The test was ended when the SaO_2 reached 80%. The mouthpiece and nose clip were removed and the subject breathed room air for ten minutes while SaO_2 is monitored.

2.3.7 Hyperoxic Hypercapnic Ventilatory Response Test

Hyperoxic hypercapnic rebreathing was performed according to a modification of the Read rebreathing test (Read, 1967). The basis of the rebreathing test is the attainment of an equilibrium between inspired and expired CO_2, which indicates that all compartments of the body (including the brain and specifically the ventrolateral

medulla where the central chemoreceptors are located) have been exposed to the inspired level of CO_2.

The circuit is filled with 100% oxygen by emptying and filling from the oxygen cylinder several times. A bolus of CO_2 is then injected into the circuit such that the end tidal CO_2 increases by approximately 8mmHg above baseline. The subject inserts the mouth piece, applies the nose peg and takes three deep breaths to facilitate the mixing of CO_2 throughout the circuit and within the airways. Recording is started. The SaO_2 remains at ~99-100% while the CO_2 rises to around 65mmHg. The absorption of expired CO_2 by the soda lime turned off is then ceased and the subject allowed to rebreathe their own CO2 through the recirculation of expired air. Rebreathing was maintained for a period of 5 minutes following the plateau i.e. the difference between inspired and expired CO_2 was greater than 3mmHg. The test was continued until the $P_{ET}CO_2$ reached 60-65mmHg, or for four minutes or until the subject was unable to tolerate further increases in CO_2. The mouthpiece and nose clip were then removed and the subject breathed normally for ten minutes while SaO_2 was monitored. The test was ended and the subject removed the mouth piece and nose peg.

2.3.8 Data Analysis

Data was continuously acquired during testing. For each breath, a number of variables were collected during the test by the software and stored for later analysis. The filtered flow signal, the $P_{ET}CO_2$ and the SaO_2 signals were recorded onto an IBM compatible AT computer with a 12-bit A/D converter sampling at 125Hz. Software controlling the ventilatory response circuit was written in Column Oriented Language (COL), designed by Dr Michael Berthon-Jones at the University of Sydney. Data

recorded in COL was converted to ASCII format and then imported into Microsoft Office Excel 2003, creating a spreadsheet of data for each individual test. Minute ventilation was then calculated by adding the inspiratory and expiratory tidal volumes and halving the product. Minute ventilation (in litres/minute) was plotted against the SaO_2 or $P_{ET}CO_2$ to give the slope of that change. All ventilatory responses to hypoxia and hypercapnia are reported as the slope of the change in ventilation plotted against change in SaO_2 or $P_{ET}CO_2$.

2.3.9 Statistical Analysis

Linear mixed-effects was used to examine the effects of increasing altitude on each breathing parameter.

Spearman's rho (ρ) and Mann-Whitney non parametric correlations were used to assess how age, gender and ventilatory responses to hypoxia and hypercapnia affected the interactions between each sleep and breathing parameter and altitude.

Regression was used to investigate the joint effects of gender and ventilatory responses on NREM periodic breathing apnea/hypopnea and the NREM periodic breathing arousal indices, and the REM central apnea/hypopnea and REM central arousal indices.

Each sleep and breathing parameter was also compared to its sea level value using paired t tests.

CHAPTER 3

SLEEP AT HIGH ALTITUDE

3.1 Introduction

Historically, sleep at high altitude has been known to be of poor quality, with frequent wakenings, gasping for breath and a sense that the sleep is unrefreshing. Much of this belief that sleep quality is poor at high altitude is due to anecdotal evidence: personal reports of mountaineers who slept poorly at high altitude and often observed their companions to have many pauses in breathing during sleep; these pauses were often described as being of the "Cheyne-Stokes" type. There have been several anecdotal reports of poor sleep at high altitude but a very good description was given by Barcroft (1925) who conducted studies on himself over six days and nights spent in a chamber in which the oxygen concentration was regulated to simulate altitudes from 3050m to 4880m. Barcroft had several undergraduate students assisting with the research and they took turns to watch him during the night as he slept in the chamber. In the morning Barcroft asked his students how he appeared to have slept and was told that he had slept well which was in contrast to Barcroft's experience which he described thus: "I thought I had been awake half the night and was unrefreshed in the morning. I was conscious of their moving about and looking through the glass to see whether or not I was awake. I used to count my pulse at intervals. The two opinions can only be reconciled on the hypothesis that whilst I spent most of the night in sleep, the slumber was very light and fitful with incessant dreams. Even some low degree of consciousness which fell short of wakefulness". This description of sleep at high altitude is similar to many other anecdotal reports.

Electrophysiological recordings of sleep have confirmed that total sleep time at high altitude is not altered but lighter sleep stages dominate and it appears that this increased light sleep contributes to subjective feelings of sleeplessness.

Early recordings of breathing during sleep were recorded by Mosso (1898) who recorded breathing during sleep in the Italian Alps at an altitude 4559 metres by an ingenious method that employed a smoked cylinder onto which the pattern of breathing was transferred from a bar resting on the chest of his sleeping brother. This early research confirmed the presence of Cheyne-Stokes breathing during sleep and was also called "periodic breathing" to describe the repetitive and regular pauses in breathing. This abnormal breathing during sleep at high altitude is thought to be the cause of the poor sleep quality.

Animal studies into sleep at simulated high altitude confirm that slow wave sleep is reduced. In one study (Pappenheimer 1977 and 1984) rats chronically implanted cortical electrodes were studied while breathing 10% oxygen, equivalent to an altitude of 5490m. The rats' normal amount of slow wave sleep was reduced from 45% to 27% when breathing this hypoxic mixture. The amplitude of the cortical EEG during sleep was also found to be reduced in the rats with a shift in the distribution of amplitudes towards the awake values. These animal studies may explain the poor subjective sleep quality consistently reported by sojourners at high altitude.

Sleep was not recorded in humans electrophysiologically until the advances in technology enabled electro-encephalography and other physiological signals to be recorded. In 1970 and 1975 the first recordings of sleep at high altitude were carried

out. Joern (1970) recorded sleep in two men in their first few days at the South Pole, which has a reduced barometric pressure similar to 3000-3800m, due to the elevation of the area and to the earth's spin. In this study Joern found that slow wave sleep, the deepest sleep stage, was markedly reduced, Stage 1 non rapid eye movement (NREM) sleep, the lightest sleep stage markedly increased with rapid eye movement (REM) sleep unchanged. It is not clear whether these changes to sleep were due entirely to the hypobaric hypoxia present at the South Pole or whether there was a contribution to sleep alterations by the changes in the light dark cycle present in the polar areas.

Reite (1975) recorded sleep in six men at the actual high altitude location of Pike's Peak at 4300m and found sleep to be markedly altered by acute exposure to high altitude with increased Stage 1 and reduced slow wave and REM sleep. Since these first studies many consequent studies have been performed, both at actual high altitude locations and in hypobaric chambers to simulate high altitude.

The recording of sleep, and breathing during sleep, have confirmed many of the early reports of poor sleep and periodic breathing. Most studies have found that Stage 1 NREM sleep is increased and slow wave sleep decreased while REM sleep has been found to be reduced in some studies and unchanged in other studies, while total sleep time is unchanged.

The reports of poor subjective sleep quality at high altitude are possibly attributable to increased lighter sleep stages, decreased deeper sleep stages but also to the documented increase in sleep fragmentation. In one study done at high altitudes from 4000-7620m, Anholm et al (1992) found that the number of brief arousals from sleep

increased from the sea level value of around 22/hour to over 160/hour at 7620m and the arousal index was markedly increased at 7620m when compared to 4572m. These brief arousals were highly negatively correlated with the sleeping oxyhemoglobin saturation (SaO_2) which led the authors to conclude that hypoxia was the main cause of these brief, repetitive arousals.

The addition of oxygen during sleep at high altitude has been found to decrease the number of arousals and improve sleep (Luks et al.1998, West et al. 1995) particularly in increasing the amount of slow wave sleep and improving subjective sleep quality.

The causes of the changes to sleep at high altitude have not been proved emphatically but the most widely accepted hypothesis is that hypoxia is the major contributing factor. Hypoxia produces increased ventilation, hypocapnia and periodic breathing during sleep. Periodic breathing is believed to be the most disruptive event of sleep at high altitude with its associated arousal from sleep and marked swings in oxyhemoglobin saturation and arterial carbon dioxide. Hypocapnia has recently been suggested as playing a major role in sleep disruption (Lovering et al 2003) but it may be the interplay between hypoxia and hypocapnia that is the dominant mechanism.

In the research presented in this chapter we demonstrate the changes to sleep in a large group of subjects who undertook a trek from 1400m to 5000m in the Nepal Himalaya over a period of ten to eleven days. Sleep studies were conducted at sea level before departure to Nepal and these baseline sleep studies were used to compare differences in sleep architecture at altitudes 1400m, 3500m, 3900m 4200m and 5000m.

This research is the first to study the sleep of a large group of subjects during real-life trekking conditions that reflect the activities undertaken by thousands of people each year, who travel to high altitude locations for the purposes of tourism and adventure. This specific aim of this research was to determine whether hypoxia, arousal from sleep or other factors present during a trek of this type contributed to the altered sleep architecture.

3.2 Aims

The aims of this Chapter were to examine the effects on sleep of incremental increases in altitude over a period of ten to eleven days' trekking in the Nepal Himalaya.

In particular the aims were:

1) To determine the changes to the composition of sleep, the number of arousals from sleep and the amounts of each sleep stage compared to sea level, baseline amounts; and

2) To determine whether previously reported changes to various sleep stages at high altitude were present in this large group of subjects.

3.3 Methods

3.3.1 Subjects

Nineteen healthy, non-smoking, sea-level dwelling subjects (Table 3.4.01) were recruited from friends and colleagues. None had been to altitudes above 1000m in the twelve months before this research was conducted. There were ten male and nine female subjects between twenty and fifty-two years of age (mean 34.1 ± 9.3 years); the mean body mass index (BMI) was 23.4 ± 2.8 kgs/m^2, (range 17.5 - 27.4kgs/m^2).

All the female subjects were pre-menopausal and none was taking oral contraceptives. Two subjects (#5 and #19) had asthma; one subject (#5) was taking Flixotide bd and Ventolin prn the other subject (#18) was taking Ventolin prn. Both asthmatic subjects had been stable for 4-6 months before departure to Nepal and remained free of exacerbations to asthma during the trek.

Each subject gave informed consent and the protocol was approved by the University of Sydney, Human Ethics Committee.

3.3.2 Measurements

Overnight sleep studies (polysomnography) were conducted on each subject before departure to Nepal. These baseline sleep studies were conducted at sea level in Sydney, Australia either at the Peninsula Private Sleep Laboratory (n = 11) or in the subject's home (n = 8). Overnight sleep studies were conducted at the following altitudes in Nepal: 1400m, 3500m, 3900m, 4200m and 5000m on either the first or second night at each altitude.

There were several unusable sleep studies due to battery failure or other technology failures. Only studies with ≥ 300 minutes of recording were used in the analysis. Sleep studies which had fewer than 300 minutes were removed from the analysis thus: one study at 1400m, one at 3900m, two at 4200m and six at 5000m. Two sleep studies failed and one had no SaO_2 data at 3500m; one sleep study failed and four had no SaO_2 data at 4200m, two sleep studies were unusable at 5000m due to battery failure after less than an hour's sleep. Therefore, nineteen sleep studies were analysed at sea level, eighteen at 1400m and 3900m; seventeen sleep studies were analysed at 3500m, sixteen at 4200m and thirteen at 5000m. A total of eighty two sleep studies from high altitudes were used in the analysis.

Sleep study equipment used was Compumedics (Melbourne, Australia) S Series in the laboratory, and portable systems (PS1 or PS2) in the home and during the time in Nepal.

Parameters measured were two electro-encephalograms (EEG) consisting of central and occipital leads (C3/A2 and O2/A1); two (right and left) electro-oculograms (EOG); submental electro-myogram (EMG); two lead electro-cardiogram (ECG); chest and abdominal respiratory inductive plethysmography (RIP); anterior tibialis EMG; body position; nasal flow and oxyhaemoglobin saturation.

3.3.3 Protocol and Equipment

Sleep studies were conducted either at the Peninsula Private Sleep Laboratory in Manly, NSW, Australia using Compumedics S Series monitoring equipment or in the

subject's home using the same portable polysomnographic equipment used in Nepal i.e. Compumedics PS1 or PS2 portable monitoring equipment.

Grass™ gold cup electrodes (Astro-Med Inc; West Warwick, RI, USA) were used to measure EEG, EOG and submental EMG.

Leg EMG was measured using piezoelectric strain gauges (Compumedics).
ECG was measured using Nikomed™ stick-on dots and Grass™ click-on electrodes.
Compumedics respiratory inductive bands were used to measure chest and abdominal movement.

Nasal flow was measured with a cannula (Salter™ 1606) and differential pressure transducer built into the Compumedics systems and sampled at 25Hz.

Oxyhaemoglobin saturation was measured using a finger probe and an oximeter built into the Compumedics systems and sampled at 1Hz.

Figure 3.3.3 Polysomnography in the Field at High Altitude

Preparing to set up for Sleep Studies at Khunde, 3900m
and, below two subjects having sleep recorded at 3900m

3.3.4 Procedure

The placement of the EEG, EOG and submental EMG electrodes followed the Ten-Twenty Electrode System of the International Federation (1958).

The skin was prepared by rubbing an abrasive gel (Nuprep™) on the area to which the electrode was to be attached.

The EEG electrodes were applied using a $2cm^2$ piece of gauze which was spread with a thick coating of water soluble paste, (Grass™ EC2® Electrode Cream), which dried to an adhesive texture. The electrodes were filled with the same paste which is also electro-conductive.

The EOG and submental EMG electrodes were filled with EC2® paste and attached with a $2cm^2$ piece of Fixomull® adhesive gauze.

ECG electrodes were Compumedics clip on and Nikomed™ stick on dots were attached to the right side of the upper chest in the mid-clavicular area and to the left side of the lower chest below the axilla in the nipple line.

Compumedics respiratory inductive plethysmography (RIP) bands were worn under the armpits and around the waist. The body position sensor was worn under the thoracic RIP band.

The anterior tibialis was identified by asking the subject to flex and extend the foot; the piezoelectric strain gauge was attached with surgical tape (Micropore™) to one leg.

Airflow was measure with an oxygen cannula (Salter™ 1606) attached via 1-2 metres of oxygen tubing to the differential pressure transducer built into the Compumedics system.

Oxyhaemoglobin saturation was measured with a finger probe and an oximeter built into the Compumedics system.

EEG, EOG, EMG and ECG were sampled at 125Hz using 0.3μV low frequency filter and 30 μV high frequency filter.

Respiratory movement (chest and abdominal RIP) was sampled at 25Hz. Nasal flow was sampled at 125Hz. Oximetry and body position were sampled at 1Hz.

The first sleep studies in Nepal were conducted in Kathmandu, altitude 1400m (see Figure 3.3.1b Trekking Map). After a 45 minute flight to Lukla (2800m) a three hour trek was undertaken to Phakding (2600m) where the first night of the trek was spent; sleep studies were not conducted at Phakding. The following day an eight hour trek to Namche Bazaar (3500m) was undertaken and two nights were spent at this altitude, sleep studies being conducted on either the first or second night. After two nights at Namche a three hour trek was undertaken to Khunde (3900m) where two nights were spent with sleep studies being conducted on night one or two. The next trek was to

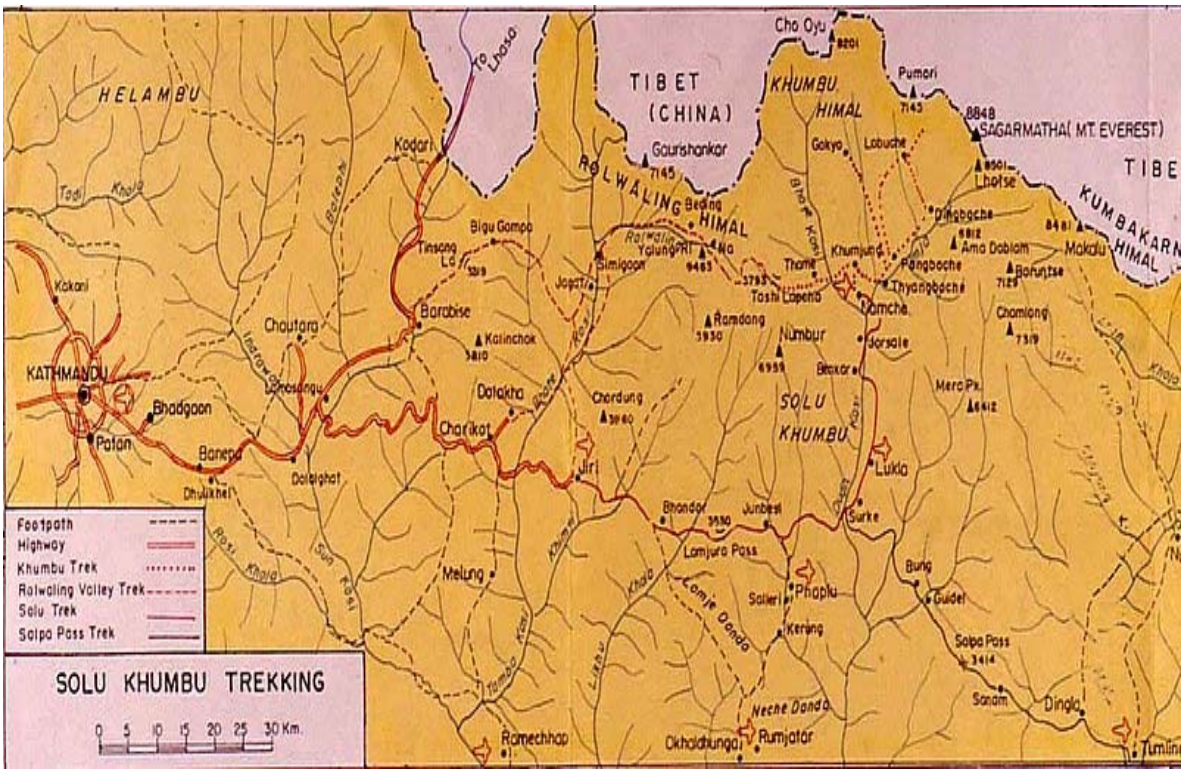
Tyangboche (3900m) which was a seven hour day involving an altitude decrease of 600m followed by an altitude increase of 600m; sleep studies were not performed during the single night spent at Tyangboche. An eight hour trek took the group to Pheriche (4200m) and two nights were spent here with sleep studies on either the first or second night. The next stage of the trek was varied in the first two groups of subjects according to the presence of illness i.e. those subjects who were unwell trekked from Pheriche to Dugla (4800m) for a one night sojourn (no sleep studies) before trekking on to Lobuche (5000m). In the first two groups three subjects spent a night at Dugla and in the second group two subjects spent a night at Dugla. Subjects who were well trekked directly from Pheriche to Lobuche. The third group of five subjects all spent a night at Dugla regardless of the presence or absence of illness. Two nights were spent at Lobuche with sleep studies on either night one or two.

Figure 3.3.1 displays the trekking map. Table 3.3.1 gives details for each subject at each altitude and the order of sleep study performed at that altitude i.e. first or second night.

Figure 3.3.4 a. Map of Nepal with Solu Khumbu region

The trekking area, Solu Khumbu, in north-eastern Nepal. The area is accessed by a flight from Kathmandu in a twelve-seater, light aircraft.

Figure 3.3.4 b. Trekking Map



The map shows the route covered by the trek from Lukla to Lobuche. The subjects flew by light aircraft from Kathmandu to Lukla and then walked to Phakding (2800m, no sleep studies) where the first night was spent. The next day the trek ascended to Namche (3500m) over a period of 6-7 hours and two nights were spent at this altitude. A 3-4 hour trek was then undertaken to Khunde (3900m) where two nights were spent then a descent of 600m followed by an ascent of 600m to Tyangboche (3900m) where one night was spent (no sleep studies). The trek then ascended over 5-6 hours to Pheriche (4200m) where two nights were spent. Some subjects then ascended to Dugla (4800m) for one night (no sleep studies) and some subjects trekked directly to Lobuche (5000m); subjects who had no signs or symptoms of Acute Mountain Sickness trekked directly to Lobuche. All subjects spent at least two nights at Lobuche. This concluded the sleep study collection. The subjects then descended to Pheriche and spent one night and then down into Namche for one night before descending into Lukla and flying out to Kathmandu the next day.

Table 3.3.4 Order of Sleep Study at each altitude in each subject

Subject	1400m night of sleep study	3500m night of sleep study	3900m night of sleep study	4200m night of sleep study	5000m night of sleep study
1	1		1	1	1
2	2	2	2	2	1
3	2	2	1	1	1
4	1	2	1		1
5	1	1	2	2	1
6	2	1	2	2	1
7	1	1	1	2	2
8	2	2	2	1	1
9	1	1	1	2	2
10	2	1	1	1	1
11	2	1	2	2	1
12	2		2	2	1
13	2	2	1	1	1
14	2	2	2	1	1
15	1	2	2	2	1
16	1	1	2	1	2
17	2	2	1	1	2
18	1	1	1	1	2
19	1	1	1	1	2

Due to the limitation of equipment to record sleep studies, the subjects were studied on either the first or second night at each new altitude and the order was randomised (by coin toss).

3.3.5 Polysomnography: Sleep Stage Scoring

Overnight sleep studies were performed at sea level and in the Nepal Himalaya following the procedures outlined above. Recording was started when the subject was ready to sleep and was ended in the morning when the subject arose from bed. Only sleep studies with 300 minutes or more of recording time were used in the analysis.

Sleep was staged according to the criteria of Reschtshaffen and Kales (1968)

Stage Wake is characterised by alpha activity and/or a low voltage, mixed frequency EEG. A high tonic EMG is usually present and often rapid eye movements and eye blinks are present in the EOG signals.

Stage 1 non rapid eye movement (NREM) sleep is defined as a "relatively low voltage, mixed frequency EEG with a prominence of activity in the 2-7 cycles per second (cps) range. Vertex sharp waves may appear at an amplitude of up to 200μV. There are no rapid eye movements but slow rolling eye movements may occur.

Stage 2 NREM sleep is defined as having 12-14 cps sleep spindles and/or K complexes on a background of relatively low voltage, mixed frequency EEG activity and in the absence of sufficient (*i.e.*<20%) slow wave activity. K complexes consist of a well delineated negative sharp wave immediately followed by a positive component. The total duration of the K complex exceeds 0.5 seconds. If less than 3 minutes of sleep time passes without the occurrence of either sleep spindles or K complexes (*i.e.* Stage 1) and in the absence of arousal, it is scored as Stage 2 but if it lasts longer than 3 minutes it is scored as Stage 1. After an arousal in Stage 2 sleep, if no spindles or K complexes occur, it is scored as Stage 1 until a spindle or K complex occurs.

Stage 3 NREM sleep is defined as high amplitude, slow wave activity for 20-50% of the 30 second epoch and Stage 4 NREM sleep as high amplitude, slow wave activity for >50% of each 30 second epoch. Slow waves are defined as 2cps or slower with an amplitude of >75μV from peak to peak.

REM sleep is defined by the concomitant appearance of a relatively low voltage, mixed frequency EEG activity and episodic rapid eye movements. The EEG pattern resembles Stage 1 NREM except that vertex sharp waves are not prominent and "saw tooth waves" may be present. Alpha activity is often prominent in REM sleep but is 1-2cps slower than during wakefulness. There is an absence of spindles and K complexes. The submental EMG is used to detect the muscle atonia present in REM sleep and may show bursts of activity during vigorous rapid eye movements.

Sleep staging was performed on the basis of visual inspection of 30 second epochs with at least half the epoch scored as the designated sleep stage.
Sleep studies were analysed by two experienced scorers and at least 95% consensus was reached in ≥ 95% of sleep studies.

3.3.6 Definition of Arousal from Sleep and Assignment of Arousal Type

In defining an arousal from sleep, the guidelines from the Report of the American Sleep Disorders Association Task Force (1992) were used.

The EEG signal was derived from the standard Reschtshaffen and Kales (1968) placement of scalp electrodes *i.e.* a central (C4 or C3) electrode referred to the opposite ear or mastoid (A1 or A2) and an occipital (O1 or O2) referred to the opposite ear or mastoid (A1 or A2). Referential electro-oculograms (LOC and ROC) referred to an electrode placed between the eyebrows on top of the nose. Submental EMG placed under the chin.

Arousal was defined as an abrupt change in EEG frequency which may include theta, alpha and/or frequencies greater than 16 Hz but not spindles. The subjects must be asleep, defined as ten continuous seconds or more of any sleep stage, before an arousal can be scored. A minimum of ten continuous seconds of intervening sleep is necessary before another arousal can be scored. The EEG shift must be a minimum of three seconds. Arousals in NREM sleep may occur without concurrent increases in submental EMG amplitude. Arousals in REM sleep can only be scored if accompanied by increases in submental EMG amplitude.

In this study arousals were assigned as being due to either an obstructive respiratory event *i.e.* obstructive apnea or hypopnea, or a central respiratory event *i.e.* central apnea or hypopnea when the termination of the respiratory event and the beginning of the arousal were 1-3 seconds apart. When no event could be assigned as the cause of the arousal, it was labelled a spontaneous arousal.

Arousal indices were calculated for each of the following arousal types 1) obstructive respiratory events, 2) central respiratory events, 3) spontaneous and 4) total arousal index.

3.3.7 Statistical Analysis

Each sleep parameter was analysed to determine the effects of increasing altitude using linear mixed-effects model. Only sleep studies with recording times of 300 minutes or more were used in the analysis.

Non-parametric correlations (Spearman's rho and Mann-Whitney rank-sum) were used to determine the effects of age and gender on the relationship between sleep and altitude.

Each sleep parameter was compared with its sea level value using paired t tests.

Statistical significance was assumed at p values < 0.05.

All results shown in the text are given as mean values ± SD unless otherwise stated.

3.4 Results

3.4.1 Subject Characteristics

Nineteen subjects were studied. Demographic details are shown in Table 3.4.1

Table 3.4.1. Nepal Subjects

Subject	***Sex***	***Age (years)***	***Height (cms)***	***BMI (kg/m^2)***
1	M	20	197	17.5
2	M	29	172	23.5
3	M	29	173	23.5
4	M	46	190	24.4
5	F	26	159	27.3
6	F	46	168	21.3
7	F	42	160	21
8	F	31	179	21.2
9	F	40	175	23
10	F	37	163	20
11	M	42	188	26
12	M	40	183	26.6
13	M	21	183	22.4
14	M	52	170	27
15	F	23	165	21.3
16	F	23	158	22.4
17	F	31	153	27.4
18	M	35	174	26.4
19	M	35	193	23.1
Means ± SD		***34.1 ± 9.3***	***174.1 ± 12.8***	***23.4 ± 2.8***

Nineteen subjects were studied at sea level and at five altitudes in the Nepal Himalaya. All were healthy volunteers who had not been to altitudes above 1000m in the previous twelve months.

3.4.2 Sleep Architecture on the First and Second Night at each Altitude

The subjects were studied on either the first or second night at each new altitude due to equipment limitation (Table 3.3.1). When the sleep architecture was compared between the two nights we found surprisingly few differences between the groups.

Only at two altitudes were there trends towards differences in any sleep parameter i.e. at 3500m there was a trend towards longer duration of REM in the group who had sleep studies on the second night at this altitude compared to the group studied on the first night : 75 ± 21 minutes in the group studied on the first night and 103 ± 37 minutes in the group studied on the second night ($p = 0.07$). Not surprisingly and perhaps due to the very vigorous exercise involved in trekking from 2600m to 3500m over eight hours, there was a trend towards a shorter latency to sleep in the group studied on the first night at this altitude, with this group having a mean sleep latency of 20 ± 8 minutes compared to the group studied on the second night whose mean sleep latency was 36 ± 22 minutes ($p = 0.07$).

Only at one other altitude was a trend towards a significant difference found in one sleep parameter i.e. at 4200m there was a longer mean duration of slow wave sleep in the group studied on the first night at this altitude: 86 ± 35 minutes of SWS versus 36 ± 22 minutes in the group studied on the second night ($p = 0.06$).

3.4.3 Total Sleep Time and Sleep Efficiency

All sleep parameters reported are the results of analysis using linear mixed effects model.

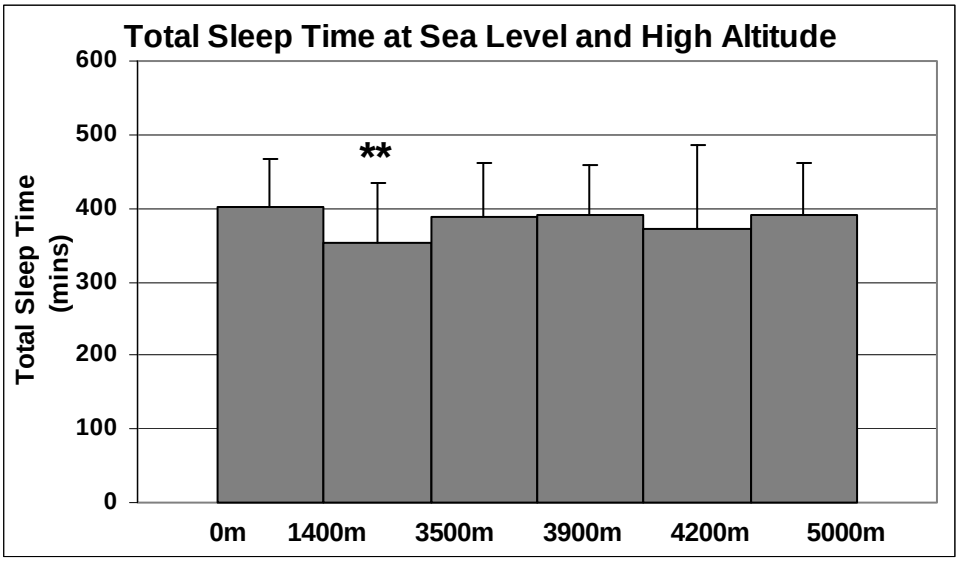
At sea level the subjects had reasonably normal amounts of sleep, with an average total sleep time (TST) of 403 ± 65 minutes and sleep efficiency (time spent asleep during recording) of 88 ± 9 % (Table 3.4.2, Figures 3.4.1 and 2).

Table 3.4.2. Sea Level

Subject	***Recording Time (mins)***	***Sleep Time (mins)***	***Latency to sleep (mins)***	***Sleep Efficiency %***
1	421	375	9	89
2	454	442	3	97
3	430	422	3	98
4	446	433	4	97
5	539	420	19	78
6	528	419	23	79
7	433	360	16	83
8	567	474	47	84
9	479	423	21	88
10	399	316	32	79
11	521	488	7	94
12	336	328	3	98
13	331	310	4	94
14	483	305	31	63
15	564	491	42	87
16	530	482	13	91
17	477	380	41	80
18	347	323	3	93
19	506	473	6	93
Means ± SD	***463 ± 73***	***403 ± 64***	***17 ± 15***	***88 ± 9***

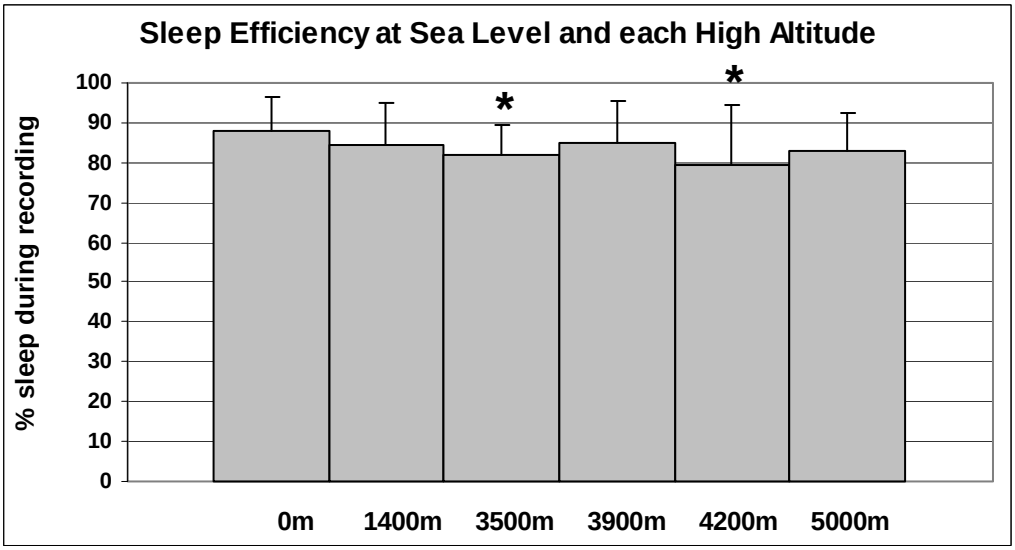
Nineteen subjects were studied at sea level before departure for Nepal; overnight sleep studies were performed either in the subject's home using portable polysomnography or in the Sleep Laboratory. Most subjects had between six and eight hours sleep.

Figure 3.4.1. Total Sleep Time in minutes



Total sleep time at sea level was 403 ± 64 minutes and this was significantly reduced only at Kathmandu (p = 0.05), while at higher altitudes sleep time was similar to sea level amounts.

Figure 3.4.2 Sleep Efficiency (percentage of recording time spent asleep)



Sleep efficiency (the percentage of recording time spent asleep) remained close to sea level values during the trek, being significantly reduced only at 3500m and 4200m (p = 0.05).

At the first and lowest altitude studied in Nepal i.e. Kathmandu at 1400m, the TST was reduced significantly to 353 ± 81 minutes (p = 0.05) with sleep efficiency (SE) of 84 ± 10% (ns).

The TST at the next four altitudes studied were not significantly different with total sleep times at 3500m, 3900m, 4200m and 5000m of 389 ± 73, 391 ± 66, 373 ± 111 and 392 ± 69 minutes.

Sleep efficiency was, however reduced significantly at two altitudes during the trek i.e. at 3500m SE was reduced to 82 ± 8% (p = 0.05) and at 4200m SE was reduced to 79 ± 15% (p = 0.05). At the other two altitudes i.e. 3900m and 5000m, SE was well maintained at near sea level values of 85 ± 10% and 83 ± 9%.

Thus, there was little variation in either the total amount of sleep or the time spent asleep during recording. Total sleep time and sleep efficiency remained near normal, sea level values at most altitudes. Tables 3.4.2-6 and Figures 3.4.1 and 2.

Table 3.4.3 1400 metres

Subject	***Recording Time (mins)***	***Sleep Time (mins)***	***Latency to sleep (mins)***	***Sleep Efficiency %***
1	375	342	3	91
2	391	344	31	88
3	434	403	3	93
4	440	374	35	85
5	414	305	34	74
6	370	342	23	92
7	415	293	23	71
8	330	272	48	82
9	464	318	37	69
10	354	223	51	63
11	360	332	20	92
12	406	301	11	74
13	383	351	15	92
14	N/A	N/A	N/A	N/A
15	521	501	3	96
16	470	439	112	94
17	300	238	45	79
18	479	474	3	99
19	565	476	4	84
Means ± SD	***415 ± 67***	***352 ± 80***	***28 ± 27***	***84 ± 10***

Eighteen subject's sleep time, sleep efficiency and latency to sleep were analysed at 1400m (Kathmandu). Total sleep time was significantly reduced ($p = 0.05$) while sleep efficiency and latency to sleep were similar to sea level values.

Table 3.4.4 3500 metres

Subject	***Recording Time (mins)***	***Sleep Time (mins)***	***Latency to sleep (mins)***	***Sleep Efficiency %***
1	N/A	N/A	N/A	N/A
2	390	353	16	90
3	496	473	8	95
4	315	255	30	81
5	429	352	12	82
6	414	329	27	79
7	514	400	10	78
8	511	403	48	79
9	448	328	31	73
10	424	342	30	81
11	442	299	15	68
12	N/A	N/A	N/A	N/A
13	511	438	24	86
14	510	344	26	67
15	602	537	40	89
16	569	481	26	85
17	544	452	70	83
18	450	414	12	92
19	483	410	30	85
Means ± SD	***474 ± 70***	***389 ± 73***	***27 ± 16***	***85 ± 11***

Seventeen subjects' sleep time, sleep efficiency and latency to sleep were analysed at 3500m (Namche). Total sleep time and latency to sleep were similar to sea level values, while sleep efficiency was reduced ($p = 0.05$).

Table 3.4.5 3900 metres

Subject	***Recording Time (mins)***	***Sleep Time (mins)***	***Latency to sleep (mins)***	***Sleep Efficiency %***
1	420	398	8	95
2	N/A	N/A	N/A	N/A
3	466	434	11	93
4	468	436	20	93
5	433	296	26	68
6	300	284	5	95
7	473	340	9	72
8	466	393	40	84
9	496	356	37	72
10	387	333	13	86
11	483	405	42	84
12	474	370	36	78
13	449	396	8	88
14	478	300	12	63
15	512	458	43	89
16	536	510	20	95
17	539	466	42	87
18	416	387	8	93
19	527	488	30	93
Means ± SD	***462 ± 58***	***391 ± 66***	***23 ± 14***	***85 ± 10***

Eighteen subjects' sleep time, latency to sleep and sleep efficiency were analysed at 3900m (Khunde) and there were no significant differences found between sea level values in any parameter measured at 3900m.

Table 3.4.6 4200 metres

Subject	***Recording Time (mins)***	***Sleep Time (mins)***	***Latency to sleep (mins)***	***Sleep Efficiency %***
1	N/A	N/A	N/A	N/A
2	502	428	27	85
3	473	443	11	94
4	N/A	N/A	N/A	N/A
5	N/A	N/A	N/A	N/A
6	302	278	3	92
7	357	332	12	93
8	579	415	54	87
9	403	294	47	73
10	472	351	85	74
11	465	367	70	79
12	387	164	36	42
13	501	404	16	80
14	320	147	6	46
15	561	505	17	90
16	601	535	16	89
17	587	504	54	86
18	451	382	16	85
19	594	425	90	72
Means ± SD	***472 ± 98***	***373 ± 112***	***31 ± 24***	***79 ± 15***

Sixteen subjects' sleep time, sleep efficiency and latency to sleep were analysed at 4200m (Pheriche). Sleep efficiency was reduced (p = 0.05), while total sleep time and latency to sleep were similar to sea level values.

Table 3.4.7 5000 metres

Subject	***Recording Time (mins)***	***Sleep Time (mins)***	***Latency to sleep (mins)***	***Sleep Efficiency %***
1	397	357	7	90
2	N/A	N/A	N/A	N/A
3	N/A	N/A	N/A	N/A
4	502	432	16	86
5	N/A	N/A	N/A	N/A
6	N/A	N/A	N/A	N/A
7	422	384	17	91
8	457	390	27	85
9	474	344	49	73
10	N/A	N/A	N/A	N/A
11	347	246	43	71
12	N/A	N/A	N/A	N/A
13	511	432	13	85
14	501	423	17	84
15	543	516	18	95
16	571	447	18	78
17	429	354	83	83
18	474	451	6	95
19	509	322	390	63
Means ± SD	***472 ± 61***	***392 ± 69***	***31 ± 28***	***83 ± 10***

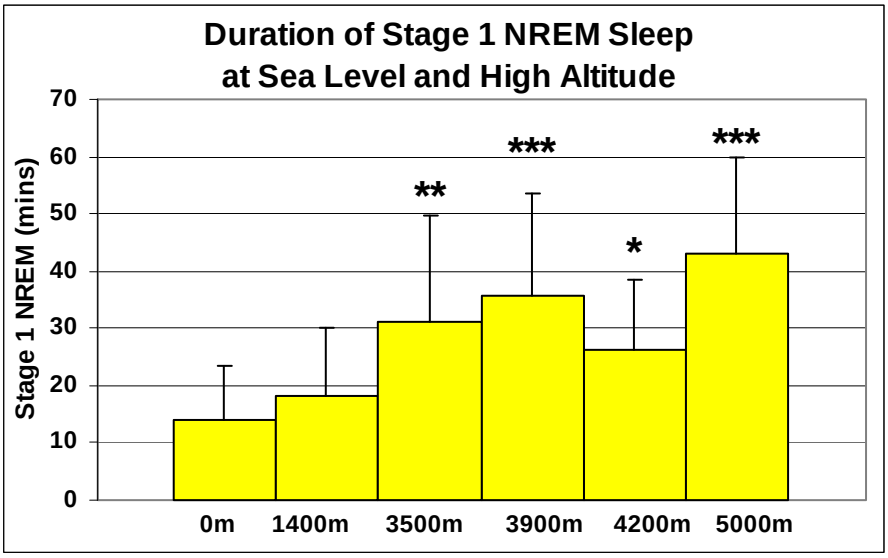
Thirteen subjects' sleep time, sleep efficiency and latency to sleep were analysed at 5000m (Lobuche). There were no significant differences found in any parameter.

3.4.4 Sleep Stages: Duration and Percentage

The lightest sleep stage, Stage 1 non rapid eye movement sleep (NREM) increased progressively with increasing altitude (Figures 3.4.3 and 3.4.4), becoming highly significantly increased from 3500m. This increase was true for both the duration of Stage 1 and its percentage of total sleep time.

At sea level Stage 1 NREM duration was 14 ± 9 minutes and was increased, but not significantly, at 1400m to 18 ± 12. At the next highest altitude, 3500m Stage 1 NREM had increased to 31 ± 19 minutes ($p < 0.001$), and then to 36 ± 18 minutes at 3900m ($p < 0.001$), 26 ± 14 minutes at 4200m ($p = 0.04$) and 43 ± 17 minutes at 5000m ($p < 0.001$).

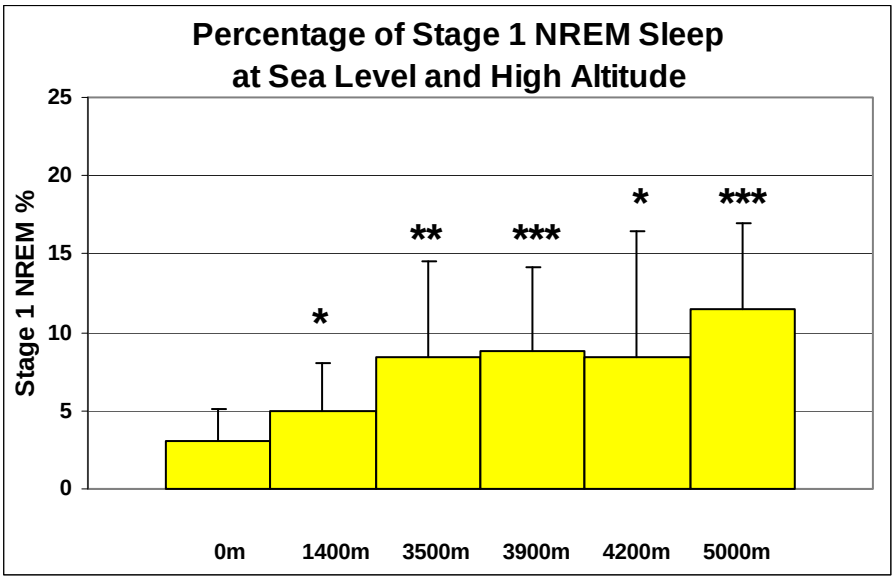
Figure 3.4.3 Duration in minutes of Stage 1 NREM Sleep



The lightest sleep stage, Stage 1 non-rapid eye movement (NREM) sleep, was increased at all altitudes in Nepal, with highly significant increases occurring at 3500m ($p < 0.001$), 3900m ($p < 0.001$), 4200m ($p = 0.04$) and 5000m ($p < 0.001$). This finding is in agreement with all previous studies of sleep at high altitude.

Stage 1 NREM percentage of total sleep was 3 ± 2% at sea level and increased to 5 ± 3% at 1400m ($p = 0.03$), 8 ± 6% at 3500m ($p = 0.004$), 9 ± 5% at 3900m ($p < 0.001$), 8 ± 8% at 4200m ($p = 0.03$) and 11 ± 6% at 5000m ($p < 0.001$).

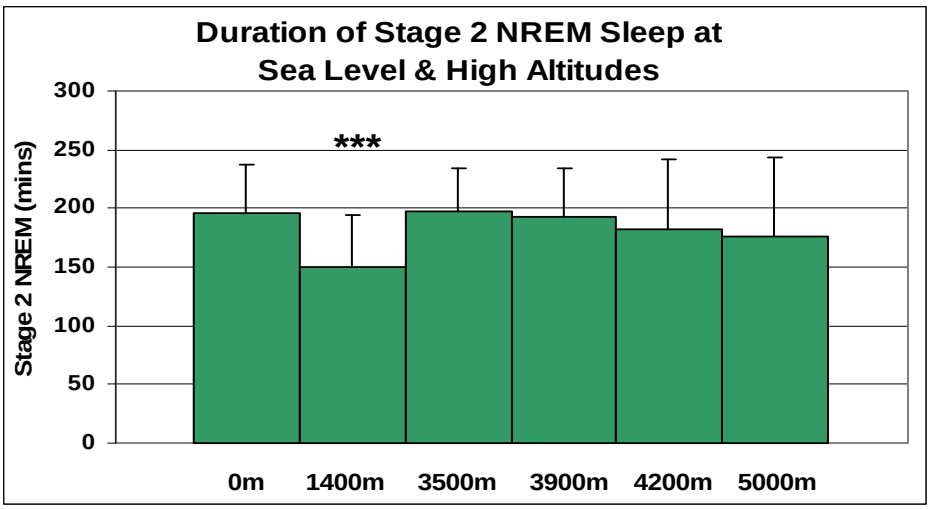
Figure 3.4.4 Percentage of Stage 1 NREM Sleep



The percentage of total sleep spent in the lightest sleep stage, Stage 1 NREM sleep, was increased at all altitudes in Nepal, with significant increases at 1400m ($p = 0.03$), 3500m ($p = 0.004$), 3900m ($p < 0.001$), 4200m ($p = 0.03$) and 5000m ($p < 0.001$).

Stage 2 NREM sleep was unaffected by moderate and high altitudes but interestingly was significantly reduced at the lowest altitude during the trek. Sea level duration of Stage 2 NREM was 196 ± 41 minutes and at 1400m this was reduced to 149 ± 45 minutes ($p < 0.001$). Stage 2 duration was maintained at near sea level values at 3500m where it was 197 ± 36 minutes, at 3900m it was 193 ± 41 minutes, at 4200m 182 ± 60 minutes and 176 ± 67 minutes at 5000m.

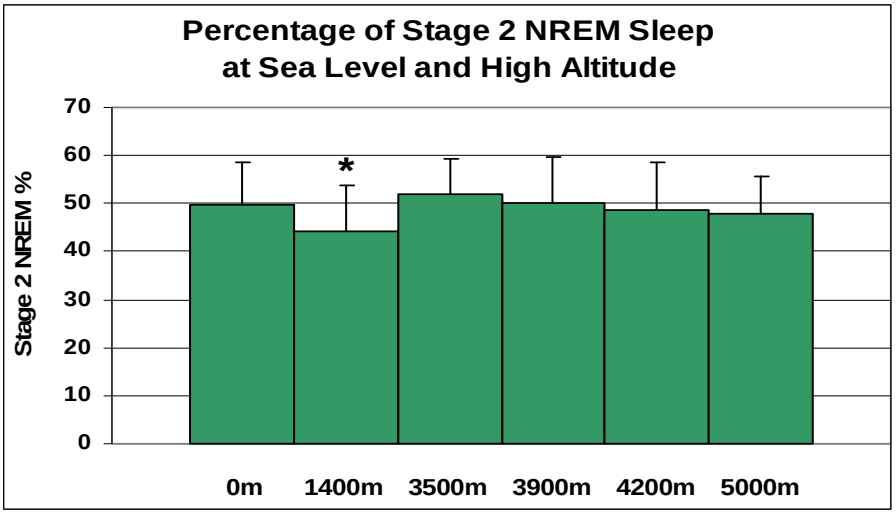
Figure 3.4.5 Duration in minutes of Stage 2 NREM Sleep



The duration of Stage 2 non-rapid eye movement (NREM) sleep was unchanged from sea level except at 1400m, where Stage 2 NREM was highly significantly reduced to only 149 ± 45 minutes ($p < 0.001$). At all other altitudes in Nepal Stage 2 NREM duration was similar to sea level.

The percentage of Stage 2 NREM was not significantly changed at moderate and high altitudes but, as with Stage 2 duration, the percentage of time spent in Stage 2 NREM was reduced at 1400m to 44 ±10% ($p = 0.05$). At sea level Stage 2 NREM percentage was 50 ± 9%, at 3500m 52 ± 7%, at 3900m 50 ± 10%, at 4200m 49 ± 10% and at 5000m 48 ± 8%.

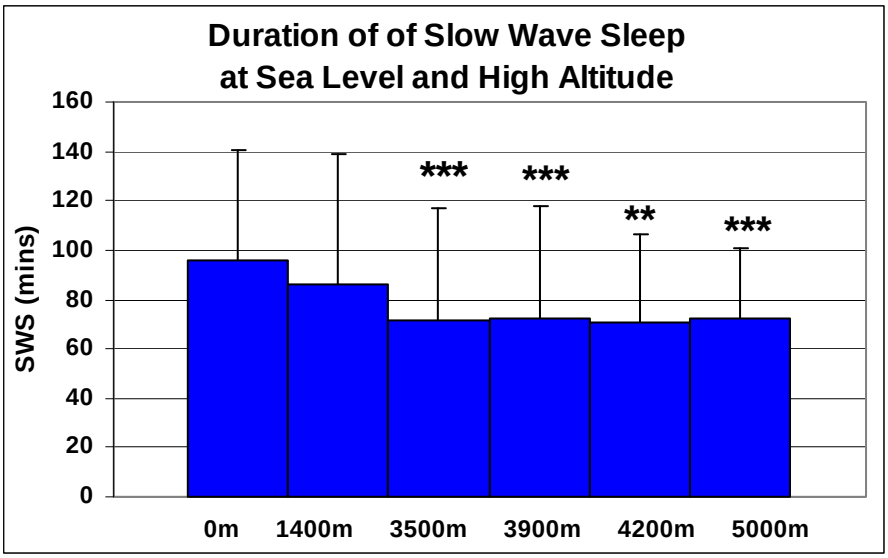
Figure 3.4.6 Percentage of Stage 2 NREM Sleep



The percentage of time spent in Stage 2 NREM sleep was reduced only at 1400m (p = 0.05). At all other altitudes in Nepal Stage 2 percentage was similar to sea level.

Slow wave sleep (SWS), comprising Stage 3 and 4 NREM sleep, decreased as expected with increasing altitude. This was true for both the duration of SWS and its percentage of total sleep. At sea level the duration of SWS was 96 ± 44 minutes and this was significantly decreased at all altitudes of 3500m and higher in Nepal. At 1400m SWS duration was 86 ± 53 minutes (ns), 71 ± 45 minutes at 3500m ($p < 0.001$), 72 ± 45 minutes at 3900m ($p < 0.001$), 70 ± 36 minutes at 4200m ($p = 002$) and 73 ± 28 minutes at 5000m ($p < 0.001$).

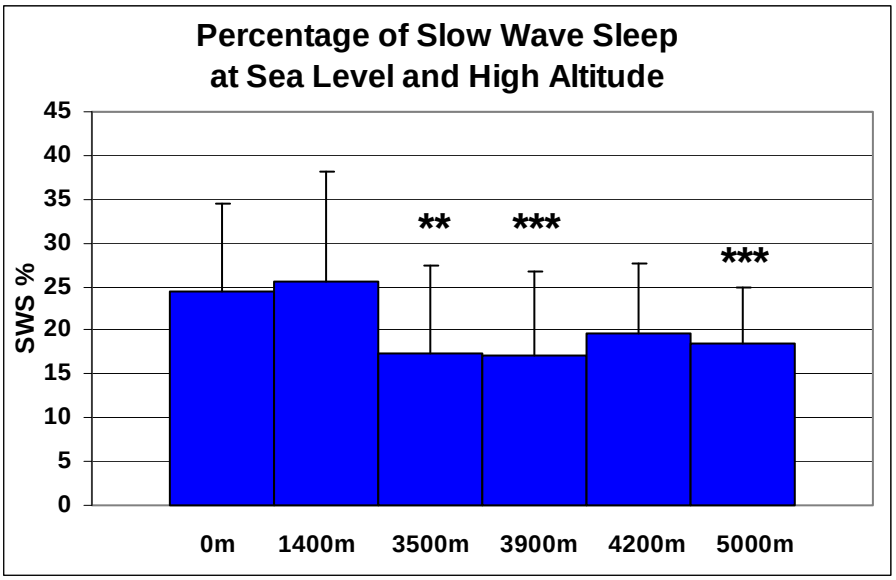
Figure 3.4.7 Duration in minutes of Slow Wave Sleep



Slow wave sleep duration, consisting of Stages 3 and 4 non-rapid eye movement (NREM) sleep was reduced from 3500m and higher, ($p < 0.001$ at 3500m, $p < 0.001$ at 3900m, $p = 0.002$ at 4200m and $p < 0.001$ at 5000m).
This finding is in agreement with most studies into sleep at high altitude

Slow wave sleep percentage at sea level was 24 ± 10% and was unaffected by 1400m, retaining close to the sea level the amount i.e. 26 ± 13%. By the next highest altitude of 3500m however, SWS had begun to be significantly decreased with a percentage of 17 ± 10% ($p = 0.006$), and then to 17 ± 10% at 3900m ($p < 0.001$) and 18 ± 6% at 5000m ($p < 0.001$). Unusually, at 4200m, the second highest altitude, SWS percentage of total sleep was 20 ± 8% which was not a significant reduction.

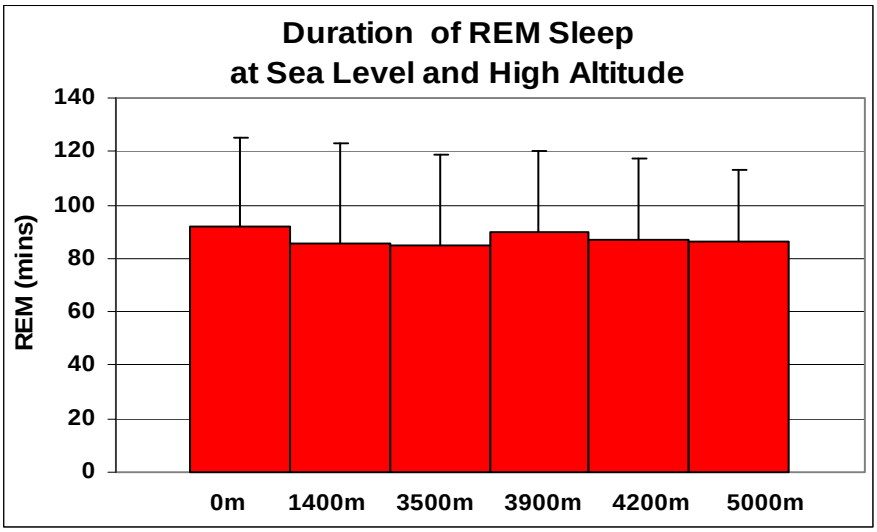
Figure 3.4.8 Percentage of Slow Wave Sleep



The percentage of time spent in slow wave sleep, comprising Stage 3 and 4 NREM sleep, was reduced at 3500m ($p = 0.006$), 3900m ($p < 0.001$) and 5000m ($p < 0.001$).

Rapid eye movement (REM) sleep was unaffected by increasing altitude. Sea level duration of REM sleep was 92 ± 33 minutes was maintained near this amount at 1400m with 86 ± 38 minutes, at 3500m with 85 ± 34 minutes, at 3900m with 90 ± 31 minutes and at 4200m with 87 ± 34 minutes, and 86 ± 27 minutes at 5000m ($p > 0.4$ for all altitudes).

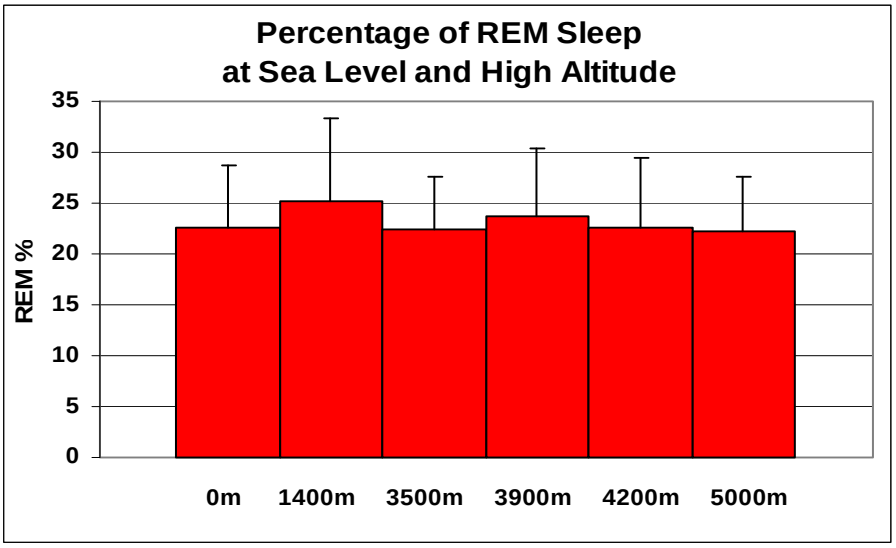
Figure 3.4.9 Duration in minutes of REM Sleep



The duration of rapid eye movement (REM) sleep was not affected by high altitude, remaining similar to sea level values throughout the trek.

REM sleep percentage at sea level was 23 ± 6% and this percentage was maintained very close to this amount at all altitudes: 25 ± 8% at 1400m, 22 ± 5% at 3500m, 24 ± 7% at 3900m, 23 ± 7% at 4200m and 22 ± 5% at 5000m ($p > 0.1$ for all altitudes).

Figure 3.4.10. Percentage of REM Sleep.



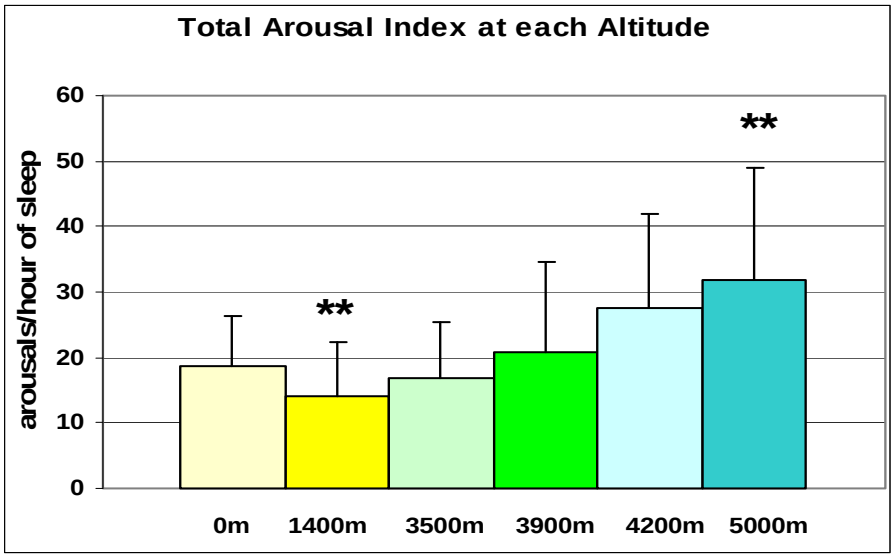
The percentage of sleep time spent in rapid eye movement (REM) sleep was not affected by high altitude, remaining similar to sea level values throughout the trek.

3.4.5 Arousal Indices

There were changes in the dominant type of arousal that occurred as altitude increased during the trek (Figures 3.4.11 – 3.4.16). This was expected, as periodic breathing and central respiratory events in REM sleep became prevalent as the trek reached higher altitudes. However, the total arousal index (AI) was not significantly increased until the highest altitude and the spontaneous arousal index was significantly decreased at the three highest altitudes. Periodic breathing and central REM events were the major contributors to the increased total arousal index. Surprisingly, arousals due to upper airway obstruction decreased significantly from 3500m, this was an unexpected phenomenon, with the subjects who had a minor degree of upper airway obstruction at sea level and 1400m having almost complete resolution of these respiratory events and of course, the arousals that were associated with them.

At 1400m the total arousal index was decreased significantly and at 5000m, increased significantly. However, at all other altitudes the total AI was unchanged; at sea level the total AI was 19 ± 8/hour, at 1400m it was 14 ± 8/hour (p = 0.001), at 3500m 17 ± 9/hour, at 3900m, 20 ± 14/hour and at 4200m 26 ± 14/hour. As the highest altitude was reached a significant increase in the total AI occurred with 29 ± 17/hour at 5000m (p = 0.004).

Figure 3.4.11 Total Arousal Indices



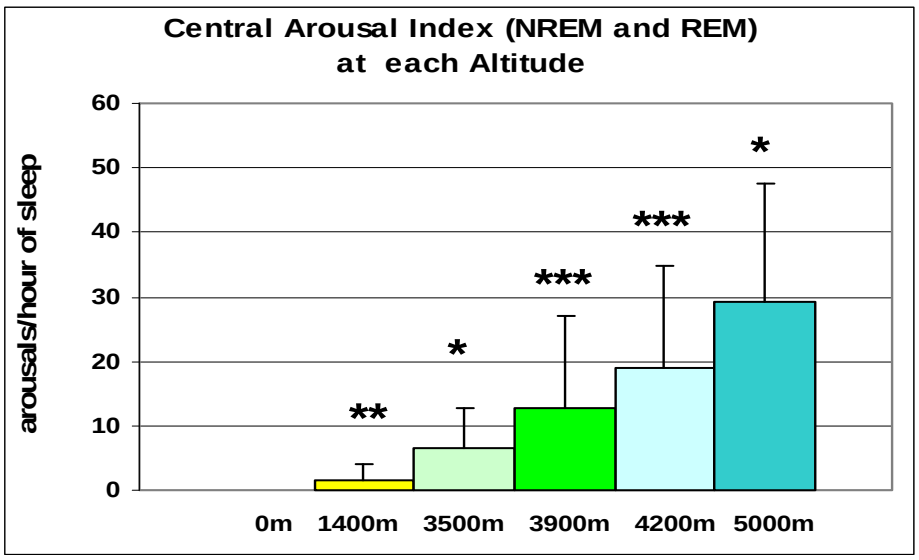
The total arousal index was significantly decreased at 1400m (p = 0.001) and significantly increased at 5000m (p = 0.004).
At all other altitudes during the trek total arousal index was similar to sea level.

This increased total AI was due to the increasing arousals of periodic breathing in NREM sleep and central respiratory events in REM sleep. Not surprisingly, at sea level there was no periodic breathing in NREM sleep in any subject but three subjects had between three and five central apneas in REM sleep which translated into a mean central AI (sleep) for the group of nineteen subjects of 0.05 ± 0.2. Periodic breathing

and central REM events were evident to a minor degree at the lowest altitude of 1400m with a mean central AI of 1.5 ± 3/hour. This was almost entirely due to the presence of NREM sleep periodic breathing in two subjects (#11 and # 15) who had central AI of 28 /hour and 15/hour. Seven subjects had central events in REM sleep at 1400m ranging from 5 – 11/hour, one of whom (#11) also had the highest NREM PB AI. Despite these low levels of central arousals at 1400m it was significantly increased from sea level ($p = 0.01$). Central arousals dominated from 1400m onwards with a mean central AI at 1400m of 2 ± 3/hour ($p = 0.007$), 6 ± 6/hour ($p = 0.01$) at 3500m, 12 ± 14/hour at 3900m ($p<0.001$), 17 ± 16/hour at 4200m ($p<0.001$) and 21 ± 18/hour at 5000m ($p = 0.01$).

There was a wide variation in the amount of central respiratory events and their associated arousals within the group. Some subjects had central AIs over 30/hour at several altitudes while others had AIs below 10/hour or below 5/hour.

Figure 3.4.12 Central Arousal Indices

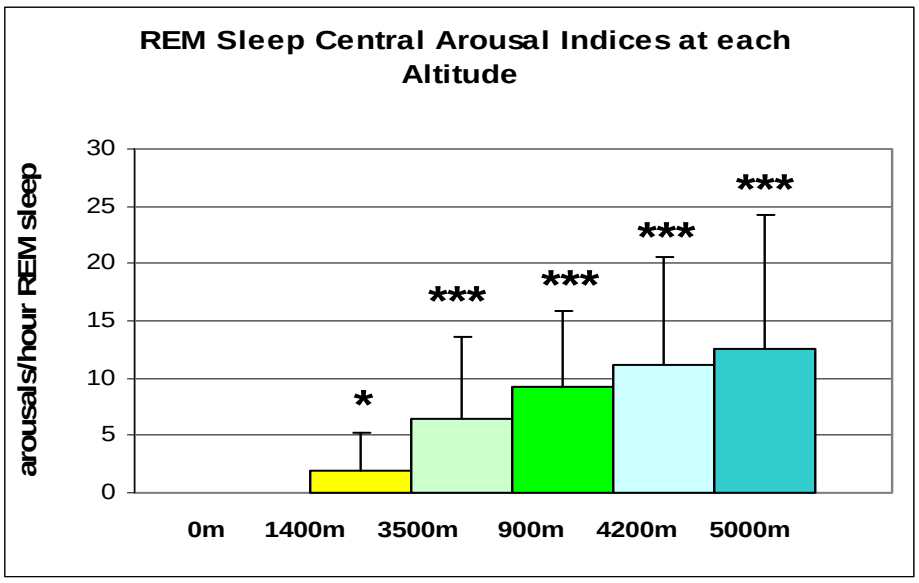


Arousals due to periodic breathing and REM sleep central respiratory events increased, as expected, with increasing altitude during the trek.
The central arousal index was significantly increased at 1400m ($p = 0.01$), at 3500m ($p = 0.007$), at 3900m ($p < 0.001$), at 4200m ($p < 0.001$) and at 5000m ($p = 0.01$).

The central arousal indices were a combination of periodic breathing, which occurred predominantly in NREM sleep, and central apneas and hypopneas that occurred in REM sleep.

The central REM AI at sea level was 0.05 ± 0.2/hour but was significantly increased even at the lowest altitude of 1400m i.e. 2 ± 3/hour ($p = 0.001$). From 3500m onwards the REM central AI was highly significantly increased ($p < 0.001$): 6 ± 6/hour at 3500m, 12 ± 14/hour at 3900m, 17 ± 16/hour at 4200m and 21 ± 18/hour at 5000m

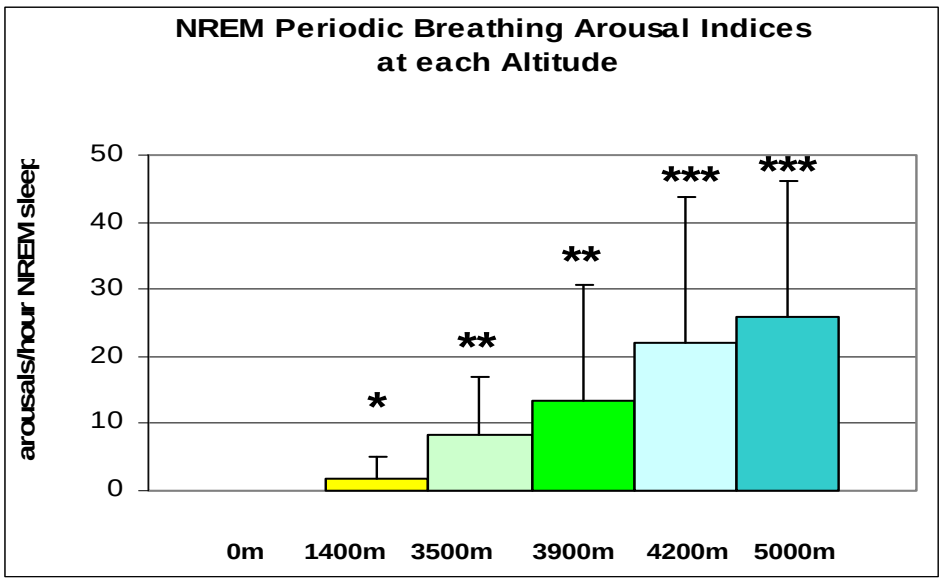
Figure 3.4.13 Central REM Sleep Arousal Indices



Arousals due to central apneas and hypopneas in REM sleep were increased, as expected, with increasing altitude during the trek.
The REM sleep central arousal index was significantly increased at 1400m ($p = 0.001$), and highly significantly increased at 3500m, 3900m, 4200m and 5000m ($p < 0.001$).

Arousals due to periodic breathing in NREM sleep were significantly increased from the lowest altitude if 1400m, with the AI increased to 2 ± 3/hour ($p = 0.01$). From 3500m this was highly significantly increased ($p < 0.001$) to 8 ± 9/hour at 3500m, 13 ± 17/hour at 3900m, 22 ± 22/hour at 4200m and 26 ± 20/hour at 5000m.

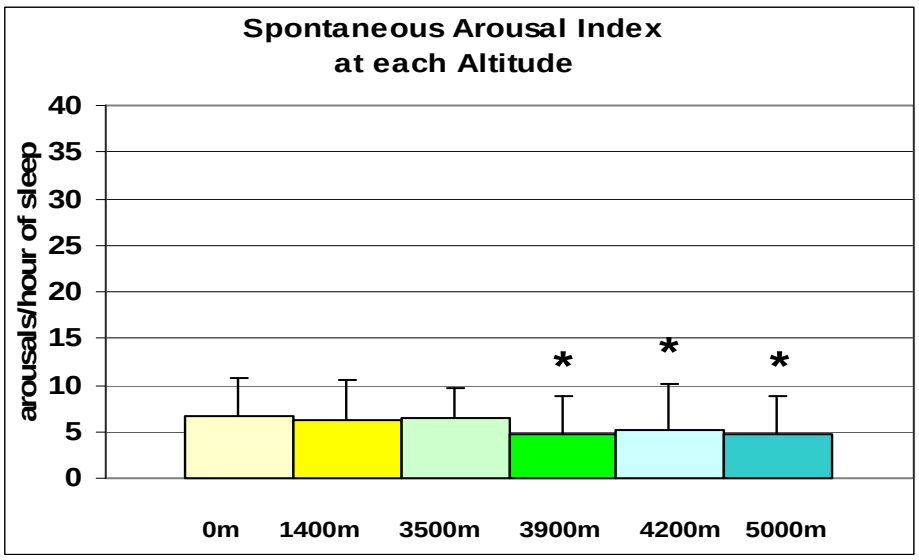
Figure 3.4.14 Periodic Breathing (NREM Sleep) Arousal Indices



Arousals due to periodic breathing (PB) in non-rapid eye movement (NREM) sleep were increased, as expected, with increasing altitude during the trek.
There was no periodic breathing in NREM in any subject at sea level but, from 1400m onwards, arousals due to PB increased significantly: $p = 0.01$ at 1400m and $p < 0.001$ at 3500m and higher.

Those arousals for which an associated event could not be determined, and deemed spontaneous arousals, were decreased at the three highest altitudes. The sea level value for the spontaneous AI was 7 ± 4/hour and at 1400m 6 ± 4/hour , 6 ± 3/hour at 3500, 5 ± 4/hour at 3900m ($p = 0.04$), 5 ± 5/hour at 4200m ($p = 0.02$) and 4 ± 4/hour at 5000m ($p = 0.03$).

Figure 3.4.15 Spontaneous Arousal Indices

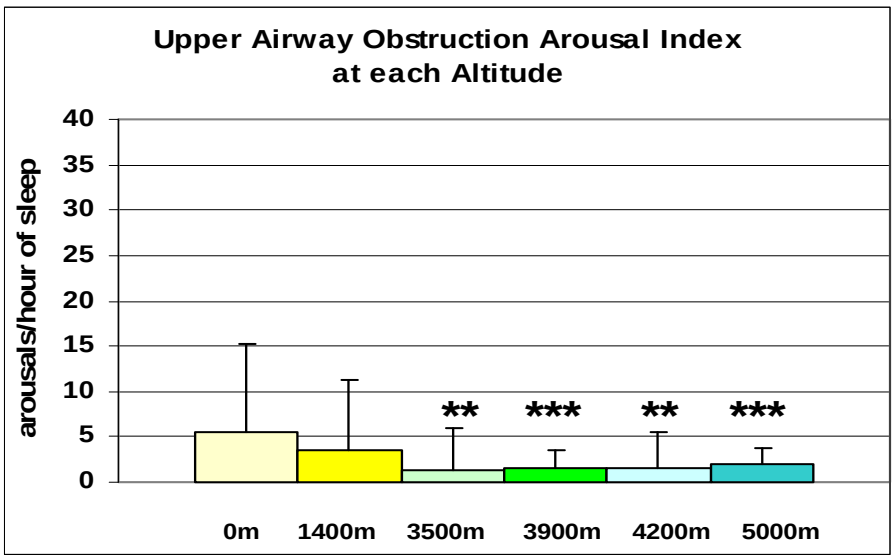


Arousals for which a cause could not be determined were called spontaneous Arousals and these were reduced at the three highest altitudes: p = 0.04 at 3900m, p = 0.02 at 4200m and p = 0.03 at 5000m.

The decreased incidence of obstructive apneas and hypopneas in the group as altitude increased translated into significantly decreased arousals associated with these events. The obstructive AI was attributable at sea level to seven subjects (#3-5, #8, #11, #13, and #14) who had a minor degree of upper airway obstruction at sea level with obstructive AI ≥ 10/hour; a further seven subjects (#1-2, #9-10, #15-16 and # 19) had obstructive AI from 6-9/hour. In these subjects very little upper airway obstruction persisted past 3500m.

The obstructive AI at sea level was 11 ± 10/hour, at 1400m 6 ± 8/hour but as altitude increased this was significantly reduced. At 3500m the obstructive AI was 4 ± 5/hour (p = 0.007), 3 ± 4/hour at 3900m (p = 0.001), 4 ± 5/hour at 4200m (p = 0.006) and 2 ± 2/hour at 5000m (pm = 0.003).

Figure 3.4.16 Upper Airway Obstruction Arousal Indices.

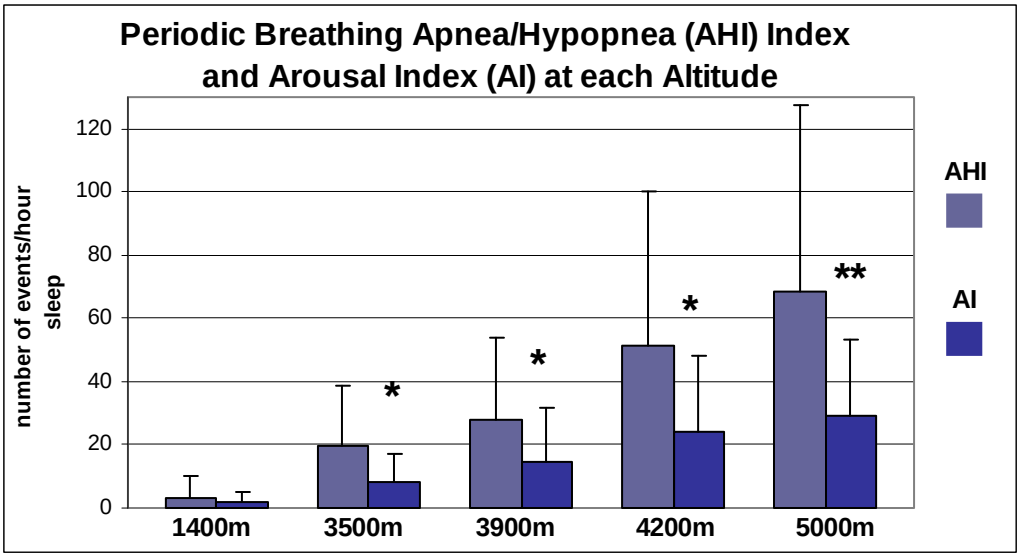


Arousals due to upper airway obstruction were significantly decreased from 3500m. At sea level several subjects had a mild degree of upper airway obstruction during sleep but this virtually resolved with increased altitude: 3500m p = 0.007, 3900m p = 0.001, 4200m p = 0.006 and 5000m p = 0.003.

3.4.6 Periodic Breathing Apnea/Hypopnea Arousal Indices in each Sleep Stage at 3500m and 5000m

Arousals due to periodic breathing (PB) in NREM sleep and central apneas and hypopneas in REM sleep increased as altitude increased (see Chapter 4) but fewer than half the PB apneas and hypopneas and the central REM apneas/hypopneas resulted in arousal from sleep. This represented significant differences between the PB apnea/hypopnea indices (AHI) and PB arousal indices (AI): at 3500m the PB AI was 9 ± 9/hour and the PB AHI 20 ± 19/hour (p = 0.01), at 3900m the PB AI was 14 ± 17/hour and the PB AHI 28 ± 26/hour (p = 0.03), at 4200m the PB AI was 24 ± 24/hour and the PB AHI 52 ± 49/hour (p = 0.02) and at 5000m the PB AI was 29 ± 27/hour and the PB AHI 74 ± 62/hour (p = 0.008).

Figure 3.4.17 Relationship between Periodic Breathing Apnea/hypopnea Index (AHI) and the Periodic Breathing Arousal Index (AI).

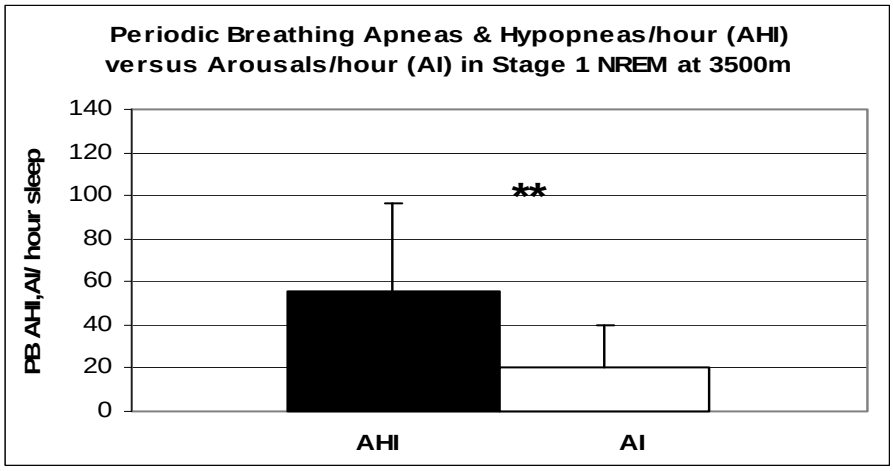


The number of central apneas and hypopneas (periodic breathing) increased with increasing altitude but fewer than half these respiratory events were associated with arousal from sleep.
The periodic breathing apnea/hypopnea index was significantly higher than the periodic breathing arousal index at all altitudes from 3500m and higher, $p \leq 0.01$

As altitude increased, the number of arousals following periodic breathing events (apneas and hypopneas) in NREM sleep and REM sleep central apneas/hypopneas were decreased in all but Stage 1 NREM sleep. Stages 1 and 2 NREM were more disrupted by PB as altitude increased than Stages 3 and 4 NREM or REM sleep.

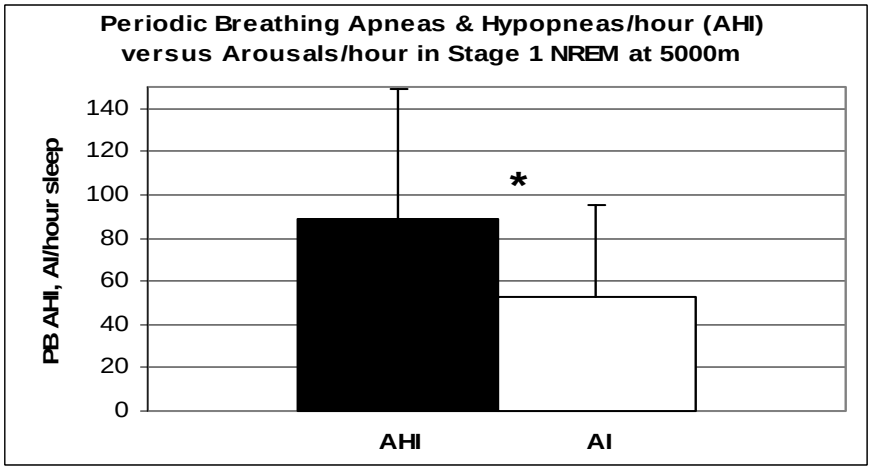
In Stage 1 NREM sleep at 3500m (Figure 3.4.18) the PB apnea/hypopnea index (AHI) was 56/hour and the PB arousal index (AI) was 21/hour. Thus, only 37% of apneas/hypopneas resulted in arousal. At 5000m (Figure 3.4.19) in Stage 1 the PB AHI was 89/hour and the PB AI 53/hour i.e. 59% of apneas/hypopneas resulted in arousal.

Figure 3.4.18 Stage 1 NREM periodic breathing and associated arousal at 3500m



In Stage 1 non-rapid eye movement (NREM) sleep at 3500m, 37% of periodic breathing events resulted in arousal from sleep.

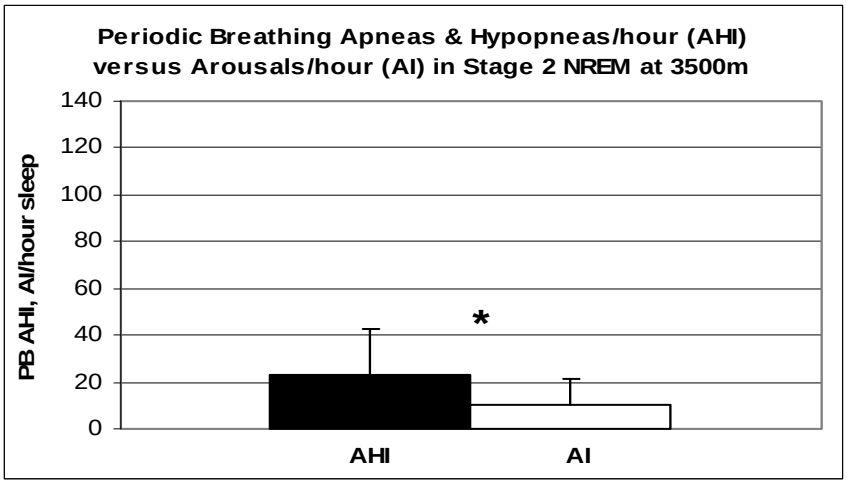
Figure 3.4.19 Stage 1 NREM periodic breathing and associated arousal at 5000m



Stage 1 non-rapid eye movement (NREM) sleep at 5000m, 59% of periodic breathing events resulted in arousal from sleep.

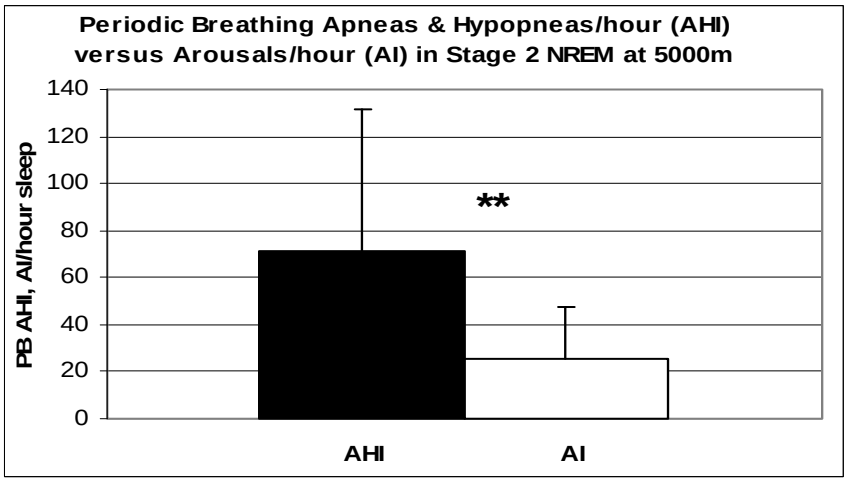
In Stage 2 NREM at 3500m (Figure 3.4.20) the PB AHI was 23/hour and the PB AI 11/hour i.e. 45% of apneas and hypopneas resulted in arousal. At 5000m in Stage 2 (Figure 3.4.21).the PB AHI was 71/hour and the PB AI 26/hour i.e. 36% of apneas/hypopneas resulted in arousal.

Figure 3.4.20 Stage 2 NREM periodic breathing and associated arousal at 3500m



In Stage 2 non-rapid eye movement (NREM) sleep at 3500m 45% of periodic breathing events resulted in arousal from sleep.

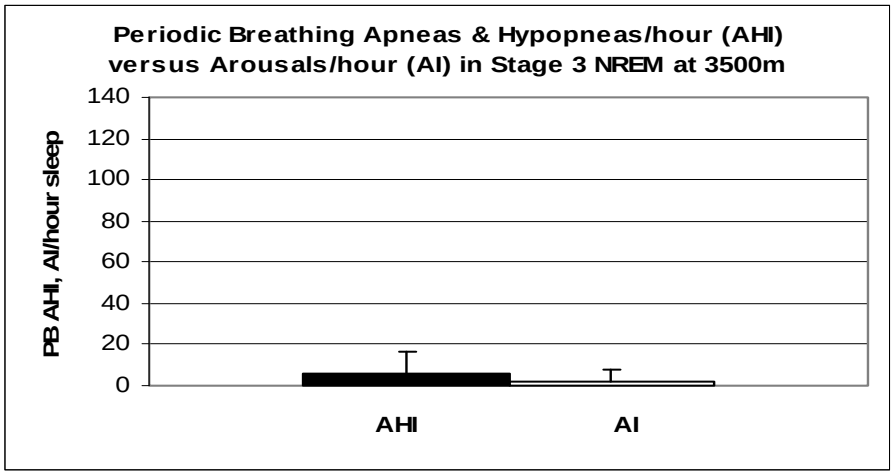
Figure 3.4.21 Stage 2 NREM periodic breathing and associated arousal at 5000m



In Stage 2 non-rapid eye movement (NREM) sleep at 5000m, 36% of periodic breathing events resulted in arousal from sleep.

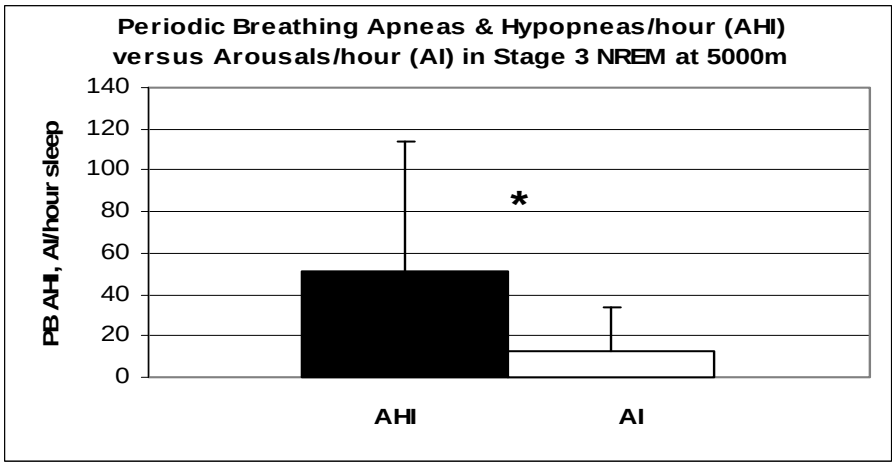
In Stage 3 NREM at 3500m (Figure 3.4.22) the PB AHI was 6/hour and the PB AI 2/hour i.e. 34% of apneas/hypopneas resulted in arousal. At 5000m in Stage 3 (Figure 3.4.23) the PB AHI was 51/hour and the PB AI 13/hour i.e. 25% of apneas/hypopneas resulted in arousal.

Figure 3.4.22 Stage 3 NREM periodic breathing and associated arousal at 3500m



In Stage 3 non-rapid eye movement (NREM) sleep at 3500m, 34% of periodic breathing events resulted in arousal from sleep.

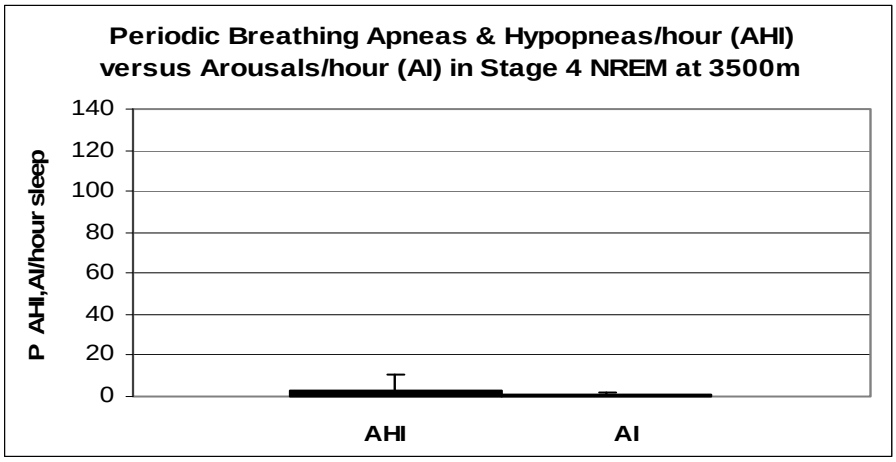
Figure 3.4.23 Stage 3 NREM periodic breathing and associated arousal at 5000m



In Stage 3 non-rapid eye movement (NREM) sleep at 5000m, 25% of periodic breathing events resulted in arousal from sleep.

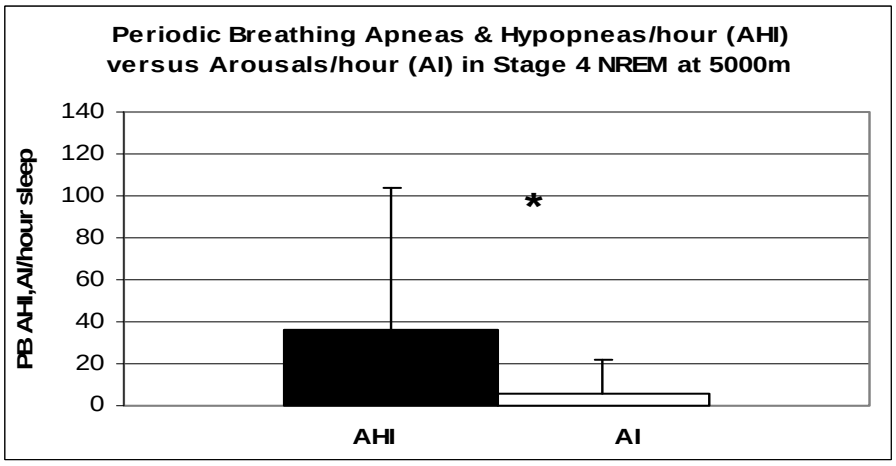
In Stage 4 NREM at 3500m (Figure 3.4.24) the PB AHI was 3/hour and the PB AI 0.5/hour i.e. 15% of apneas/hypopneas resulted in arousal. At 5000m in Stage 4 (Figure 3.4.25) the PB AHI was 36/hour and the PB AI 6/hour i.e. 15% of apneas/hypopneas resulted in arousal.

Figure 3.4.24 Stage 4 NREM periodic breathing and associated arousal at 3500m



In Stage 4 non-rapid eye movement (NREM) sleep at 3500m, 15% of periodic breathing events resulted in arousal from sleep.

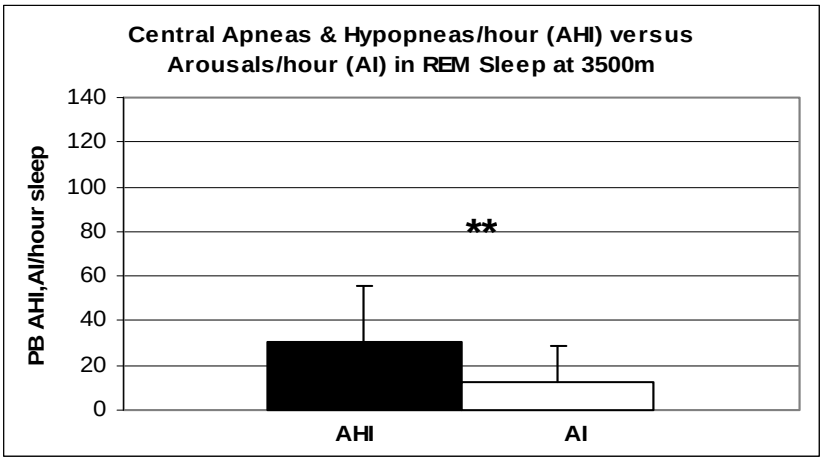
Figure 3.4.25. Stage 4 NREM periodic breathing and associated arousal at 5000m



In Stage 4 non-rapid eye movement (NREM) sleep at 5000m, 15% of periodic breathing events resulted in arousal from sleep.

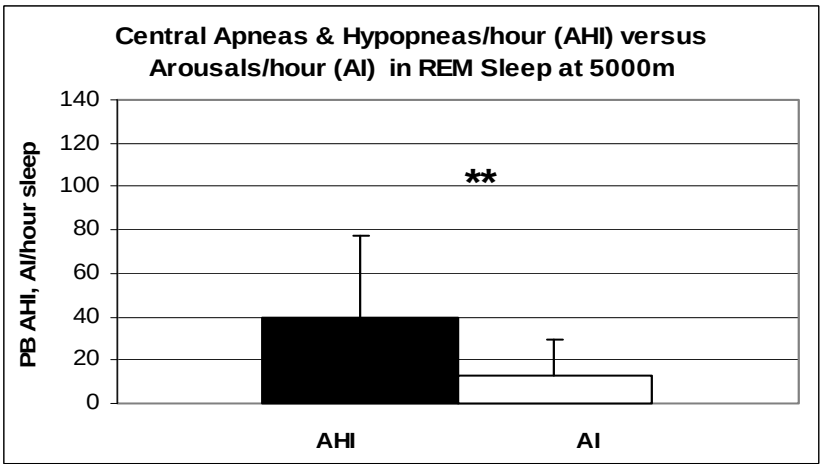
In REM sleep at 3500m (Figure 3.4.26) the central AHI was 31/hour and the central AI 12/hour i.e. 41% of apneas/hypopneas resulted in arousal. At 5000m in REM sleep (Figure 3.4.27) the central AHI was 40/hour and the central AI 13/hour i.e. 33% of apneas/hypopneas resulted in arousal.

Figure 3.4.26 Central apneas and hypopneas in REM sleep and associated arousal at 3500m



In rapid eye movement (REM) sleep at 3500m, 41% of periodic breathing events resulted in arousal from sleep.

Figure 3.4.27 Central apneas and hypopneas in REM sleep and associated arousal at 5000m



In rapid eye movement (REM) sleep at 5000m, 33% of periodic breathing events resulted in arousal from sleep.

Thus as sleep became deeper (Stages 3 and 4 NREM) fewer central events resulted in arousal from sleep. Arousal resulted more frequently when the central events occurred in Stages 1 and 2 NREM and in REM sleep, but in most cases fewer than half were associated with arousal from sleep.

3.5 Discussion

The most important finding of this research was that most sleep parameters were largely unaffected by high altitude. Total sleep time, sleep efficiency, Stage 2 NREM and REM sleep all retained near normal amounts. Slow wave sleep was reduced at 3500m and higher, apparently replaced by Stage 1 sleep. The most consistent and significant change to sleep architecture was in Stage 1 NREM sleep, which was increased at each altitude of 3500m and higher ($p < 0.001$). Both the duration of Stage 1 NREM sleep and the percentage of total sleep time that it occupied increased at 3500m and remained at a much higher level than normal for each of the next three altitudes. As the lightest sleep stage, Stage 1, increased slow wave sleep decreased with significant reductions in duration and percentage at all altitudes of 3500m and higher. Stage 2 and total sleep time were reduced only at the lowest altitude of 1400m, and REM sleep was unaffected by altitude, maintaining near normal durations and percentages at every altitude in Nepal.

The total arousal index (AI) was increased significantly only at the highest altitude and the main contributor to this increased total AI was the increased number of arousals due to periodic breathing, which occurred mainly in NREM sleep, and the central events in REM sleep. The spontaneous AI did not contribute to the increased total AI as spontaneous arousals were decreased at the three highest altitudes. A surprising finding was that arousals due to upper airway obstruction were significantly decreased from even the lowest altitude of 1400m.

This research was conducted under field conditions in the Nepal Himalaya and there were several sleep studies that failed to record, others that had too few hours of sleep

recorded to allow their use in the analysis and, at one altitude in particular, five sleep studies failed to record the oxygen saturation. Most of these losses of data were due to the failure of the batteries in the recording devices. Electricity availability was unreliable at two altitudes in the first two treks; batteries failed to fully charge and therefore recordings were incomplete. There was also illness in many of the subjects; most subjects suffered from one or more of the following: upper respiratory tract infection, gastroenteritis or acute mountain sickness, with one subject developing pneumonia at 3900m and another suffering from severe acute mountain sickness from 3900m onwards.

These problems made the data collection difficult at times, particularly when illness affected the investigators as well as the subjects. Cognitive function deteriorates with increasing altitude (Tune 1964; Denison et al, 1966; McFarland 1969; Fowler et al., 1982; Townes et al, 1984; Cavaletti et al, 1987; Fowler and Porlier 1987; Regard et al, 1989) and problem solving or troubleshooting faulty equipment became more challenging as the trek ascended. Nevertheless, eighty two sleep studies from the Nepal data collection were usable and, although a full data set would have been preferred, we think that this is a large enough number of studies to ensure meaningful outcomes for the research.

Our findings that Stage 1 NREM sleep is increased with increasing altitude is in agreement with all previous findings but most studies have reported a marked reduction in, or even absence of slow wave sleep following acute exposure, but returning to near normal after three to four weeks at high altitude. We found that slow wave sleep persisted at high altitude, with all subjects maintaining some SWS, but it

was significantly reduced from 3500m. Differences in our findings and those of previous studies are most likely due to the differing protocols. Most investigations of high altitude sleep have been performed on subjects who have been acutely exposed to high altitude whereas in our research sleep studies were performed on either the first or second night of exposure to each new, higher altitude after the subjects had spent many hours trekking to reach that altitude. Our research, therefore investigated the effects on sleep of acute exposure to a series of ascending altitudes with 4-8 hours of vigorous exercise between each new altitude. The subjects trekked over rough paths and, as altitude increased, the degree of difficulty of the trekking increased proportionally to increasing hypobaric hypoxia.

One other study (Salvaggio et al, 1998) had a similar protocol to ours in that the five subjects trekked from 2800m to 5000m over six days in the Nepal Himalaya. However, in this group of five trekkers, SWS was absent in four subjects in the first week at 5000m. This discrepancy between the two studies is perhaps best explained by the length of time the subjects took to reach 5000m. Salvaggio's group trekked to 5000m in half the time that was taken by our group. Therefore the discrepancy between the two groups is most likely due to the rapid ascent undertaken by Salvaggio's group.

The effects of acute exercise on sleep architecture have been found in some studies to be small increases in total sleep time, Stage 2 NREM and slow wave sleep and small reductions in REM sleep [109-111]. We suspect that exercise did not have a major effect on the sleep architecture in our subjects, particularly as there were no significant differences in the sleep architecture of those studied on the first night at the new

altitude (after a day's trekking) and those studied on the second night following a day with only incidental exercise.

The underlying physiological change of high altitude is hypobaric hypoxia, but this is known to be a poor stimulus to arousal. Studies in humans have found that hypoxia failed to cause arousal (Berthon-Jones and Sullivan 1982 and 1984) in subjects with oxyhemoglobin saturations as low as 80%. In our study the mean and minimum oxyhemoglobin levels during sleep were near or below 80% in most of our subjects during sleep at altitudes higher than 3900m. A number of experimental studies in rats subjected to sustained hypoxia have shown major disruption of normal sleep patterns with a particular reduction of REM sleep (Megirian et al, 1980; Ryan et al, 1983; Ryan and Megirian, 1982; Pappenheimer, 1984). We did not find this effect on REM sleep but our findings of increased Stage 1 and reduced slow wave sleep were similar. The obvious mechanism for reducing sleep times is hypoxia. There are at least two different mechanisms that could underly this effect. The first is the induction of arousal by carotid chemoreceptor afferents. Acute animal experiments show that hypoxia induces arousal from NREM sleep at higher saturation levels than in REM sleep (Phillipson et al., 1978). Thus, animals can stay in REM sleep without arousal at lower levels of arterial oxyhemoglobin saturation than they can in NREM sleep. This could be the explanation for the clear reduction of SWS at the two highest altitudes in our study, but more subtle change in REM sleep. However, the hypothesis that the sleep structure is changed by hypoxia induced arousals is not easily supported by our findings. Subjects seemed to maintain contiguous epochs of sleep even when there was periodic breathing and more importantly, there was no clear relationship between the occurrence of periodic breathing and the reduction of SWS. Thus, the

reduction in SWS occurred in subjects independently of the occurrence of periodic breathing, despite the fact that periodic breathing did cause an increase in the total number of arousals (see Chapter 4).

Stage 1 NREM sleep is the lightest sleep stage and normally contributes less than 5% of total sleep time. This finding of increased Stage 1 sleep is consistent with all other findings in research into sleep at high altitude. Increased Stage 1 NREM is thought to contribute to complaints of poor sleep quality by those who travel to high altitude locations because Stage 1 NREM sleep is the lightest sleep stage, and is also called "transitional sleep" to indicate that it is not quite sleep but rather a drowsy wakefulness.

The increase in Stage 1 sleep is most likely due to the large number of arousals that occur in this sleep stage with increasing altitude. In Stage 1 sleep at 3500m the percentage of periodic breathing events that were associated with arousal from sleep was 37% but by the time 5000m was reached 59% of the periodic breathing events caused arousal. Thus it appears that the increased amounts of Stage 1 NREM sleep are directly linked to the increasing frequency of arousals that occur in this sleep stage. Sleep was not able to deepen into Stages 2, 3 and 4 due to the repetitive brief awakenings that occurred in Stage 1 NREM sleep.

In patients with the obstructive sleep apnea syndrome (OSAS), sleep fragmentation results from the repetitive upper airway obstructions (Sullivan and Issa 1985) and this fragmentation appears to affect sleep architecture in a similar way as the sleep fragmentation present in high altitude newcomers. Slow wave sleep is reduced in

patients with OSAS; the mechanism of this reduction in SWS is not known but it is thought that the repetitive arousals from sleep prevent the consolidation of sleep with resulting increase in Stage 1 NREM sleep and reduction in Stage 3 and 4 NREM sleep. In our study arousals were much more common in Stage 1 due to the more frequent central apneas and hypopneas of periodic breathing e.g. at 5000m the arousal index due to periodic breathing was 86/hour in Stage 1while in slow wave sleep the PB AI was less than half this amount. At 3500m, in Stage 1, arousals due to PB were frequent i.e. ~60/hour but were fewer than 5/hour at the same altitude in SWS. Thus, with increasing altitude slow wave sleep becomes more disrupted by periodic breathing; as the arousal index increases the amount of slow wave sleep decreases. As altitude increased SWS was decreased while Stage 1 sleep increased; this change in the lightest and deepest stages of NREM sleep appear to be directly linked to increasing arousals due to periodic breathing.

Increased arousals also occurred in Stage 2 NREM and in REM sleep as altitude increased but did not appear to be similarly related to decreased amounts of these sleep stages.

Although our studies showed a clear effect of altitude on sleep architecture, with the most obvious effect being increased Stage 1 NREM sleep, the studies of Ryan and Megirian, (1982 and 1983) of hypoxia on sleep in rats showed a proportionately larger effect of hypoxia. There was a major reduction of REM. Because of this animal data, we had thought we would see a much larger effect of high altitude on sleep structure. However, in their study of hypoxia in the sleep of rats, lower levels of oxyhemoglobin saturation levels were reached as the rats breathed 10% oxygen. It is also likely that

acclimatisation to the high altitude that occurs during the time of the trek would have had a role in potentially reducing the effects of hypoxia. More recent data have suggested that the impact of hypoxia on sleep architecture may be mediated through changes in CO_2 levels. Lovering et al (2003), have shown in a cat model that changes in sleep architecture, and specifically reductions in REM sleep, that are associated with hypoxia are absent when supplemental CO_2 is given to reverse hypoxia-driven hypocapnia; in this study hypocapnia also reduced REM sleep in normoxic conditions. Lovering also suggests that hypocapnia, rather than hypoxia, is responsible for the increased sleep fragmentation that occurs with increasing altitude.

Hypocapnia causes increased/more alkaline pH, which may affect sleep, but there are no data available. The administration of acetazolamide, a carbonic anhydrase inhibitor, is often used at high altitude to improve sleep quality and reduce periodic breathing (Nicholson et al, 1988; Hackett et al., 1987); it is thought that this effect is due to improved oxygen saturation brought about by respiratory stimulation but acetazolamide also induces a bicarbonate diuresis with resultant metabolic acidosis and it may be this acidification that improves sleep quality.

While there are currently no data available in regards to changes in pH that are specifically associated with sleep at high altitude, it is likely that hypocapnia associated with increments in altitude has been at least partially compensated for by changes in the bicarbonate system by the time subjects underwent sleep studies. Fourteen of our subjects had arterial blood gas analysis at each new altitude and these data demonstrated progressive hypocapnia along with worsening hypoxia as altitude

increased. Alterations in sleep architecture may be the result of hypoxia, hypocapnia or other changes that we did not measure.

Future studies comparing the effects of a rapid ascent to high altitude to this slower change that occurs in real-life trekking would be needed to determine what if any role acclimatisation would have played. The roles played by hypoxia and hypocapnia need further investigation as it appears that hypocapnia is an important disruptive influence on sleep at high altitude. The role of pH, which becomes more alkaline with increased altitude may also have a major role in sleep disruption at high altitude.

Conclusion

This research studied sleep under real-life conditions of trekking to increasing altitudes over ten to eleven days. Our results showed significant changes in sleep architecture; particularly to Stage 1 and slow wave sleep with little change to Stage 2, REM or total sleep time. The magnitude of the effect on sleep at high altitude was far less than would be predicted from experimental studies in animals and likely represents a range of acclimatisations that occur during a slowly progressive increase in altitude.

CHAPTER 4

BREATHING DURING SLEEP AT HIGH ALTITUDE

4.1 Introduction

It has been known for centuries that breathing during sleep at high altitude is abnormal; anecdotal reports of pauses in breathing during sleep and waking, gasping for air, have been commonly reported since man first wrote about ascents to high altitudes by those who normally resided at or near sea level.

Well known reports of periodic breathing at high altitude from the nineteenth century are those of the English physicist Tyndall (1860) a keen alpinist, and Egli-Sinclair (1891) a physician and mountaineer. They reported breathing of the "Stokes character" which was later to be called Cheyne-Stokes breathing after the two Irish physicians who described it in separate publications in 1818 and 1854.

Breathing during sleep at high altitude was first recorded by Angelo Mosso, a professor of physiology at the University of Turin, Italy in 1898 at an altitude of 4559 metres in the Italian Alps. He used a bar that rested on the chest and connected to a smoked cylinder onto which respiratory movement was recorded. Despite this clear recording of periodic breathing Mosso did not think that ventilation was increased at high altitude; he believed, like others at this time, that there was no increase in ventilation and he attributed the reduced alveolar PCO_2 to carbon dioxide being extracted from the blood because of the low barometric pressure at high altitude.

It was to be many years before the cause of periodic breathing was linked to increased ventilation and its resulting hypocapnia.

Douglas and Haldane (1909) conducted simple but ingenious experiments to investigate the control of breathing in relation to pO_2 and pCO_2 (described in detail on pages 69-71 of this thesis). Through voluntary hyperventilation in awake subjects breathing either air or air enriched with oxygen, and the use of soda lime in the breathing circuit, they were able to make conclusions about the mechanism of periodic breathing and the interplay of pO_2 and pCO_2.

Since these early experiments by Douglas and Haldane, others have examined breathing under conditions of hypoxia during sleep (Berssenbrugge et al, 1983 & 1984; Reite et al, 1975; Miller and Horvath, 1977; Normand et al, 1990; Salvaggio et al, 1998 and others) either in simulated or actual high altitude. It has been confirmed that periodic breathing is very common during sleep at high altitude, but not ubiquitous.

The cause of periodic breathing during sleep at high altitude is hyperventilation-induced hypocapnia (West et al, 1986; Ghazanshahi and Khoo, 1993). As altitude increases barometric pressure falls, inducing hypobaric hypoxia. The physiological response to hypoxia is hyperventilation, mediated by the peripheral chemoreceptors, which optimises the available oxygen and aims to maintain the arterial oxygen levels as close to normal as possible. A side effect of this hypobaric hypoxia induced hyperventilation is hypocapnia. During sleep the arterial carbon dioxide level falls to

below the apneic threshold (Skatrud and Dempsey 1983, Dempsey et al. 2004) i.e. the stimulation to breathe is lost due to higher pH in the area of the central chemoreceptor. During this centrally mediated apnea arterial oxygen level falls, CO_2 levels rise and pH falls thus stimulating a return to ventilation. However, breathing restarts in several large breaths which have the effect of again driving the CO_2 to below the apnea threshold; thus the cycle is repeated.

Loop gain theory has been used to explain periodic breathing (Khoo et al, 1982). According to this theory, two factors are necessary for self sustained oscillatory behaviour in a control system, such as that which controls breathing. In such a system a "disturbance", e.g. a change in alveolar ventilation due to a factor such as a sigh or change in body position is followed by a "corrective action" which tends to suppress the disturbance. In the case of a sigh, alveolar ventilation is increased and the corrective action is a lowering of the pCO_2 which tends to reduce ventilation by its action on the chemoreceptors; this constitutes negative feedback. In order for oscillatory behaviour to be sustained the first requirement is that the magnitude of the corrective action must exceed the original disturbance. The ratio of the magnitude of the disturbance in relation to the magnitude of the corrective action is known as loop gain. The second requirement needed for sustained oscillatory behaviour is that the corrective action be presented 180º out of phase with the disturbance, so that what would otherwise inhibit ventilation now augments it. This sustained oscillatory behaviour occurs when the loop gain exceeds unity at a phase difference of 180º. Loop gain theory predicts that the higher the loop gain, the more likely it is that periodic breathing will occur. Hypobaric hypoxia, present at high altitude, increases

the loop gain through its action on the chemoreceptors. Predicting who will develop periodic breathing should thus be a simple matter of testing each individual's ventilatory response to hypoxia; the brisker an individual's response to hypoxia the higher the loop gain and the more likely it is that the individual will develop periodic breathing at high altitude.

Studies at high altitude (Lahiri et al, 1983; Severinghaus et al, 1966) have found that high altitude natives have a blunted ventilatory response to hypoxia and do not have periodic breathing during sleep. Another study (Matsuyama et al, 1989) found that there was a significant correlation between the hypoxic and the hypercapnic ventilatory responses measured at sea level and the development of periodic breathing in lowlanders studied at 7170m.

The development of periodic breathing during sleep at high altitude is believed to be more likely in those individuals with steeper ventilatory responses to hypoxia and hypercapnia (Lahiri et al. 1983, White et al.1987, Matsuyama et al. 1989) i.e. individuals with a higher loop gain, and therefore brisker ventilatory responses hypoxia and hypercapnia, are more likely to develop prolonged breathing instability (periodic breathing) during sleep (Khoo et al. 1982).

Periodic breathing is common during sleep at altitudes above 3000m (Reite et al, 1975; Miller and Horvath, 1977; Berssenbrugge et al, 1983 and 1984; Finnegan et al, 1984; Selvamurthy et al, 1986; Nicholson et al, 1988; Goldenberg, 1988; Normand et al, 1990; Anholm et al, 1992; Mizuno et al, 1993; Salvaggio et al, 1998; Zielinski et al, 2000; Mizuno et al, 2005) but not everyone develops periodic breathing (PB). It is

believed by some high altitude physiologists that an individual's ventilatory response to hypoxia and hypercapnia determines if PB will develop (Lahiri et al, 1983; West et al, 1986; Matsuyama et al, 1989) i.e. those with more marked ventilatory responses to hypoxia will tolerate less hypoxia before arousal from sleep and a return of ventilation. This theory has not been proved. Studies into sleep and breathing at high altitude have found that not all PB apneas result in arousal from sleep despite marked falls in oxygen (Khoo and Berry 1996).

Women are thought to have greater ventilatory responses than men to hypoxia and hypercapnia, due to the effects of ovarian hormones on receptor mediated mechanisms at both the peripheral and central sites (Bayliss et al. 1987, Brodeur et al. 1986, Hannhart et al. 1989, Regensteiner et al. 1989, Tatsumi et al. 1997). Progesterone increases carotid body sensitivity and estradiol raises central nervous system translation of the carotid body signal into increased ventilation (Hannhart et al. 1990, Hannhart et al.1989). Furthermore, estradiol is needed to induce progesterone receptors (Brodeur et al. 1986). Therefore gender may influence ventilatory responses to the hypoxia of high altitude, with men and women developing periodic breathing in differing amounts. The effects of menstrual phase effects on ventilatory responses to hypoxia and hypercapnia have proved difficult to demonstrate, with some studies finding increased HVR during the luteal phase (higher progesterone) compared to the follicular phase (Schoene et al. 1981, Takano 1984, White et al. 1983) and some other studies finding HVR unchanged (Dombovy et al. 1987, Regensteiner et al. 1990, Beidlman et al. 1999). Similarly, studies that made repeated measures of the ventilatory response to hypercapnia (HCVR) throughout the menstrual cycle, also had

differing results i.e. finding that HCVR was increased during the luteal compared to the follicular (Jurkowski et al.1981, Schoene et al. 1981, Dombovy et al. 1987, Dutton et al. 1989, Edwards et al. 1996, Williams and Krahenbuhl 1997) while others found no change (Takano et al. 1981, White et al.1983, Regensteiner et al. 1990, Beidleman et al. 1999, Takano 1988).

It has been suggested that PB helps to keep sleeping oxygen saturation higher during sleep because of the repetitive hyperpneas that follow pauses in breathing (West et al 1986; Ghazanshahi & Khoo 1993) This theory is not supported, however by other studies which found that the sleeping oxygen saturation was not higher during periodic breathing at high altitude (Mizuno et al 1993; Normand et al 1990).

Sleep-induced hypoventilation, which has no detrimental effects on the sleeping SaO_2 in normal, healthy individuals at sea level, has a profound effect at high altitude with the sleeping SaO_2 being considerably lower than awake levels, the severity being proportional to altitude.

This chapter reports the findings from investigations of breathing during sleep in nineteen subjects from sleep studies performed at sea level and at each of the five high altitudes in the Himalaya. This chapter also examines the relationship between ventilatory responses to hypoxia and hypercapnia, measured at sea level, and the development of periodic breathing at high altitude.

4.2 Hypothesis and Aims

Breathing during sleep at high altitude is known to be uneven, with periodic breathing being present in many people. High altitude natives have been found to have a blunted ventilatory response to hypoxia and less periodic breathing than lowlanders who ascend to high altitudes. Loop gain theory predicts that the higher the loop gain the more likely it is that periodic breathing (sustained respiratory oscillation) will occur and that a brisk ventilatory response to hypoxia would predispose towards an increased loop gain.

Ventilatory response to hypoxia and hypercapnia may have an effect on breathing during sleep at high altitude and the development of periodic breathing is thought to be related to a steep hypoxic ventilatory response which would drive increased ventilation and result in low arterial CO2, promoting central apnea with sleep onset.

Women are believed to have steeper ventilatory responses than men due to the effects of ovarian hormones and thus may be more likely to develop periodic breathing at high altitude.

Therefore, the aims of this Chapter were to examine the effects of incremental increases in altitude on breathing during sleep over a period of ten to eleven days' trekking in the Nepal Himalaya. A further aim was to determine the relationship, if any, of breathing during sleep at high altitude and the individual subject's ventilatory

responses to hypoxia and hypercapnia measured at sea level with particular interest in whether gender influenced the development of periodic breathing.

In particular the aims were:

1) to determine the changes in breathing during sleep and the interaction between periodic breathing, sleep stage and arousal from sleep;

2) to determine whether sea level ventilatory responses to hypoxia and hypercapnia affect breathing during sleep, sleeping oxygen saturation and morning arterial blood gases and whether gender affected these developments;

3) to determine whether periodic breathing has an effect on the sleeping oxygen saturation and morning arterial blood gases;

4) to determine whether gender affects the development of periodic breathing during sleep, the sleeping oxygen saturation and morning arterial blood gases; and

5) to determine whether previously reported changes to breathing during sleep at high altitude were present in this large group of subjects.

4.3 Methods

4.3.1 Subjects

Nineteen healthy, non-smoking, sea-level dwelling subjects were recruited from friends and colleagues. There were ten male and nine female subjects aged between twenty and fifty-two years of age (mean 34.1 ± 9 years); the mean body mass index (BMI) was 23.4 ± 2.8 kgs/m^2 (range 17.5 - 27.4kgs/m^2).

All the female subjects were pre-menopausal and none was taking oral contraceptives. Two subjects (#5 and #19) had asthma; one (#5) was taking Flixotide bd and Ventolin prn the other (#19) was taking Ventolin prn. Both asthmatic subjects had been stable for 4-6 months before departure to Nepal and remained free of exacerbations to asthma during the trek.

4.3.2 Ventilatory Response Testing

4.3.2.1 Measurements

Ventilatory response tests were conducted using a computer controlled, closed loop, biased flow circuit as described in Chapter 2. The ventilatory response testing apparatus and the software used to analyse the ventilatory responses were designed by Dr Michael Berthon-Jones. The circuit is comprised of a fixed speed blower (50L/minute), a bypassable soda lime absorber and a six litre flow through bag. The bag was encased within a sealed box connected to a Fleisch no. 3 pneumotachograph which was coupled to a differential pressure transducer (model DP-45 Validyne, Northridge, CA, USA). The subject's end tidal pCO_2 ($P_{ET}CO_2$) was controlled by the computer software, which adjusted the proportion of flow passing through the soda

lime absorber, or added CO_2 from a medical cylinder supply to the circuit, according to the $P_{ET}CO_2$ of the preceding breath. Arterial SaO_2 was lowered rapidly by adding N_2 to the circuit.

Each subject's $P_{ET}CO_2$ was measured at the mouthpiece using an infrared CO_2 analyser (Hewlett-Packard, Waltham, MA, USA). SaO_2 and heart rate were measured using a pulse oximeter with a finger probe, set in fast response mode (model 3700e, Ohmeda, Boulder, CO, USA). The concentration of inspired oxygen (FiO_2) was measured at the mouthpiece by a fast response paramagnetic oxygen analyser (Datex, Helsinki, Finland) and displayed continuously to the operator.

Tidal volume (V_T) inspiratory and expiratory times (Ti and Te respectively), respiratory frequency (Freq) and breath-by-breath minute ventilation (V_I) were calculated from the flow signal produced by the pneumotachograph. Mean values for SaO_2 were calculated and $P_{ET}CO_2$ was measured for each breath. All data were digitally stored and processed using a computer with a 12 bit analog-to-digital converter sampling at 125Hz.

4.3.2.2 Protocol

All ventilatory response tests were conducted in the afternoon, between 13:00 and 16:00 hours. All subjects had abstained from caffeine and other stimulants for the previous 12 hours. Tests were conducted with subjects sitting upright, wearing a nose clip and breathing via a mouthpiece attached to the ventilatory response circuit.

Female subjects were tested during the follicular and again in the luteal phase of their menstrual cycles. Menstrual cycles were confirmed by analysis of venous blood for

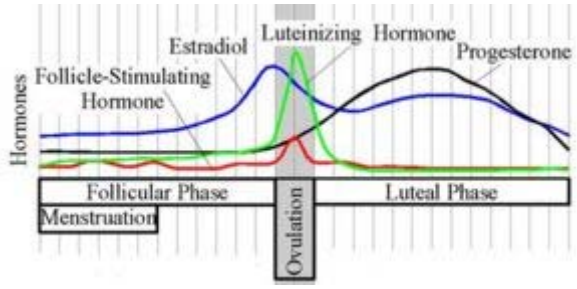
follicle stimulating hormone (FSH), luteinising hormone (LH), oestradiol and progesterone. These blood tests were performed by the Department of Endocrinology at Royal Prince Alfred Hospital, and the Institute of Clinical Pathology and Medical Research at Westmead Hospital. Normal ranges are displayed in Table 4.3.2.2 and the hormonal peaks and troughs of each hormone across the menstrual cycle in Figure 4.3.2.2.

Table 4.3.1 Reference ranges for female hormones across the menstrual cycle.

Phase of the Menstrual cycle	Follicle stimulating hormone IU/L	Luteinising Hormone IU/L	Oestradiol pmol/L	Progesterone nmol/L
Follicular	3 - 20	2 - 15	<980	0.5 – 4.5
Mid-cycle	9 - 26	22 - 105	430 - 1300	
Luteal	1 - 12	0.6 - 19	130 - 900	>15

The peak time for estradiol in the menstrual cycle is just before ovulation, while progesterone, a known respiratory stimulant, peaks during the luteal phase.

Figure 4.3.1 Hormonal changes in the menstrual cycle



Changes in female hormones during the menstrual cycle. Estradiol rises during the follicular phase and peaks just before ovulation. The peak for progesterone occurs after ovulation. Progesterone is a known respiratory stimulant.

Ventilatory response testing equipment and procedures are explained fully in Chapter 2. Each study consisted of three stages. Initially a five minute control period was recorded, where the subject breathed air via a mouth piece with CO_2 extracted from the circuit by soda lime absorption and O_2 added to maintain 21%. The subject's mean $P_{ET}CO_2$ mmHg was noted during that time. In the second (hypoxic) stage of the study, the subject's SaO_2 percentage was lowered to 80% over 90-120 seconds by the addition to the circuit of nitrogen at 8% per minute; $P_{ET}CO_2$ was maintained at the control value throughout this stage. When SaO_2 reached 80% the test was ended. In the third stage of the study the subject removed the mouthpiece and nose clip and breathed room air for ten minutes while SaO_2 was continually monitored.

The next study (hypercapnic hypoxia) was conducted in a similar manner to the hypoxic study; with the mouthpiece being inserted and the subject breathing room air for five minutes. The subject's mean $P_{ET}CO_2$ was noted and the target was set on the computer for the $P_{ET}CO_2$ to reach 8mmHg above this control value. The subject's $P_{ET}CO_2$ was increased (by injecting a bolus of CO_2 into the circuit) until it was 8-9mmHg above the control value. When this PETCO2 value was reached the subject's SaO_2 was lowered to 80% over 90-120 seconds in the same method as the hypoxic study. The test was ended when the SaO_2 reached 80%. The mouthpiece and nose clip were removed and the subject breathed room air for ten minutes while SaO_2 is monitored.

The final study (hyperoxic hypercapnic) was conducted with the mouthpiece re-inserted and the subject breathing room air for 5 minutes. The $P_{ET}CO_2$ was noted. The

system was filled with oxygen by emptying and filling the circuit with pure oxygen from the cylinder and a bolus of CO2 was injected into the circuit. The subject was then asked to take three deep breaths to facilitate mixing of the CO2 throughout the circuit and within the airways and then resume normal breathing through the mouthpiece. The soda lime was bypassed and the subject re-breathed expired air. The test was continued until the $P_{ET}CO_2$ reached 60-65mmHg or for 4 minutes. The mouthpiece and nose clip were then removed and the subject breathed normally for ten minutes while SaO_2 was monitored.

4.3.2.3 Analysis

Data was continuously acquired during testing. For each breath, a number of variables were collected during the test by the software and stored for later analysis. The filtered flow signal, the $P_{ET}CO_2$ and the SaO_2 signals were recorded onto an IBM compatible AT computer with a 12-bit A/D converter sampling at 125Hz. Software controlling the ventilatory response circuit was written in Column Oriented Language (COL), designed by Dr Michael Berthon-Jones at the University of Sydney. Data recorded in COL was converted to ASCII format and then imported into Microsoft Office Excel 2003, creating a spreadsheet of data for each individual test. Minute ventilation was then calculated by adding the inspiratory and expiratory tidal volumes and halving the product. Minute ventilation (in litres/minute) plotted against the SaO_2 or $P_{ET}CO_2$ to give the slope of that change. All ventilatory responses to hypoxia and hypercapnia are reported as the slope of the change in ventilation plotted against change in SaO_2 or $P_{ET}CO_2$. The hypoxic tests are reported as the change in ventilation in litres per minute per percentage change in the oxygen saturation i.e. L/min/%. The

hyperoxic hypercapnic tests are reported as change in ventilation in litres per minute per change in the end tidal CO_2 pressure i.e. L/min/mmHg.

4.3.3 Measurements of Breathing during Sleep

All sleep studies were recorded using Compumedics (Melbourne, Australia) S series at sea level in the sleep laboratory (eleven subjects) and portable systems PS1 or PS2 in the subject's home (eight subjects) at sea level and in the Himalaya. Sleep parameters that were recorded are described in detail in Chapter 3. The following table gives approximate barometric pressures and inspired oxygen at sea level and five high altitudes.

Table 4.3.4 Barometric pressures and inspired oxygen at sea level and high altitudes.

Altitude in metres	**Barometric pressure mmHg**	**Inspired pO_2 mmHg**
0	760	149
1000	679	132
2000	604	117
3000	537	103
4000	475	90
5000	420	78

The barometric pressure decreases as altitude increases with resulting decreases in the partial pressures of the atmospheric gases. The partial pressure of inspired oxygen is shown in relation to sea level and increasing altitude.

Breathing during sleep was recorded at sea level, 1400m, 3500m, 3900m, 4200m and 5000m. The respiratory inductive plethysmography (RIP) bands were placed around the chest at the level of the nipples, and around the abdomen at the level of the umbilicus. RIP bands were adjusted to ensure good breathing movement signals; RIP was recorded at a sampling rate of 25Hz. The nasal cannula (Salter™ 1606) was placed in the nares and taped to the cheeks to ensure all night recording. The cannula was connected to the recording equipment via 2 metres of oxygen tubing and airflow was recorded at a sampling rate of 25Hz. Oxyhemoglobin saturation was recorded at 1Hz with a finger probe and oximeter built into the recording equipment. The finger probes used were fold over infra-red sensors and were secured in position, with the infra-red light at the base of the fingernail, by surgical tape. The finger probe was connected via a cable to the recording equipment.

Morning arterial blood gases were collected and analysed in the morning after sleep studies, before food or fluid intake, in fourteen subjects (#1-14, 8 male, 6 female).

4.3.4 Arterial Blood Gases: Equipment and Procedure

Fourteen subjects had arterial blood collected for analysis of pO_2, pCO_2 and pH. Blood was collected in the morning from the radial artery within an hour of waking from the overnight sleep study. The blood gas analysis was performed at sea level and at each of the five altitudes in Nepal. Blood was drawn from the radial artery using 2mL syringe and 25 gauge needle.

The equipment used was i STAT (I-STAT Corporation, East Windsor, NJ, USA), a portable hand-held unit designed to analyse and provide data on human blood. The unit uses cartridges and a very small amount of blood. The unit runs on two 9v lithium batteries and weighs 515 grams. The i STAT analyser was electronically calibrated each morning before running a batch of three or four samples. The i STAT blood gas analyser, syringes and needles were placed in the subject's sleeping bag for 20-30 minutes to warm the equipment to close to body temperature; this was a recommendation from the manufacturer's of the equipment to ensure accurate blood gas analysis. The blood gas results were printed onto a paper strip and also stored in the i STAT analyser.

There was no failure in the collection or analysis of blood gases.

All used i STAT cartridges, needles and syringes were disposed of into a metal container with a lid and were brought back to Sydney for disposal.

4.3.5 Sleep Studies: Equipment and Procedure

The equipment used to record sleep and breathing was the Compumedics S Series, PS1 or PS2 (equipment described in detail in Chapter 3).

Recording was started when the subject retired to sleep for the night and was ended when the subject awoke the next morning.

4.3.6 Polysomnography: Scoring Respiratory Events

Respiratory event scoring was performed visually, after sleep stage scoring, using two and five minute epochs of recordings. Airflow was measured on the nasal flow signal,

breathing movement was measured on the chest and abdominal RIP and oximetry from the finger probe and oximeter built into the recording equipment.

4.3.7 Definitions of Respiratory Events

Respiratory scoring was in accordance with the criteria of the American Academy of Sleep Medicine Task Force (1999) in which:

Apnea is defined as an absence of airflow lasting for ≥10 seconds using a valid measure of breathing during sleep. In this study nasal flow via a cannula and pressure transducer was used as the valid measure of flow.

Hypopnea is defined as an amplitude reduction in airflow of ≥ 50% or a detectable reduction of airflow that is associated with either oxygen desaturation of ≥ 3% and/or arousal from sleep.

Central apnea is defined as cessation of airflow and respiratory effort lasting for ≥10 seconds. In this study respiratory effort was measured by respiratory inductive plethysmography.

Central hypopnea is defined as reduction of airflow and respiratory effort ≥ 50% lasting for ≥10 seconds.

Periodic breathing is defined as a series of three or more central apneas or hypopneas with each apnea or hypopnea terminating in three or four hyperpneic breaths. In this research, periodic breathing was scored only in non rapid eye movement sleep.

Central apneas and hypopneas occurring in rapid eye movement (REM) sleep did not occur in a periodic breathing pattern; these REM events occurred predominantly in phasic REM, in which disordered breathing is a normal occurrence and results in isolated central apneas and hypoventilation (Guilleminault, 1978). During disordered breathing in phasic REM at sea level in healthy people oxygen desaturation does not occur Guilleminault, 1978). However, at high altitude under conditions of hypobaric hypoxia, disordered breathing results in oxygen desaturation and sometimes arousal from sleep. These respiratory events in REM were called central apneas and hypopneas (Figure 4.4.3b) and lasted from 10-25 seconds; oxygen desaturation was usually associated with these events and this desaturation increased with increasing altitude. Arousal from sleep occurred in fewer than half these events.

Obstructive apnea is defined as cessation of airflow for ≥10 seconds in the presence of unchanged or increased respiratory effort.

Obstructive hypopnea is defined as the reduction of airflow ≥10 seconds in the presence of unchanged or increased respiratory effort.

An apnea/hypopnea index (AHI) was calculated for obstructive, periodic breathing and central events thus:

Number of respiratory events X 60/number of minutes of sleep.

The numbers derived were called the obstructive AHI, periodic breathing (NREM) AHI and central (REM) AHI.

4.3.8 Analysis of Respiratory Events

The respiratory events were analysed for the group as a whole at sea level and at each altitude. The respiratory events were also analysed according to gender, age, presence or absence of PB, and sea level ventilatory response to hypoxia and hypercapnia.

Arousal following apneas or hypopneas may increase ventilation during the hyperpneic phase of PB (Khoo et al, 1996), therefore the relationship between the AI/AHI ratio and sleeping oxygen saturation (mean and minimum) and the AI/AHI ratio and morning arterial blood gases were analysed.

The subjects who developed PB were compared, at altitudes 3500m and higher, to those who did not develop PB to detect differences in the mean and minimum sleeping oxygen saturation, morning arterial blood gases and the AI/AHI ratio.

Two sleep study recordings at 3500m were unusable because of equipment failure and one had no SaO_2 data, therefore sixteen sleep studies were analysed for sleeping oxygen saturation at this altitude. One sleep study recording at 3900m had no SaO_2 data, therefore eighteen sleep studies were analysed for SaO_2. One sleep study at 4200m was unusable and four had no SaO_2 data, therefore fourteen sleep studies were analysed for SaO_2 at this altitude. Nineteen sleep studies were analysed for breathing and SaO_2 at 5000m.

4.3.9 Statistical Analysis

Each breathing parameter was analysed to determine the effects of increasing altitude using a linear mixed-effects model. Breathing parameters were examined to determine the relationship between altitude and the development of periodic breathing, sleeping oxygen saturation, arterial blood gases and ventilatory responses to hypoxia and hypercapnia.

The effects of gender and age on these relationships were examined using non-parametric correlations i.e. Spearman's correlation and Mann-Whitney rank-sum test.

Regression analysis was also performed to determine any relationship between periodic breathing, ventilatory responses, sleeping oxygen saturation and arterial blood gases. Each breathing parameter was compared with its sea level value using paired t tests. The alpha was set at 0.05.

All results shown in the text are given as mean values ± SD unless otherwise stated.

4.4 Results

4.4.1 Subject Characteristics

Nineteen subjects were studied. Demographic details are shown in Table 3.4.01; ten subjects were male, nine female; mean age (± standard deviation) was 34.1 ± 9.3 years for nineteen subjects, 34.9 ± 10.4 years for male subjects and 33.2 ± 8.3 years for female subjects..

Mean body mass index (BMI) was 23.4 ± 2.8 kg/m^2 for the nineteen subjects, 24.1 ± 2.8kg/m^2 for male subjects and 22.5 ± 2.8kg/m^2 for females.

All subjects were healthy, sea level-dwelling individuals who had not been to altitudes above 1000m for the twelve months before this research was conducted.

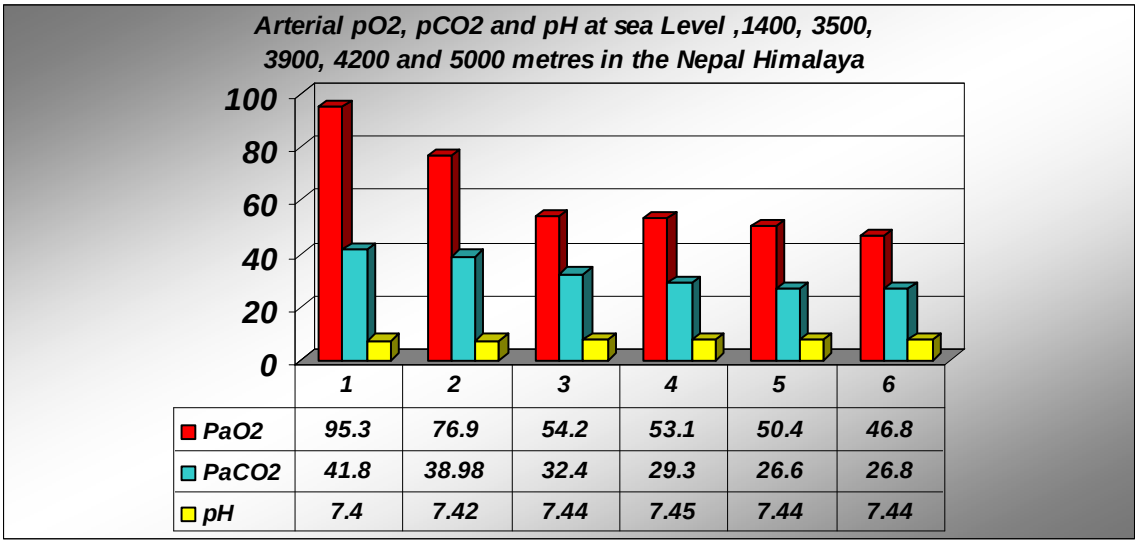
4.4.2 Arterial Blood Gases

In fourteen subjects arterial blood gas analyses were performed at each altitude. All arterial blood gases were normal, as expected, at sea level in these healthy subjects with mean pO_2 95.3 ± 6.6 mmHg, pCO_2 41.9 ± 3 mmHg and pH 7.40 ± 0.03 (Figure 4.4.2, Table 4.4.2).

There was a marked change in arterial blood gases compared to sea level at even the lowest altitude of 1400m. There was a profound decrease in the pO_2 at 1400m to 76.9 ± 5.5 mmHg ($p < 0.001$) with pCO_2 also decreasing significantly to 39.0 ± 3.1mmHg (p 0.02) and pH rising to 7.42 ± 0.02 ($p = 0.04$).

These changes in arterial blood gases continued with increasing altitude; at 3500m the pO_2 was 54.2 ± 8.5 mmHg ($p < 0.0001$), the pCO_2 32.4 3 mmHg ($p < 0.0001$) and the pH 7.44 ± 0.03 ($p = 0.002$). At 3900m the pO_2 was 53.1 ± 6.6 mmHg ($p < 0.0001$), pCO_2 29.3 ± 3.6 mmHg ($p < 0.0001$) and the pH 7.45 ± 0.03 ($p = 0.0003$). At 4200m the pO_2 was 50.4 ± 9 mmHg ($p < 0.0001$), the pCO_2 was 29.6 ± 2.4 mmHg ($p < 0.0001$) and the pH was 7.44 ± 0.02 ($p = 0.0003$). At 5000m the pO_2 was 46.8 ± 7.7 mmHg ($p < 0.0001$), the pCO_2 was 26.8 ± 3.5 mmHg ($p < 0.0001$) and the pH was 7.44 ± 0.04 ($p = 0.006$).

Figure 4.4.2 Arterial blood gases at sea level and high altitudes.



The effects of increasing altitude became apparent at even the lowest elevation i.e. 1400 meters, with marked decreases in pO_2, pCO_2 and the pH becoming more alkaline. This clearly demonstrates the challenges to the ventilatory system at high altitude.

Table 4.4.2 Arterial blood gases at sea level and high altitudes

	0 m	1400 m	3500 m	3900 m	4200 m	5000 m
pO2 mmHg	**95 ± 7**	**77 ± 6‡**	**54 ± 9‡**	**53 ± 7‡**	**50 ± 9‡**	**47 ± 8‡**
pCO2 mmHg	**42 ± 3**	**39 ± 3***	**32 ± 3‡**	**29 ± 4‡**	**30 ± 2‡**	**27 ± 4‡**
pH	**7.39 ± 0.03**	**7.42 ± 0.02***	**7.44 ± 0.03†**	**7.45 ± 0.02‡**	**7.44 ± 0.02‡**	**7.44 ± 0.04‡**

*Results of morning arterial blood gases at sea level and at the five high altitude locations. There were significant effects on pO_2, pCO_2 and pH at even the lowest altitude in Nepal: subjects became increasingly hypoxic, hypocapnic and alkalotic as altitude increased. *$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$*

4.4.3 Respiratory event type at sea level and high altitude

At sea level, as expected in these normal individuals, there was no periodic breathing (PB) in any subject. Occasional central apneas is a common occurrence in healthy individuals during phasic rapid eye movement (REM) sleep and, in our group of subjects, three females (#5, #6, #15) had two or three central apneas during phasic REM sleep at sea level resulting in central REM apnea/hypopnea index (AHI) of 0.7/hour, 0.8/hour and 1/hour.

At the first and lowest altitude studied in Nepal (Kathmandu at 1400m) two subjects (#12 and #15) developed periodic breathing in non rapid eye movement (NREM) sleep with PB AHI of 27.5/hour and 14.5/hour; the average NREM PB AHI for the whole group was 3.3 ± 6.6/hour. One of these subjects was male and the other, female.

As altitude increased so did the NREM PB AHI, with five subjects out of seventeen developing periodic breathing at 3500m during NREM sleep. These five subjects had an average AHI of 46 ± 13/hour while the eleven subjects without PB (AHI < 20/hour) had an average of 8 ± 6/hour. At the next altitude, 3900m, eleven subjects out of nineteen developed PB and seven did not. The group with PB had an average AHI of 45 ± 24/hour while those subjects without PB had an average AHI of 3 ± 4/hour.

Not surprisingly, by the two highest altitudes PB AHI had increased markedly. At 4200m eleven of the eighteen subjects had PB AHI average of 73 ± 43/hour while seven subjects had an average AHI of 8 ± 8/hour. Most subjects had developed PB by

the time 5000m was reached with an average AHI of 85 ± 45/hour while only four subjects (all of whom were female) did not have PB, having an average AHI of 3 ± 3/hour.

Central apneas and hypopneas in REM sleep also increased with increasing altitude. At sea level three female subjects had central apneas in phasic REM with the average for this group 0.8 ± 0.2/hour. The remaining sixteen subjects had no central events in REM sleep. The number of subjects with central REM events increased even at the lowest altitude of 1400m but the AHI remained below 20/hour for the nineteen subjects, with an average for the group of 4 ± 4/hour. At the next altitude i.e. 3500m, eight subjects now had central REM events with AHI > 20/hour, the average AHI for this group being 29 ± 10/hour. However another nine subjects had few central REM events with an average of 8 ± 5/ hour. The average AHI for the whole group of nineteen subjects at 3500m was 20 ± 16/ hour.

Central REM events continued to increase with increasing altitude so that by 3900m eleven of the nineteen subjects had an average AHI of 42 ± 21/hour and eight with an average AHI of 11 ± 6/hour. The whole group average was 30 ± 25/hour.

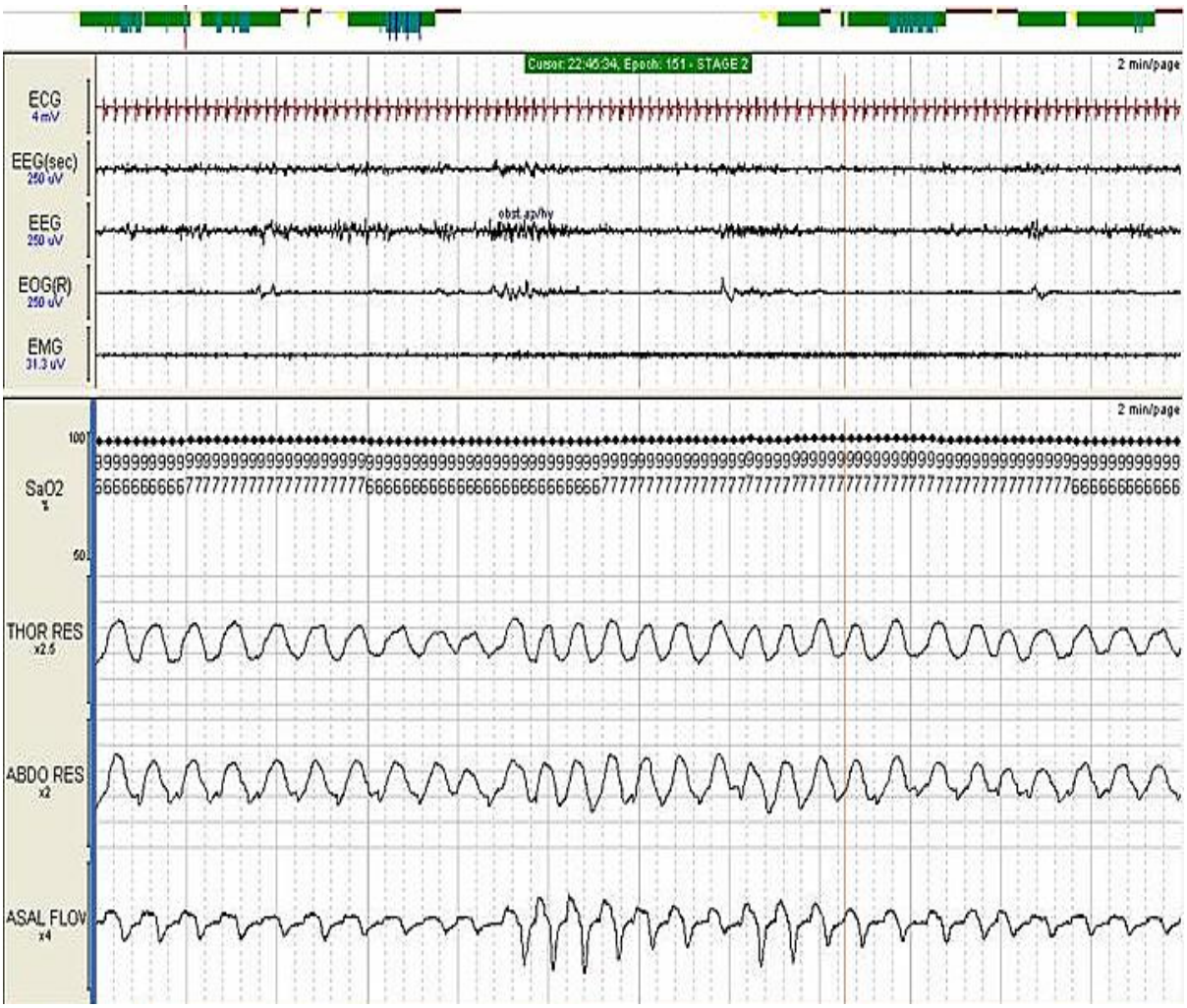
This did not increase significantly at the next altitude i.e. 4200m, with eleven of the eighteen subjects having a central REM AHI average of 41 ± 15/hour, seven subjects with low levels of central REM events with an average AHI of 7 ± 7/hour. The average AHI for the group of eighteen subjects was 32 ± 26/hour.

The number of subjects with high central REM AHI did not increase at 5000m, with eleven out of seventeen subjects having an average AHI of 53 ± 30/hour while five subjects had an average AHI of 13 ± 4/hour. The average for the whole group of seventeen subjects was 43 ± 39/hour.

There was a minor degree of upper airway obstruction in the subjects at sea level, particularly in REM sleep, with ten of the nineteen subjects having an obstructive AHI in REM sleep of ≥ 5/hour (ranging from 5 – 30/hour). This group of ten subjects had an average REM obstructive AHI of 12 ± 8/hour with the group as a whole having an average obstructive AHI of 7 ± 6/hour in REM sleep. Upper airway obstruction was at much lower levels in NREM sleep with only two subjects having an AHI ≥ 5/hour (17/hour and 6/hour in these two subjects) and the average for the whole group was 3 ± 5/hour.

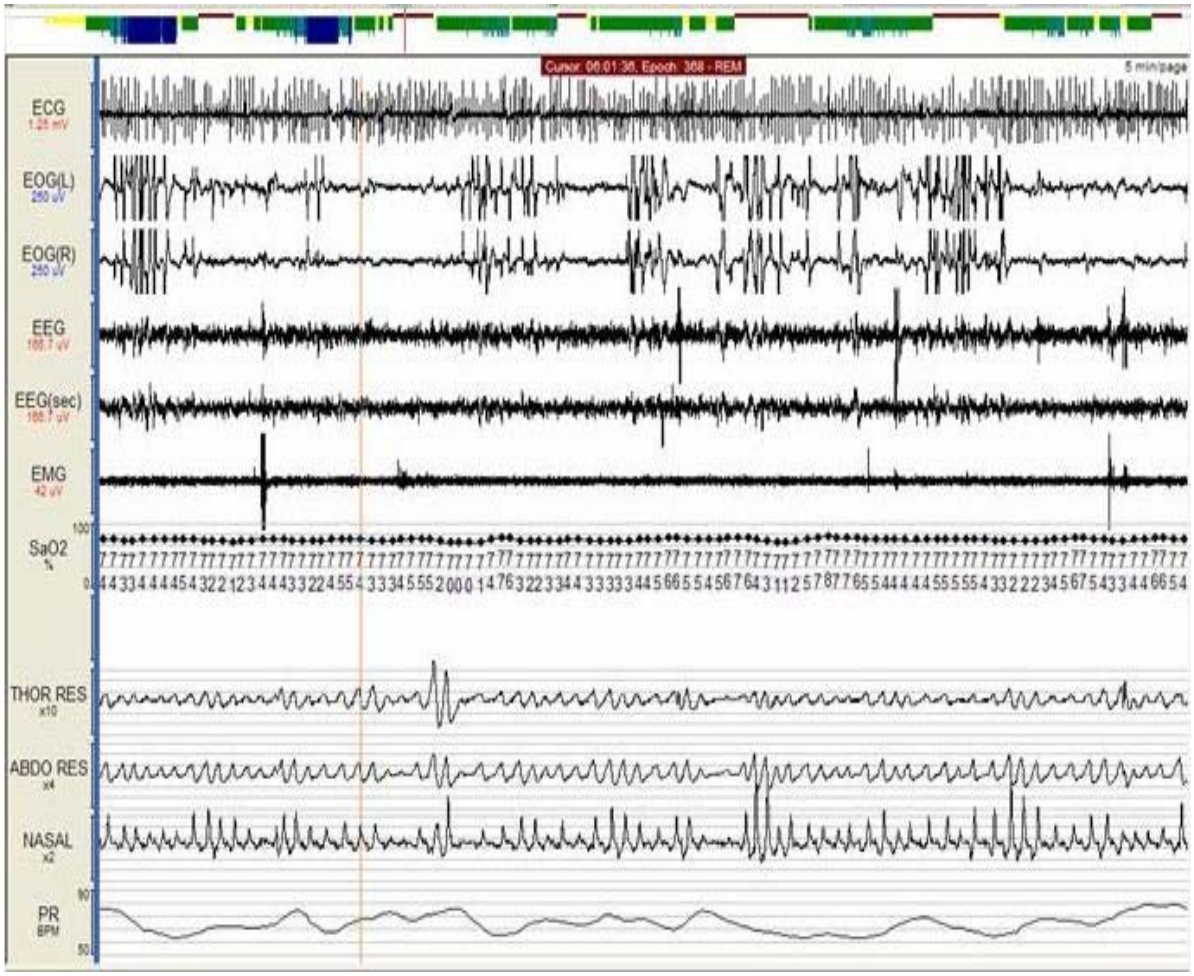
This minor upper airway obstruction was significantly decreased from the lowest altitude; the obstructive AHI fell at 1400m to 1 ± 3/hour in NREM sleep ($p < 0.01$) and 10 ± 5/hour in REM sleep ($p < 0.01$). This continued to decrease significantly with increasing altitude with an average AHI in NREM of 1 ± 3/hour at 1400m and then to below 1/hour at 3900m, 4200m and 5000m ($p < 0.001$). A similar pattern occurred with the obstructive AHI in REM sleep, falling significantly at 1400m to 3 ± 5/hour ($p < 0.001$), and then to ≤1/hour at 3500m, 3900m, 4200m and 5000m ($p < 0.001$).

Figure 4.4.3a Respiratory Event Types at Sea level and Altitude: Obstructive Hypopnea



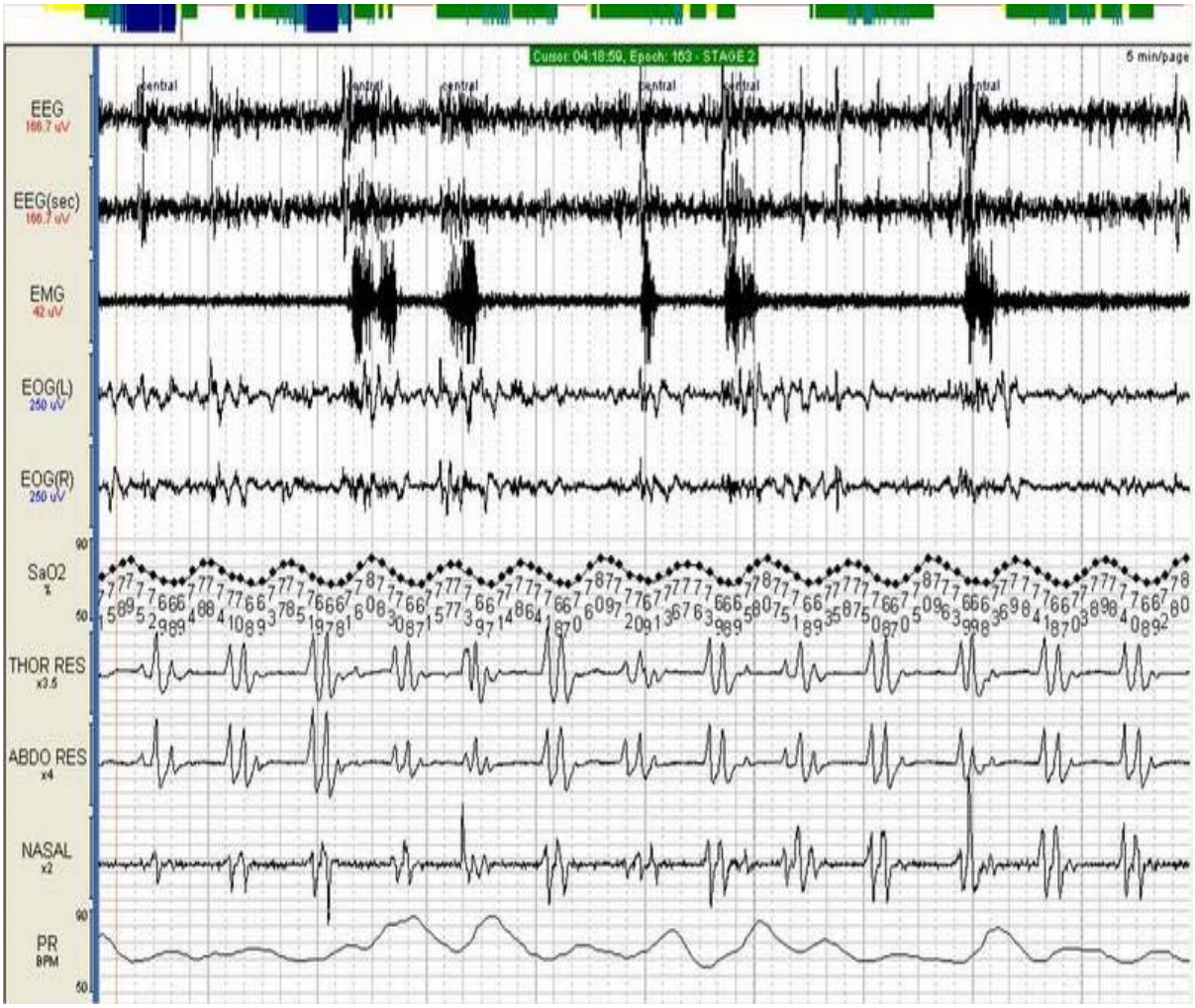
There was a mild degree of upper airway obstruction in some subjects at sea level. This two minute epoch of sleep is an example of an obstructive hypopnea in Stage 2 NREM sleep in subject #13. Breathing was monitored with respiratory inductive plethysmography (RIP) bands around the chest (THOR RES) and abdomen (ABDO RES). Airflow was monitored using oxygen cannula and pressure transducer (NASAL FLOW). Flow limitation is seen on the flow signal.

Figure 4.4.3b Respiratory Event Type High Altitude: Central Hypopneas in REM Sleep at 5000m.



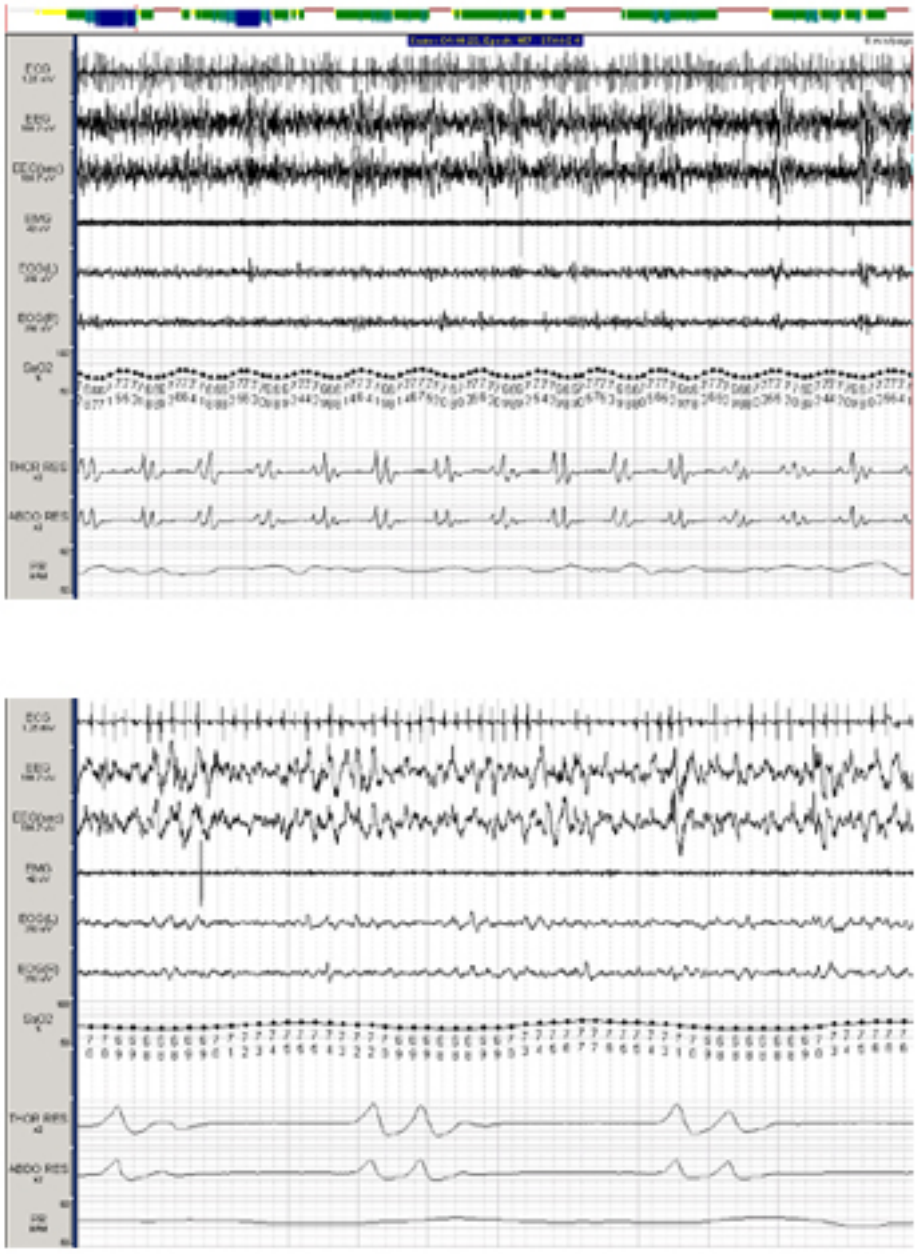
During phasic REM at 5000m central hypopneas occurred and were associated with decreases in oxyhemoglobin saturation from a low base line level (low 70s). Heart rate variations (seen on pulse rate (PR) , signal) appear to be in response to phasic events in REM sleep.

Figure 4.4.3c. Respiratory Event Type at High Altitude: Central Apneas (Periodic Breathing) in NREM Sleep at 5000m



Periodic breathing during Stage 2 NREM sleep at 5000m demonstrates the profound oxyhemoglobin desaturations/resaturations that typically occur in periodic breathing. Of particular interest is the lack of cortical arousal associated with over half of these central apneas, and autonomic arousal (pulse rate increases with apnea termination).

Figure 4.4.3.d. Detail of central apneas of periodic breathing



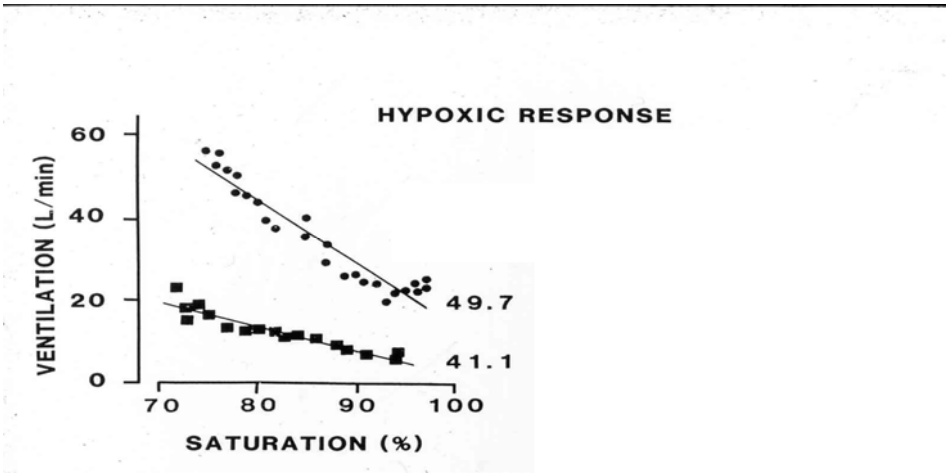
Two minute epoch with 30 second detail from the same epoch.

4.4.4 Sleeping Oxygen Saturation with increasing Altitude

The subjects all had normal SaO_2 during sleep at sea level, as expected, with the mean SaO_2 for the group of nineteen subjects being 97 ± 2% and the minimum SaO_2 91 ± 3%. (Table 4.4.4a)

During sleep at each higher altitude the SaO2 became progressively lower with significant reductions in both the mean and minimum from 1400m ($p \leq 0.001$ at all altitudes ≥1400m). At the lowest altitude during the trek (i.e.1400m) the mean SaO_2 was 95 ± 2% and the minimum 87 ± 4% (Table 4.4.4b), at 3500m the mean SaO_2 was 84 ± 5 % and minimum 71 ± 7% (Table 4.4.4c), at 3900m the mean was 80 ± 9% and the minimum 68 ± 10% (Table 4.4.4d), at 4200m the mean was 80 ± 8% and the minimum 69 ± 8% (Table 4.4.4e) and at 5000m the mean was 74 ± 8% and the minimum 64 ± 7%.

Figure 4.4.4 The ventilatory response to hypoxia



As altitude increases, the pressure of inspired oxygen decreases and hypoxia results. The ventilatory response to hypoxia is increased ventilation. This graph demonstrates the increase in ventilation in response to decreased oxyhemoglobin saturation.

Table 4.4.4a Mean and minimum sleep oxyhemoglobin saturation (SaO2), apnea/hypopnea indices (AHI) for central and obstructive events in NREM and REM sleep at sea level in nineteen subjects.

Subject	***Mean sleeping SaO_2 %***	***Minimum sleeping SaO_2 %***	***NREM Periodic breathing AHI***	***REM central AHI***	***NREM obstructive AHI***	***REM obstructive AHI***
1	98	96	0	0	0	0
2	96	89	0	0	3.4	0
3	97	90	0	0	1.4	6.2
4	96	92	0	0	2	8.2
5	97	87	0	0.8	2.9	3.3
6	99	94	0	0.7	0	0.7
7	97	92	0	0	0	0
8	96	92	0	0	3.2	29.7
9	97	93	0	0.2	0.2	10.2
10	96	94	0	0	0.7	0
11	95	81	0	0	16.8	19.7
12	98	92	0	0.9	1.1	0.9
13	97	91	0	0	3.6	0
14	97	93	0	0	5.8	18.2
15	98	92	0	1	0.5	6.1
16	100	94	0	0	0	0.9
17	98	91	0	0	0	11.6
18	93	89	0	0	0.3	9.6
19	97	90	0	0	1.8	4.9
Means ± SD	***97 ± 2***	***91 ± 3***	***0 ± 0***	***0.1 ± 0.3***	***2.3 ± 3.9***	***6.9 ± 8.2***

The mean sleeping oxygen saturation at sea level was ≥93% in all subjects while four subjects desaturated to <90% due to obstructive hypopneas. There was no periodic breathing at sea level but there was a minor degree of upper airway obstruction, particularly in REM sleep.

Table 4.4.4b Mean and minimum sleep oxyhemoglobin saturation (SaO2), apnea/hypopnea indices (AHI) for central and obstructive events in NREM and REM sleep at 1400m in nineteen subjects.

Subject	***Mean sleeping SaO_2 %***	***Minimum sleeping SaO_2 %***	***NREM Periodic breathing AHI***	***REM central AHI***	***NREM obstructive AHI***	***REM obstructive AHI***
1	96	91	1.7	0	0	0
2	94	89	2.5	0.5	2.3	0
3	95	87	5.3	7.2	1.2	0
4	90	84	0.6	3.3	1.4	3.3
5	94	89	5.5	15.8	0.5	0.8
6	94	86	0.7	3	0	0
7	96	92	0.3	5.6	0	0
8	95	89	0.6	8.7	0	0
9	96	90	2.4	1.4	0.3	1.4
10	96	89	0.3	8.1	0	0
11	96	89	3.4	4.6	2.1	4.6
12	94	89	27.5	10.9	0	0
13	93	75	0	0	0	0
14	93	81	0	0	12.2	0
15	95	86	14.5	4.1	0.5	2.6
16	96	87	0	1.9	0.4	2.4
17	96	90	0	1.6	0.4	12.4
18	93	88	0	0	1.1	3
19	94	85	0.5	2	4.2	19.7
Means ± SD	***95 ± 2***	***87 ± 4***	***3 ± 7***	***4 ± 7***	***1 ± 3***	***3 ± 3***

The mean and minimum oxygen saturations were reduced during sleep at 1400m. Central apneas and hypopneas occurred in several subjects with two subjects developing a minor degree of periodic breathing. The mean obstructive apnea/hypopnea index was halved from sea level values.

Table 4.4.4c Mean and minimum sleep oxyhemoglobin saturation (SaO2), apnea/hypopnea indices (AHI) for central and obstructive events in NREM and REM sleep in sixteen subjects at 3500m.

Subject	***Mean sleeping SaO_2 %***	***Minimum sleeping SaO_2 %***	***NREM Periodic breathing AHI***	***REM central AHI***	***NREM obstructive AHI***	***REM obstructive AHI***
1						
2	82	73	47.3	4.3	0	0
3			14.4	10.8	1.3	4.5
4	86	81	8	2.2	0	0
5	84	72	17	9.5	0	0
6	72	64	3.4	4.9	0	0
7	81	73	4.9	3	0	0
8	72	53	10.2	24	0.2	0
9	87	74	18	29.8	0	0
10	86	64	0.9	27.6	0.2	0
11	88	78	68.2	32.7	0	0
12						
13	87	78	35.7	18.5	0	0
14	88	76	33.8	28.3	0	0
15	88	73	40.8	51.5	0.5	0
16	81	67	0.6	6.4	0.4	0
17	86	74	1.2	21.8	0.8	0
18	85	73	12.2	12.7	0	13.3
19	83	86	9.2	20	1.3	5.8
Means ± SD	***84 ± 5***	***71 ± 7***	***19 ± 19***	***18 ± 13***	***0.3 ± 0.4***	***1 ± 4***

The mean and minimum sleeping oxygen saturations at 3500m were significantly reduced in association with increasing altitude. Periodic breathing now appeared in five subjects while obstructive events were now almost abolished.

Table 4.4.4d Mean and minimum sleep oxyhemoglobin saturation (SaO2), apnea/hypopnea indices (AHI) for central and obstructive events in NREM and REM sleep in eighteen subjects at 3900m.

Subject	***Mean sleeping SaO_2 %***	***Minimum sleeping SaO_2 %***	***NREM Periodic breathing AHI***	***REM central AHI***	***NREM obstructive AHI***	***REM obstructive AHI***
1	81	75	36.3	31.7	0	0
2	83	78	83.9	25.6	0	0
3	81	72	2.2	8.6	2.2	15.6
4	77	70	19.5	5.3	0.2	1.2
5	83	71	24.3	77.6	0.6	0
6	53	50	3.1	13.9	0	0
7	78	68	4	19.6	0	0
8	65	42	0	0.6	1	6.8
9	83	68	26.1	35.5	0.7	0
10	83	58	24.4	53.4	0	0
11			33.5	15.6	0	0
12	87	78	48.3	37.7	0	0
13	84	70	29.1	11.5	0	0
14	81	59	54.5	19	0.7	0
15	85	71	77.1	78.1	0.2	0
16	89	75	1.1	15	0	2.1
17	85	68	1.3	24.4	0.2	0.5
18	84	75	11.7	25.9	1	3.6
19	84	71	27.2	54.1	1.9	5.1
Means ± SD	***80 ± 9***	***64 ± 7***	***27 ± 25***	***29 ± 22***	***0.5 ± 1***	***2 ± 4***

The mean and minimum sleeping oxygen saturations at 3900m continued to be decreased in association with increasing altitude. Periodic breathing now had developed in twelve subjects with the same subjects also demonstrating central apneas and hypopneas in REM sleep. Obstructive apneas and hypopneas continued to occur only rarely.

Table 4.4.4e Mean and minimum sleep oxyhemoglobin saturation (SaO2), in fourteen subjects and apnea/hypopnea indices (AHI) for central and obstructive events in NREM and REM sleep in eighteen subjects at 4200m

Subject	***Mean sleeping SaO_2 %***	***Minimum sleeping SaO_2 %***	***NREM Periodic breathing AHI***	***REM central AHI***	***NREM obstructive AHI***	***REM obstructive AHI***
1	80	72	88.9	55.8	0	0
2	79	72	141.7	25.8	30	0
3	81	72	17.6	12.2	3.3	10.9
4						
5	77	70	12.5	3.6	0.3	0
6	54	50	132.3	42.9	0	0
7			0	0.8	0	0
8			1	3.2	0	0
9			2.1	20.2	0.3	2
10			45.9	12.2	0	0.7
11	86	76	39.5	33.7	0	0
12	86	73	96	59	0	0
13	86	76	29.3	18.4	0.4	5
14	82	65	96.5	0	0.4	5
15	85	71	83.8	68.7	0	0
16	80	71	5.3	29.6	0	0
17	80	66	15.6	34.3	0	0
18	85	73	22	44	0.2	0
19	84	73	26.5	32	4.2	3
Means ± SD	***80 ± 8***	***69 ± 8***	***48 ± 46***	***28 ± 21***	***0.5 ± 1***	***1 ± 3***

Oxygen saturation data was lost in five subjects at 4200m due to equipment failure but both values continued to decrease in association with increased altitude. Most subjects' mean SaO_2 remained ≥80% and the minimum >70% while three subjects had minimum SaO_2 ≤ 66%. Obstructive events occurred rarely.

Table 4.4.4f Mean and minimum sleep oxyhemoglobin saturation (SaO2), apnea/hypopnea indices (AHI) for central and obstructive events in NREM and REM sleep at 5000m in nineteen subjects.

Subject	***Mean sleeping SaO_2 %***	***Minimum sleeping SaO_2 %***	***NREM Periodic breathing AHI***	***REM central AHI***	***NREM obstructive AHI***	***REM obstructive AHI***
1	69	62	129.9	67.3	0.9	0
2	76	70	148.6		0	
3	77	70	27	11.5	1.8	0
4	76	69	25.3	10.3	0.2	0
5	68	62	40.5	54.5	0	0
6	51	50	30	0	1.9	0
7	70	56	1.1	23.3	0	0
8	59	50	8.2	28.6	0	0
9	80	70	3.5	18.9	0	0.7
10	70	62	21.2		0	
11	82	67	94.3	42.6	0	0
12	79	64	127	14.1	0	0
13	80	65	101.2	102.9	0	0
14	81	67	37.5	40	1.2	1.8
15	75	63	148.7	111	0	0
16	81	70	0.8	10	0	0
17	71	58	58.7	52	0	0
18	80	70	85.4	28.4	0	0
19	79	70	79.2	30.6	1.8	18.9
Means ± SD	***74 ± 8***	***64 ± 8***	***60 ± 53***	***38 ± 32***	***0.4 ± 1***	***1 ± 4***

The mean sleeping oxygen saturation remained >80% in most subjects with a wider range occurring in the minimum SaO_2 and values in four subjects <60% while most maintained a minimum SaO_2 >70%. Periodic breathing occurred in fifteen subjects with a wide range of severity. Obstructive events occurred rarely at this altitude. Subject #2 had no REM sleep.

4.4.5 Breathing during sleep and sleeping oxygen saturation in subjects with and without periodic breathing.

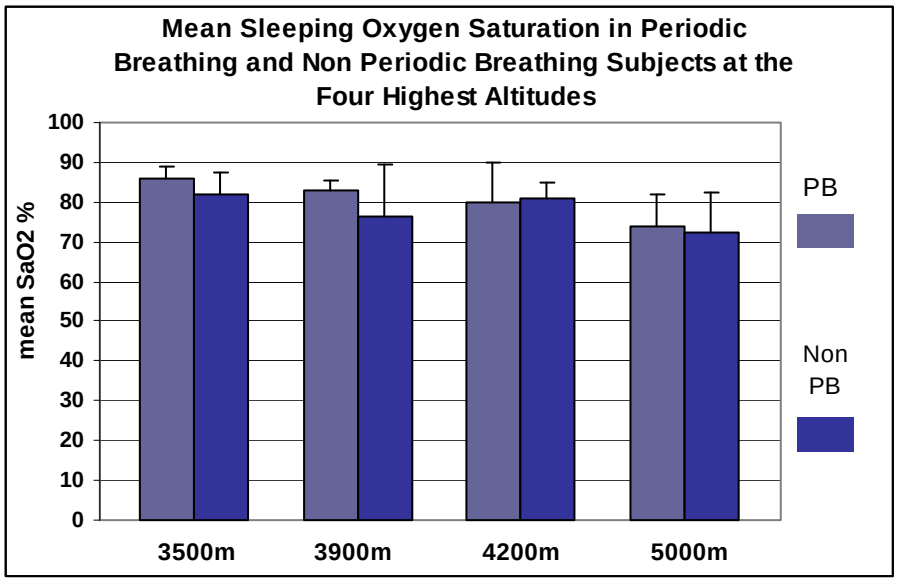
There was a wide range of periodic breathing apneas/hypopneas in the group, with some subjects having very high levels of periodic breathing (PB) from 3500m and higher; for example six subjects had PB AHI from 34-77/hour at 3900m while six subjects, who were deemed to have developed PB because their PB apnea/hypopnea index (AHI) was ≥ 20/hour at 3900m, had AHI of closer to 20/hour. At each altitude there were several subjects who did not have any PB (i.e. AHI < 5/hour). Thus the degree and range of PB was widely varied in these subjects. However, sixteen of the subjects developed PB at one or more altitudes during the trek. (Tables 4.4.4a – 3f).

Two subjects developed a minor degree of PB at 1400m with PB apnea/hypopnea indices (AHI) of 27.5/hour and 14.5/hour, therefore the sleeping mean and minimum oxygen saturation were compared in subjects with PB and those without at 3500m and higher.

The incidence and severity of periodic breathing increased with increasing altitude with five subjects developing PB at 3500m (mean AHI 45 ± 14/hour), twelve at 3900 (AHI 40 ± 21/hour), eleven at 4200m (AHI 73 ± 43/hour) and fifteen at 5000m (AHI 77 ± 46/hour). At each altitude there were some subjects who did not have periodic breathing but there were three subjects who did not develop PB at any altitude, while a further one subject developed PB only at 5000m. The mean AHI of the twelve subjects without PB at 3500m was 8 ± 6/hour, in the eight without PB at 3900m 3 ± 4/hour, in the ten without PB at 4200m ± 7/hour and in the four without PB at 5000m AHI 3 ± 3/hour.

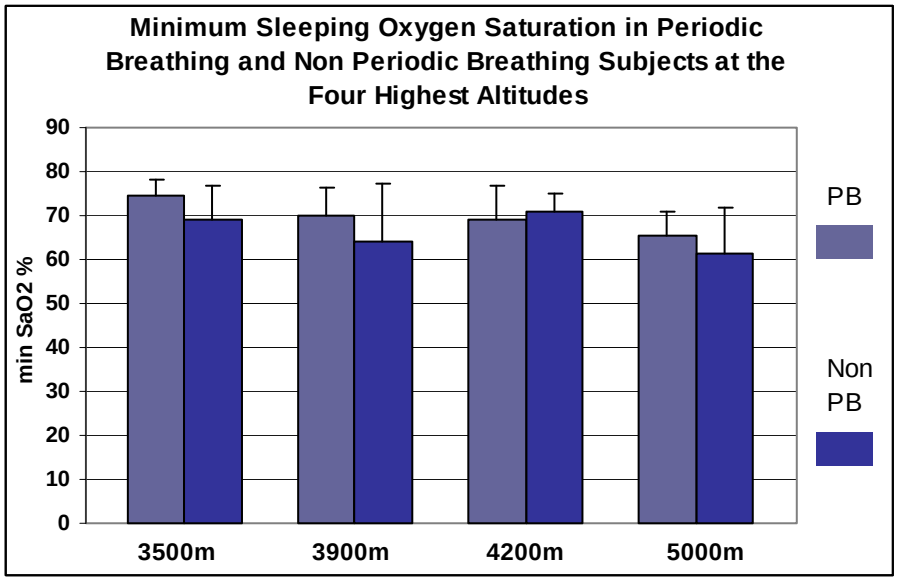
There were no significant differences in the sleeping mean oxygen saturation (SaO_2) or minimum sleeping SaO_2 in those subjects with or without PB ($p \geq 0.1$).

Figure 4.4.5a Mean Sleeping Oxygen Saturation in Subjects with and without Periodic Breathing



There were no significant differences between the sleeping mean oxygen saturations at any altitude in subjects who developed periodic breathing and those who did not.

Figure 4.4.5b Minimum Sleeping Oxygen Saturation in subjects with and without Periodic Breathing



There were no significant differences in the minimum sleeping oxygen saturations at any altitude in those subjects who developed periodic breathing and those who did not.

4.4.6 Breathing during sleep and sleeping oxygen saturation in male and female subjects.

The majority of subjects who did not develop significant periodic breathing were female. Eight out of the ten male subjects had a mean PB AHI, for all altitudes of 3500m and higher, of 20/hour, while only two of the nine female subjects had similar mean PB AHI. Conversely, seven of the nine female subjects had low mean PB AHI for ≥ 3500m, i.e. ≤ 17/hour while only two of the ten male subjects had a similarly low mean AHI. Periodic breathing parameters were significantly different in the nine female and ten male subjects at three altitudes (Figure 4.4.6b): 3500m, 4200m and 5000m.

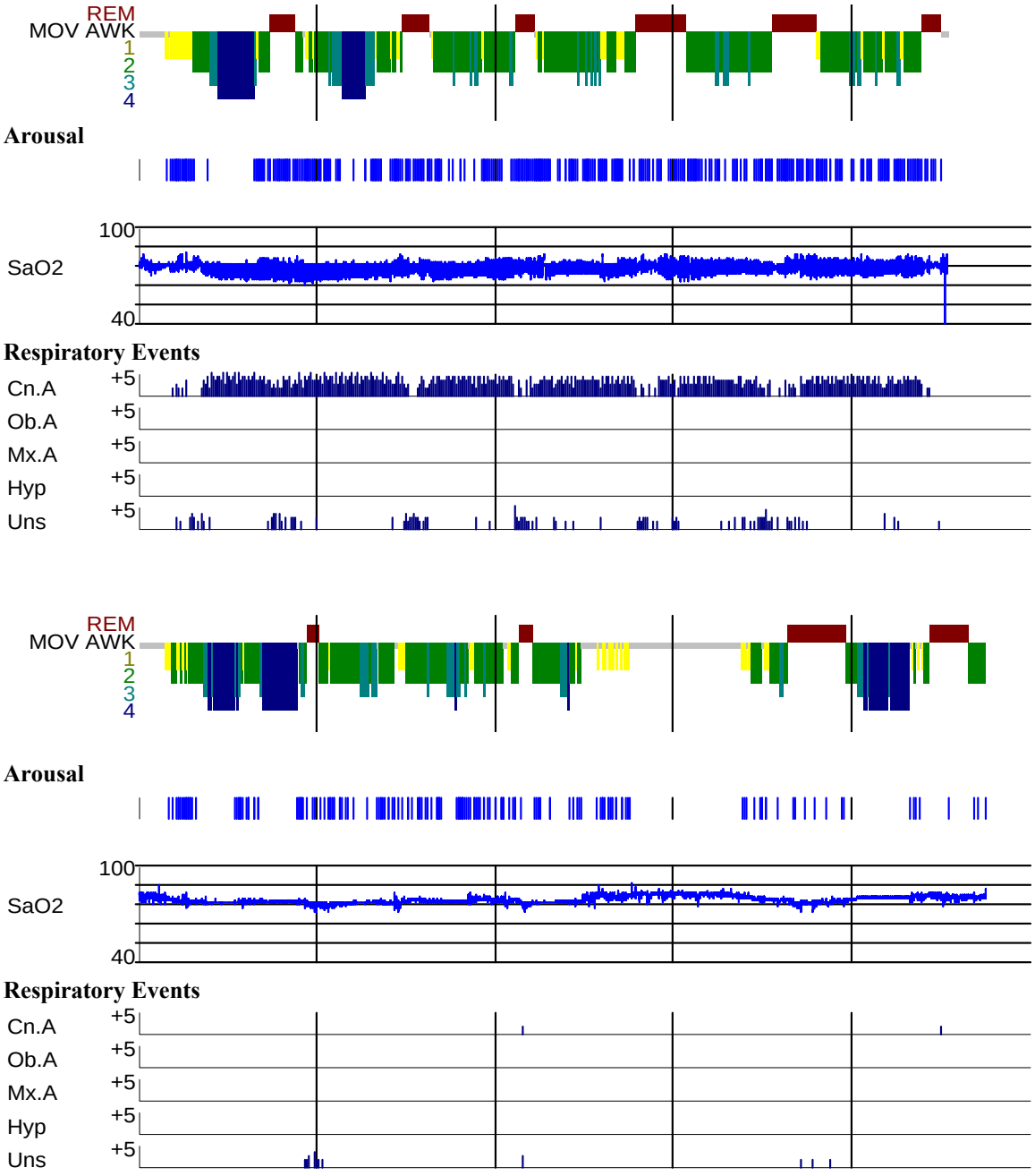
The periodic breathing apnea/hypopnea index (PB AHI) was higher in males at 3500m: the female PB AHI was 10.8 ± 3.1/hour and the male 28.6 ± 21.6/hour, ($p = 0.05$). The PB AHI was higher in males at 5000m: the female PB AHI was 34.7 ± 47.1 and the male 84.9 ± 44.9, ($p = 0.03$).

The arousal index (AI) associated with termination of PB apneas and hypopnea (PB AI) was also higher in male subjects at 3500m and 5000m. The female PB AI at 3500m was 3 ± 3/hour and the male 14 ± 10/hour ($p = 0.005$). The female PB AI at 5000m was 15 ± 17/hour and the male 35 ± 20/hour ($p = 0.03$).

When the sleeping oxygen saturations were compared between the male and female subjects at each altitude, significant differences were found in the minimum SaO_2 at 3500m, 4200m and 5000m (Figures 4.4.6b-c). At 3500m the female minimum SaO_2 was 68 ± 7% and the male 75 ± 5% ($p = 0.05$); at 4200m the female minimum SaO_2 was 65 ± 9% and the male 72 ± 3% ($p = 0.03$) and at 5000m the female minimum SaO_2 was 60 ± 7% and the male 67 ± 3% ($p = 0.01$).

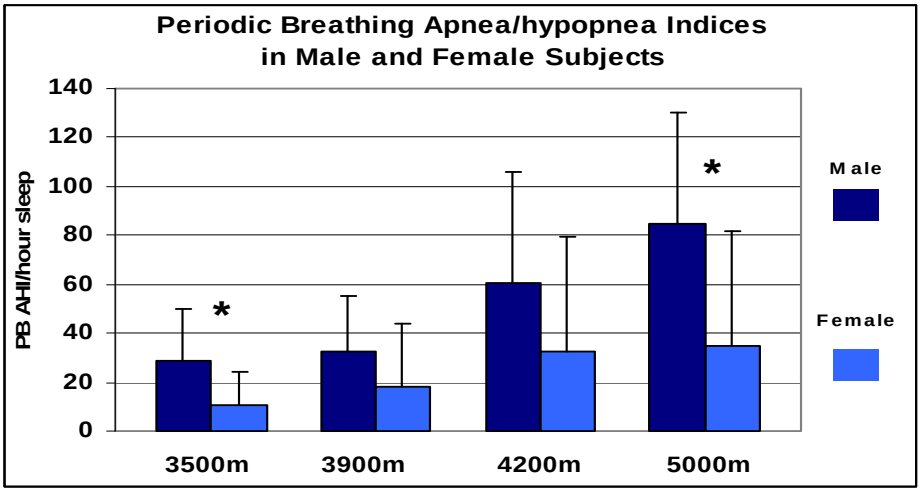
The mean sleeping SaO_2 was lower in female subjects at only one altitude i.e.5000m, with the female mean SaO_2 70 ± 10% and male 78 ± 4% ($p = 0.02$).

Figure 4.4.6a Oxyhemoglobin Saturation during Sleep at 5000m in a Subject with Periodic Breathing and a Subject without Periodic Breathing.



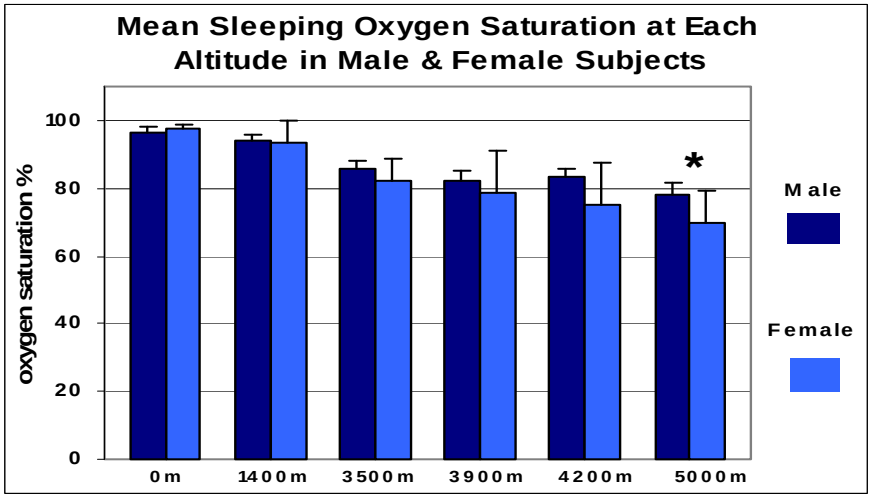
Sleep reports on two subjects at 5000m. Both subjects were 23 year old females. One subject had a periodic breathing (PB) apnea/hypopnea index of 149/hour while the other subject had no PB. The mean oxyhemoglobin saturations were similar in the two despite profound desaturations/resaturations that occurred with PB. (CnA=central apnea, Uns=central hypopnea) Both subjects are in lateral positions & sleeping flat with one pillow..

Figure 4.4.6b Periodic Breathing in Male and Female Subjects.



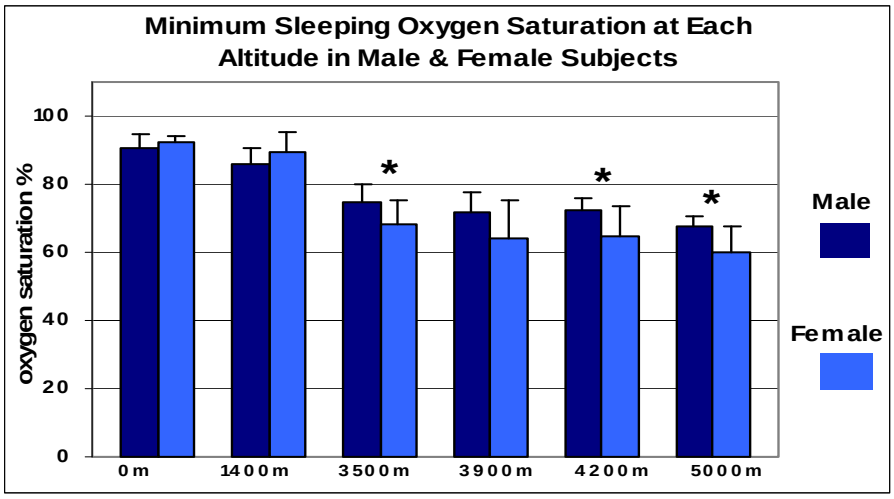
Periodic breathing occurred more in male subjects at every altitude but the apnea/hypopnea indices were significantly higher in male subjects only at 3500m (p = 0.05) and 5000m (p = 0.03).

Figure 4.4.6c Mean Sleeping Oxygen Saturation in Male versus Female Subjects.



The mean sleeping oxygen saturation was significantly lower in female subjects only at 5000m (p = 0.02).

Figure 4.4.6d Minimum Sleeping Oxygen Saturation in Male and Female Subjects.

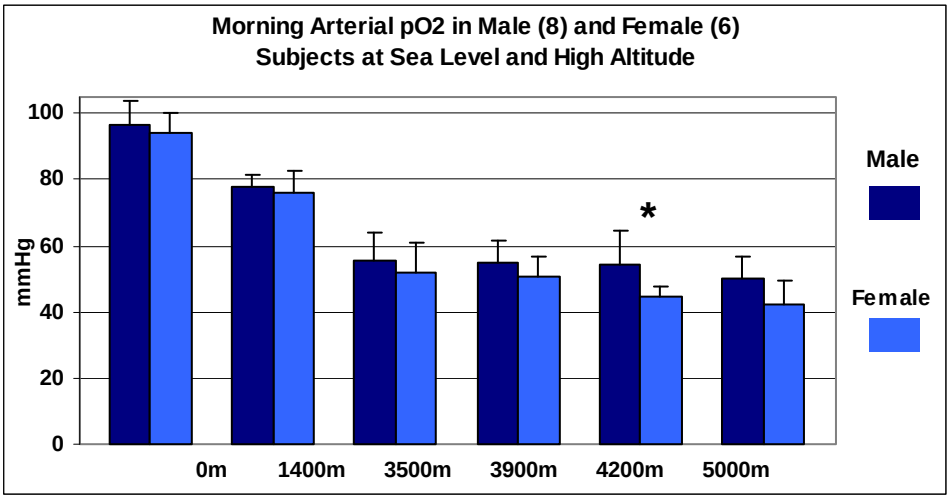


Female subjects desaturated during sleep more than male subjects at the three altitudes, with the minimum SaO_2 being significantly lower in females at 3500m (p = 0.05), 4200m (p = 0.03) and at 5000m (p = 0.01).

4.4.7 Male and female arterial blood gases

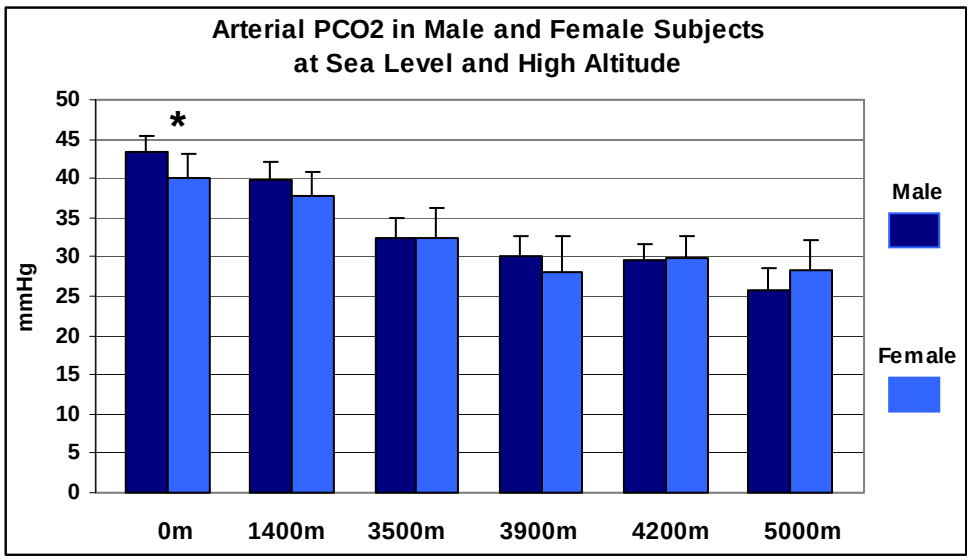
There were very few differences between the male and female arterial blood gases, either at sea level or high altitude. The pCO_2 of the female subjects were significantly lower at sea level than male i.e. the mean female pCO2 was 40 ± 3.2mmHg versus 43.3 ± 2.1mmHg in the male subjects (p = 0.04). At 4200m the pO_2 was lower in the female subjects compared to the male subjects i.e. pO_2 44.7 ± 2.7 mmHg for females versus 54.6 ± 9.8 mmHg for males (p = 0.03). There was a trend towards a lower pO_2 in females at 5000m, 42.5 ± 7 mmHg versus 50 ± 6.8 mmHg in males (p = 0.07) with no other differences in any blood gas parameter at any altitude.

Figure 4.4.7a Arterial pO_2 in Male (8) and Female (6) Subjects



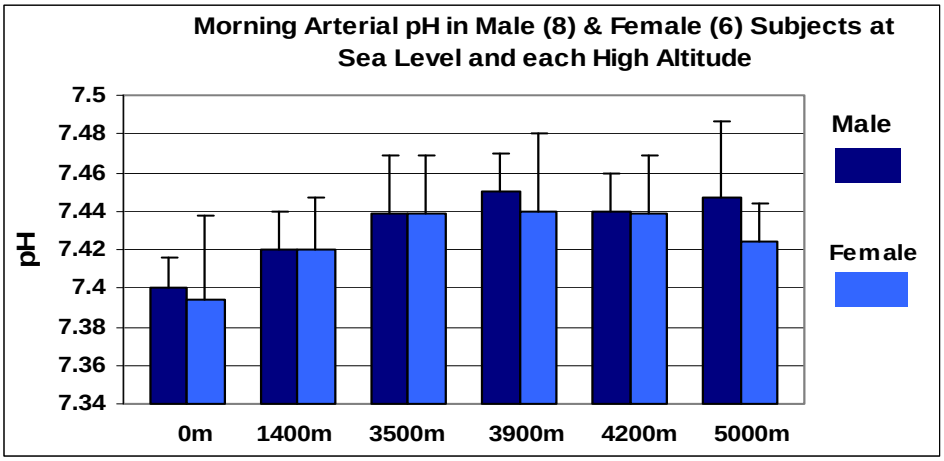
There were no significant differences between male and female subjects' arterial oxygen measurements except at 4200m, where the male pO_2 was significantly higher than female pO_2 ($p = 0.03$).

Figure 4.4.7b Arterial pCO_2 in Male (8) and Female (6) Subjects.



The arterial carbon dioxide measurement was significantly different in male and female subjects only at sea level ($p = 0.04$).

Figure 4.4.7c Arterial pH in Male (8) and Female (6) Subjects.

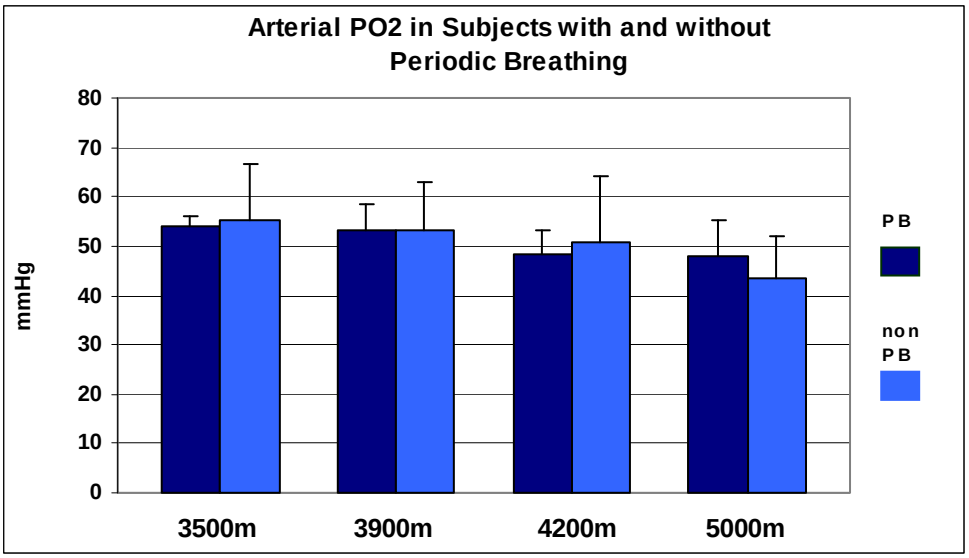


There were no significant differences in the arterial pH of male subjects compared to female subjects at any altitude.

4.4.8 Arterial Blood Gases in Subjects with and without Periodic Breathing

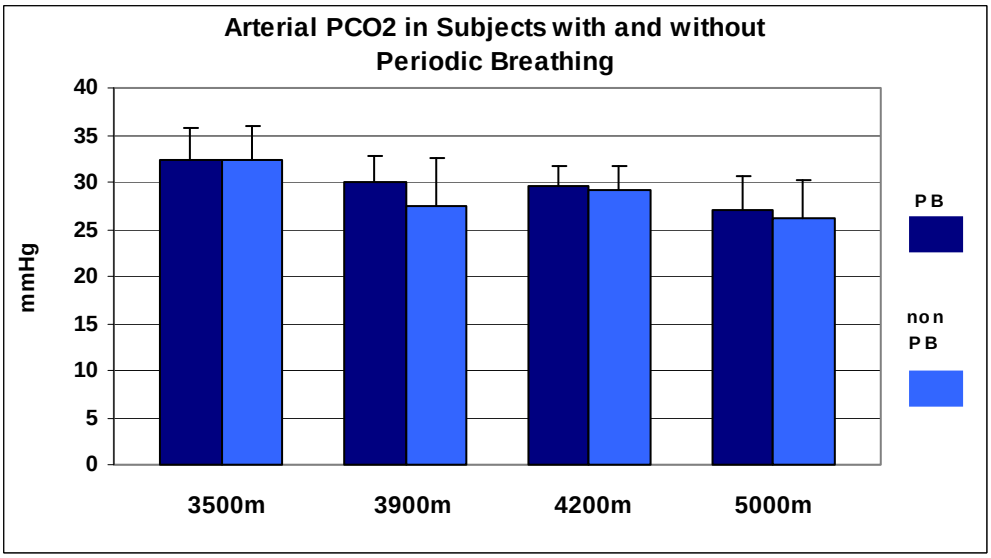
The arterial blood gas analysis in subjects who developed periodic breathing and those who didn't were not significantly different at any altitude. (Figure 4.4.8a-c). However, there was a trend towards a more alkaline pH at 3900m in subjects with periodic breathing compared to subjects without periodic breathing i.e. 7.45 ± 0.02 in PB and 7.42 ± 0.03 in non PB subjects ($p = 0.07$).

Figure 4.4.8a Morning Arterial pO_2 in Periodic Breathing and non Periodic Breathing



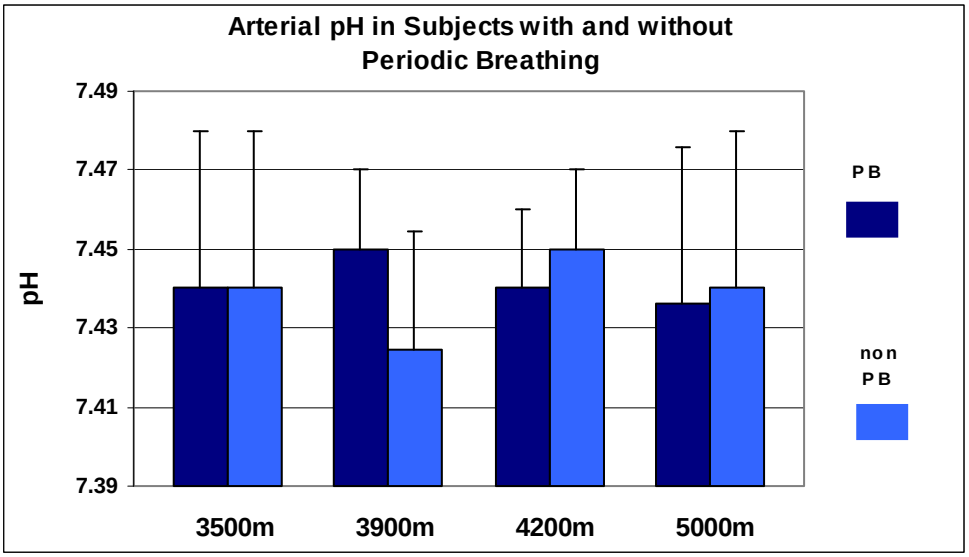
There were no significant differences at any altitude in the arterial oxygen measurements in those subjects who developed periodic breathing compared to those who did not develop periodic breathing.

Figure 4.4.8b Morning Arterial pCO2 in PB and non PB



There were no significant differences at any altitude in the arterial carbon dioxide measurements in those subjects who developed periodic breathing compared to those who did not develop periodic breathing.

Figure 4.4.8c Morning Arterial pH in PB and non PB.



There were no significant differences at any altitude in the arterial pH measurements in those subjects who developed periodic breathing compared to those who did not develop periodic breathing.

4.4.9 Ventilatory Responses at Sea Level

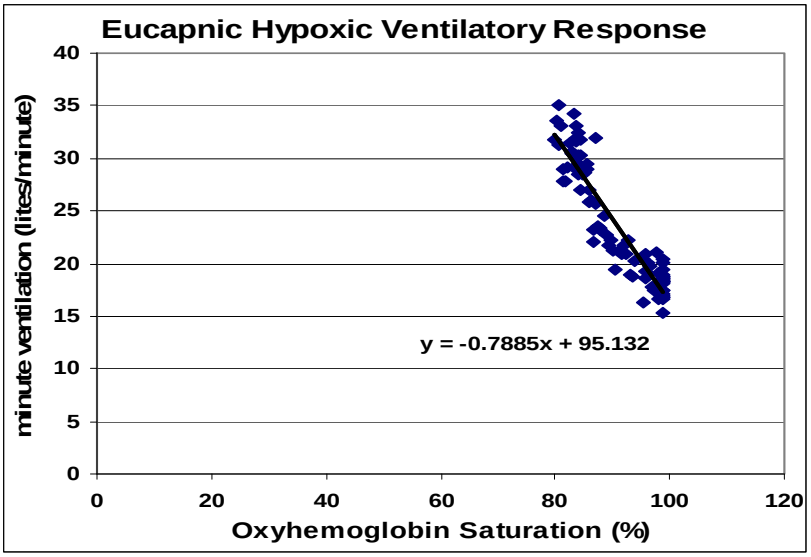
There was a wide range of ventilatory responses to hypoxia and hypercapnia in the nineteen subjects tested at sea level (Figure 4.4.10a).

Most subjects had HVR in the range of 0 - 0.7L/min/% but one subject had a very steep HVR of 1.85L/min/%. The mean HVR for the nineteen subjects was 0.018 ± 0.53.

The hypercapnic HVR was below 1.4 L/min/% in most of the subjects, but one subject had a much steeper hypercapnic HVR of 3.5L/min/%. The mean for the group was 0.31 ± 0.97.

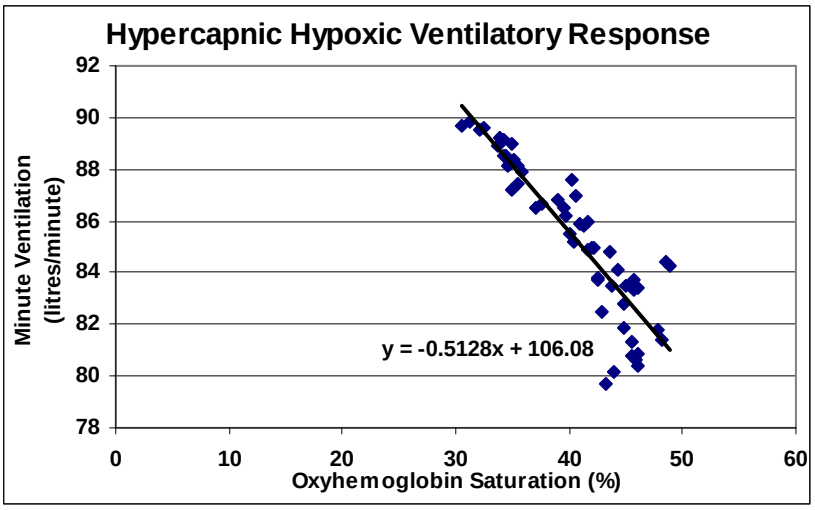
The hypercapnic (hyperoxic) ventilatory response (HCVR) was had a much wider range than either HVR of hypercapnic HVR. The lowest response was 0.07L/min/% and the highest, 4.23L/min/mmHg with five subjects having steep responses (> 3.5), four subjects having responses in the 1.5 – 2.3L/min/% range and the remaining ten subjects in the lower response range of 0 – 1.5L/min/%. The mean for the group of nineteen subjects was 1.92 ± 1.48L/min/%. Figures 4.4.9a-c demonstrate the slopes of each of the three ventilatory response tests in one subject.

Figure 4.4.9a Slope of Ventilatory Response to Eucapnic Hypoxia in One Subject



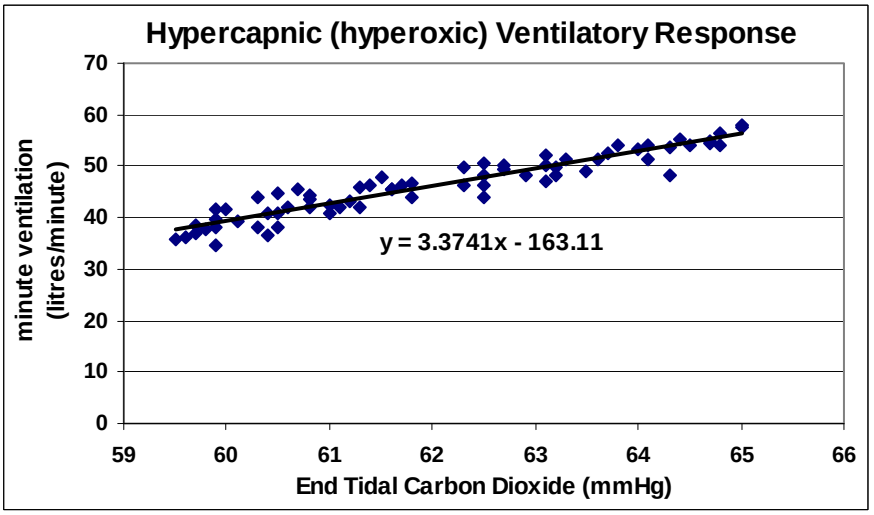
An example of the plot used to calculate the ventilatory response to hypoxia in one subject. The change in ventilation, measured in litres per minute is plotted against the percentage oxygen saturation. As oxygen saturation falls, minute ventilation increases and the slope of this change is calculated using linear regression analysis.

Figure 4.4.9b Slope of Ventilatory Response to Hypercapnic Hypoxia in One Subject



An example of the plot used to calculate the ventilatory response to hypercapnic hypoxia in one subject. The change in ventilation, measured in litres per minute, is plotted against the percentage oxygen saturation. As oxygen saturation falls, minute ventilation increases and the slope of this change is calculated using linear regression analysis.

Figure 4.4.9c Slope of Hypercapnic (Hyperoxic) Ventilatory Response in One Subject



An example of the plot used to calculate the ventilatory response to hypercapnia (hyperoxic) in one subject. The change in ventilation, measured in litres per minute, is plotted against the end tidal carbon dioxide. As end tidal carbon dioxide increases, minute ventilation increases and the slope of this change is calculated using linear regression analysis.

4.4.10 Ventilatory Responses to Hypoxia and Hypercapnia: Relationship to Periodic Breathing during Sleep.

There was a wide range of ventilatory responses (VR) to hypoxia and hypercapnia in the group of nineteen subjects (see section 4.4.9). In some cases these VR measurements were related to the development of periodic breathing or central REM events but these findings were not consistent and there were few significant relationships present.

Figures 4.4.10a-b display the ventilatory responses of each subject and the amount of periodic breathing at the four highest altitudes.

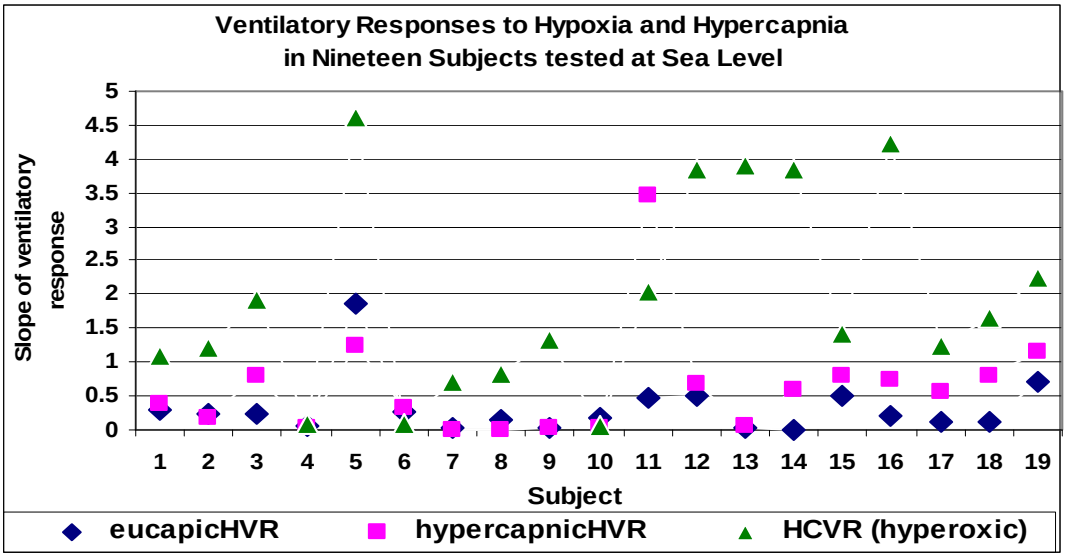
There was a significant relationship between the hypercapnic HVR and the NREM sleep periodic breathing apnea/hypopnea index (AHI) at 3500m, (correlation = 0.58, $r^2 = 0.33$, $p = 0.01$). There was also a significant relationship between the eucapnic HVR and the REM sleep central AHI at 1400m (correlation = 0.625, $r^2 = 0.391$, $p = 0.003$) and at 3900m (correlation = 0.61, $r^2 = 0.37$, $p = 0.005$). (Figures 4.4.10c-q)

When the group was split into those who had periodic breathing at all altitudes of 3500m and higher (mean PB AHI 47 ± 18/hour, n = 10) and those who had low levels of PB at one or two altitudes only (mean PB AHI 6 ± 4/hour, n = 6) and the ventilatory responses compared, it was found that the HVR was significantly higher in the group with PB at all altitudes of 3500m and higher ($p = 0.05$). There were no differences in the hypercapnic HVR or in the HCVR when this test was applied to these VRs.

There were no other significant correlations or relationships between ventilatory responses and periodic breathing index in NREM sleep at any altitude; nor were there any correlations or relationships between the REM sleep central AHI at any altitude and any VR.

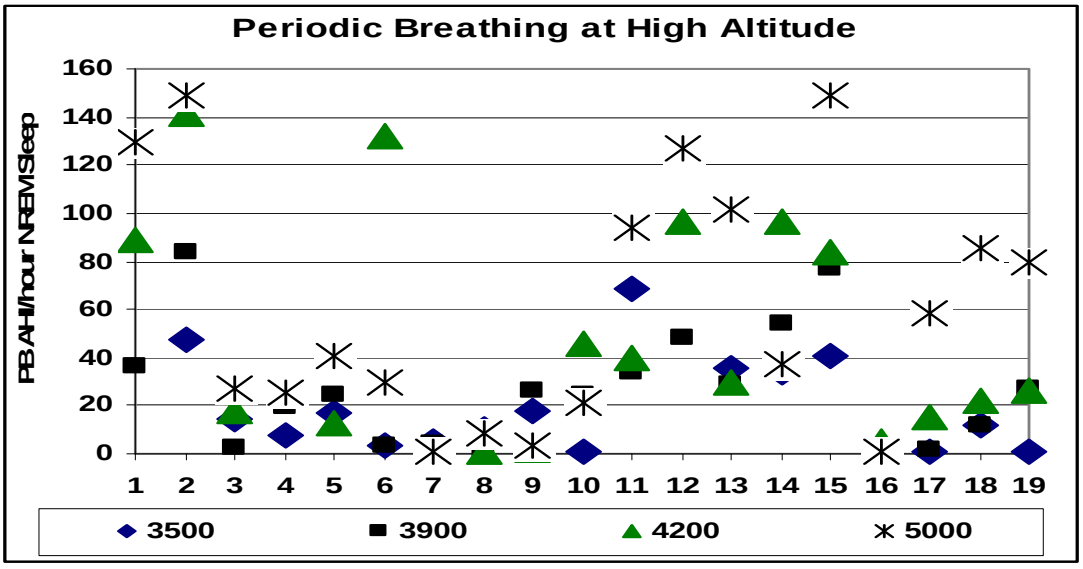
Although there were very few significant statistical relationships between ventilatory responses measured at sea level and the degree of periodic breathing at high altitudes, it is interesting to view the data after separating the subjects into groups according to each one's ventilatory response to eucapnic hypoxia (HVR), hypercapnic HVR and to hypercapnia alone (HCVR). The subjects were split into groups to observe the degree of periodic breathing at each altitude viewed in relationship to the steepness of each subject's VR. Tables 4.4.10a-h subjects with high HVR (n = 5) had higher mean periodic breathing apnea/hypopnea index (AHI) than subjects with flat HVR (n = 9) at all altitudes. Similarly, subjects with high HCVR (n = 5) had much higher AHI than subjects with low HCVR (n = 5). There was not such a noticeable difference in subjects with high (n = 10) and low (n = 9) hypercapnic HVR but the wide variation in the severity of periodic breathing is reflected in high standard deviations.

Figure 4.4.10a



There was a wide range of ventilatory responses in the nineteen subjects, with the hypoxic ventilatory response ranging from 0 – 1.85L/min/%, the hypercapnic hypoxic ventilatory response ranging from 0.01 – 3.46 L/min/% and the hyperoxic hypercapnic ventilatory response ranging from 0.07 – 4.23L/min/mmHg.

Figure 4.4.10b



There was a wide range of periodic breathing apnea/hypopnea indices (PB AHI) In the nineteen subjects with some subjects having very low levels of PB, others had high levels at every altitude, while others had high levels at one or two altitudes only. There does not seem to be relationships between ventilatory responses to hypoxia or hypercapnia and the extent of PB at high altitudes.

Tables 4.4.10a-c Subjects with high, medium and low hypercapnic (hyperoxic) ventilatory responses (HCVR), and the periodic breathing apnea/hypopneas indices (PB AHI) at the four highest altitudes.

High HCVR (> 3)

Subject	3500m	3900m	4200m	5000m
5	17	24	13	41
12		48	96	127
13	36	29	29	101
14	34	55	97	38
16	1	1	5	1
Mean ± SD	**22 ± 16**	**31± 21**	**48± 45**	**62 ± 51**

Medium HCVR (1 - 2.3)

Subject	3500m	3900m	4200m	5000m
1		36	89	130
2	47	84	142	149
3	14	2	18	27
9	18	26	2	4
11	68	34	40	94
15	41	77	84	149
17	1	1	16	59
18	12	12	22	85
9	1	27	27	79
Mean ± SD	**25± 24**	**33± 30**	**49± 46**	**86± 51**

Low HCVR (≤ 0.7)

Subject	3500m	3900m	4200m	5000m
4	8	20		25
6	3	3	132	30
7	5	4	0	1
8	10	0	1	8
10	1	24	46	21
Mean ± SD	**5 ± 4**	**10±11**	**38±56**	**17±12**

Although there were no statistical relationships between the ventilatory responses to hypercapnia without hypoxia (HCVR), when viewed in groups that were divided according to the steepness of their HCVR, it can be seen that most subjects with a steeper HCVR (>1) had more periodic breathing than those subjects with lower HCVR (< 0.7). One subject with a low HCVR had very high levels of periodic breathing at 4200m only while most subjects in this group had PB AHI levels of less than 25/hour. Subjects who had high PB AHI levels at most altitudes were in the groups with HCVR >1.

Table 4.4.10d Subjects with high hypercapnic hypoxic ventilatory responses and the periodic breathing apnea/hypopneas indices (PB AHI) at the four highest altitudes.

High Hypercapnic Hypoxic VR (> 0.5)

Subject	3500m	3900m	4200m	5000m
3	14	2	18	27
5	17	24	13	41
11	68	34	40	94
12		48	96	127
14	34	55	97	38
15	41	77	84	149
16	1	1	5	1
17	1	1	16	59
18	12	12	22	85
19	1	27	27	79
Mean ± SD	**21± 23**	**28 ± 26**	**42 ± 36**	**70± 46**

There was a wide range of periodic breathing apnea/hypopnea indices (PB AHI) in the subjects who were grouped according to a their steeper ventilatory responses to hypercapnic hypoxia; several subjects who had steeper VR to hypercapnic hypoxia had quite low levels of PB while others in this group had very high levels of PB.

Table 4.4.10e Subjects with low hypercapnic hypoxic ventilatory responses and the periodic breathing apnea/hypopneas indices (PB AHI) at the four highest altitudes.

Subject	3500m	3900m	4200m	5000m
1		36	89	130
2	47	84	142	149
4	8	20		25
6	3	3	132	30
7	5	4	0	1
8	10	0	1	8
9	18	26	2	4
10	1	24	46	21
13	36	29	29	101
Mean ± SD	**16±17**	**25± 25**	**55± 59**	**52±58**

Subjects who were assigned to the lower ventilatory responses to hypercapnic hypoxia group also had a wide range of periodic breathing, with some subjects in this group having very little PB at any altitude while others had very high levels of PB. Although the mean PB AHI was similar in this group to the subjects with steeper hypercapnic HVR, there is wider range of PB and this is reflected by in the standard deviations, which are very similar to, or higher than the means.

Table 4.4.10 f-h Subjects with high, low and flat hypoxic ventilatory responses (HVR) and the periodic breathing apnea/hypopneas indices (PB AHI) at the four highest altitudes.

Hypoxic Ventilatory Response ≥ 0.5 (high HVR)

Subject	3500m	3900m	4200m	5000m
5	17	24	13	41
11	68	34	40	94
12		48	96	127
15	41	77	84	149
19	9	27	27	79
Mean ± SD	**34 ± 27**	**42± 22**	**52± 36**	**98± 42**

Subjects who were assigned to the high hypoxic ventilatory response group had a wide range of periodic breathing apnea/hypopnea indices (PB AHI) but most subjects had high levels of PB at each altitude. The variation of the severity of PB is reflected in the high standard deviations.

Hypoxic Ventilatory Response 0 – 0.07 (Flat HVR)

Subject	3500m	3900m	4200m	5000m
4	8	20		25
7	5	4	0	1
9	18	26	2	4
13	36	29	29	101
14	34	55	97	38
Mean ± SD	**20 ± 14**	**27± 18**	**32± 45**	**34± 41**

Subjects who were assigned to the flat hypoxic ventilatory response group had a wide range of periodic breathing apnea/hypopnea indices (PB AHI), with most subjects in this group having low to moderate levels of PB and two having high levels of PB at each altitude. This wide range is reflected in the standard deviations being very similar to or higher than the means.

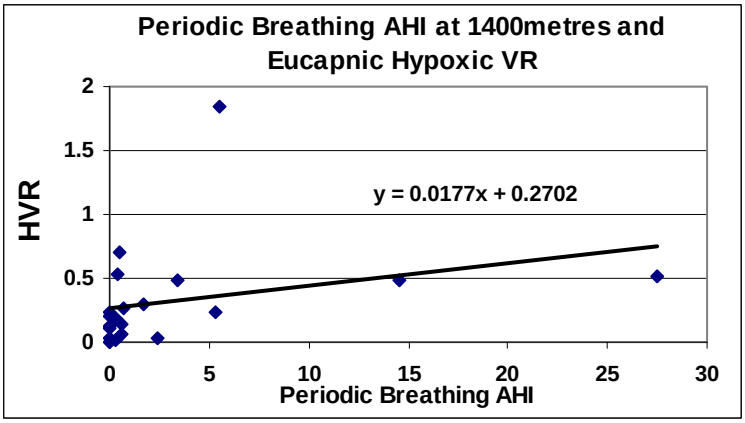
Hypoxic ventilatory response 0.12-0.29 (Low HVR)

Subject	3500m	3900m	4200m	5000m
1		36	89	130
2	47	84	142	149
3	14	2	18	27
6	3	3	132	30
8	10	0	1	8
10	1	24	46	21
16	1	1	5	1
17	1	1	16	59
18	12	12	22	85
Mean ± SD	**11 ± 15**	**18± 28**	**52± 55**	**57± 54**

Subjects who were assigned to the lower hypoxic ventilatory response group also had a wide range of periodic breathing apnea/hypopnea indices (PB AHI) but most were in the lower range. Two subjects in this group had high PB increasing with altitude but most had low levels of PB. One subject had very high PB only at the second highest altitude while two others had moderately high PB only at the highest altitude. This wide range is reflected in the standard deviations being similar to or higher than the means.

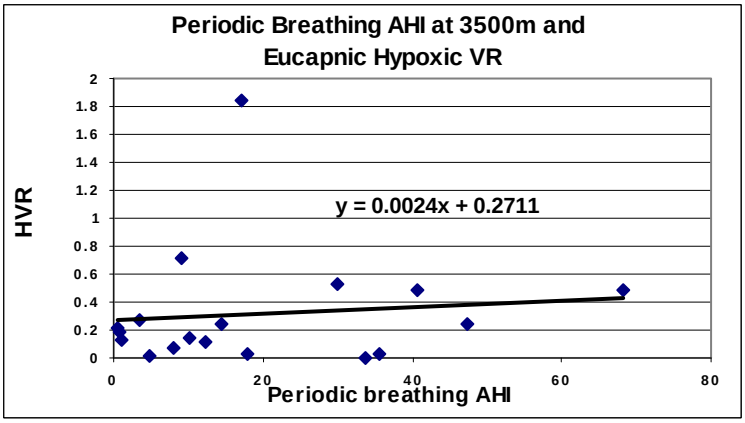
Figures 4.4.10c-g Ventilatory Responses to Eucapnic Hypoxia and Periodic Breathing Indices at High Altitudes.

4.4.10 c



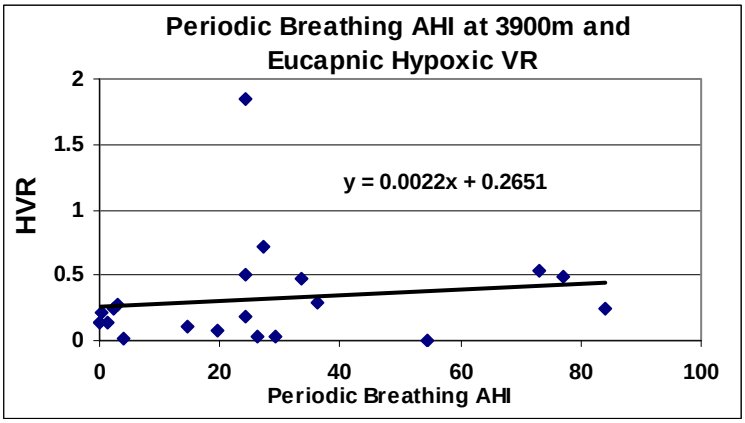
The subjects' ventilatory responses to eucapnic hypoxia were plotted against the periodic breathing apnea/hypopnea indices at 1400m. There was no significant relationship found (correlation = 0.29).

4.4.10 d



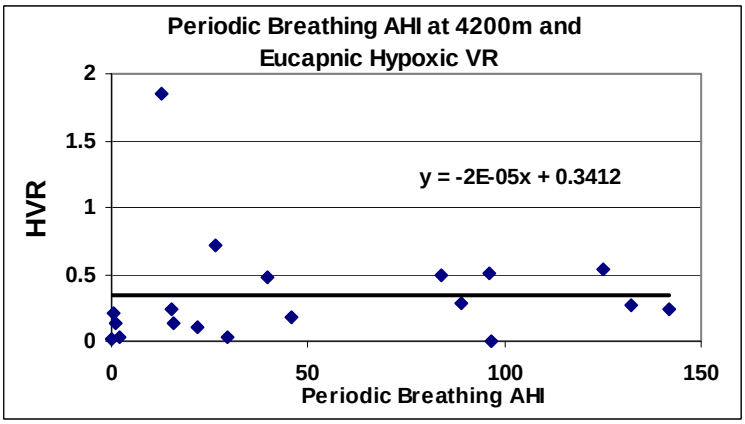
The subjects' ventilatory responses to eucapnic hypoxia were plotted against the periodic breathing apnea/hypopnea indices at 3500m. There was no significant relationship found (correlation = 0.1).

4.4.10 e



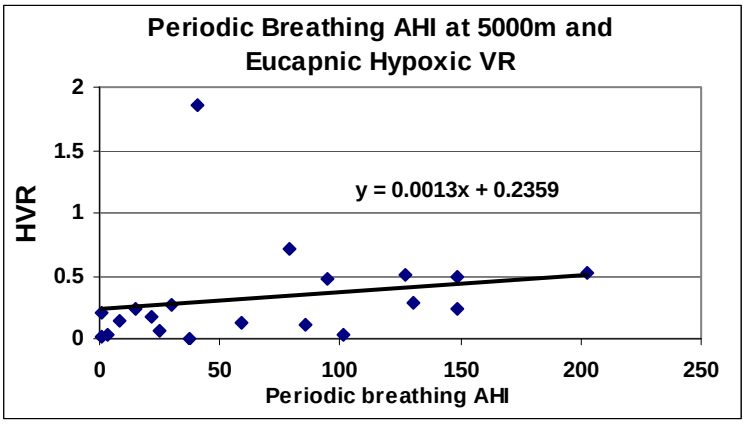
The subjects' ventilatory responses to eucapnic hypoxia were plotted against the periodic breathing apnea/hypopnea indices at 3900m. There was no significant relationship found (correlation = 0.14).

4.4.10 f



The subjects' ventilatory responses to eucapnic hypoxia were plotted against the periodic breathing apnea/hypopnea indices at 4200m. There was no significant relationship found (correlation = -0.003).

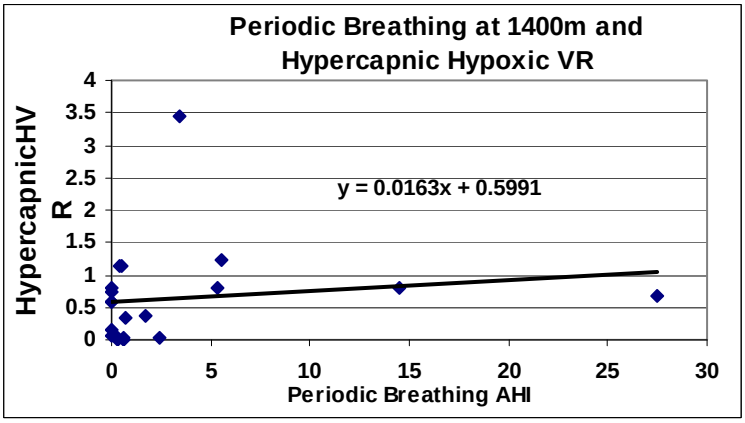
4.4.10 g



The subjects' ventilatory responses to eucapnic hypoxia were plotted against the periodic breathing apnea/hypopnea indices at 5000m. There was no significant relationship found (correlation = 0.29).

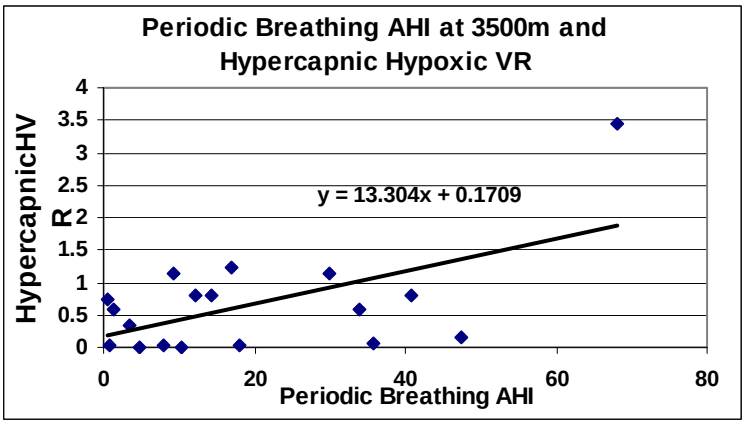
Figures 4.4.10h-l Hypercapnic Hypoxic Ventilatory Responses and Periodic Breathing Indices at High Altitude

4.4.10 h



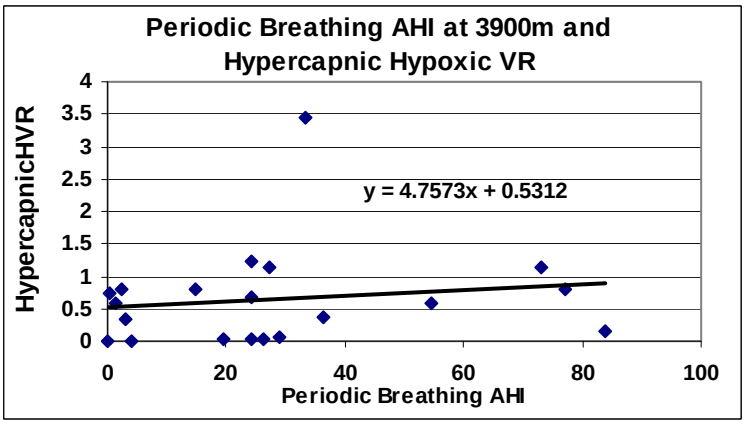
The subjects' ventilatory responses to hypercapnic hypoxia were plotted against the periodic breathing apnea/hypopnea indices at 1400m. There was no significant relationship found (correlation = 0.19).

4.4.10 i



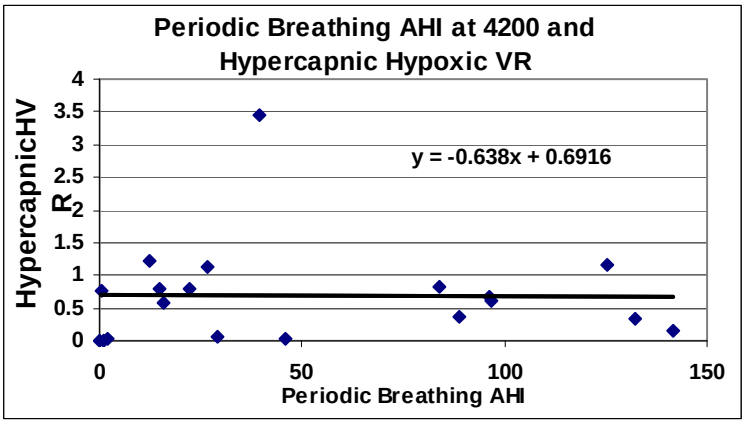
The subjects' ventilatory responses to hypercapnic hypoxia were plotted against the periodic breathing apnea/hypopnea indices at 3500m. There was a significant relationship found (correlation = 0.58, p = 0.01).

4.4.10 j



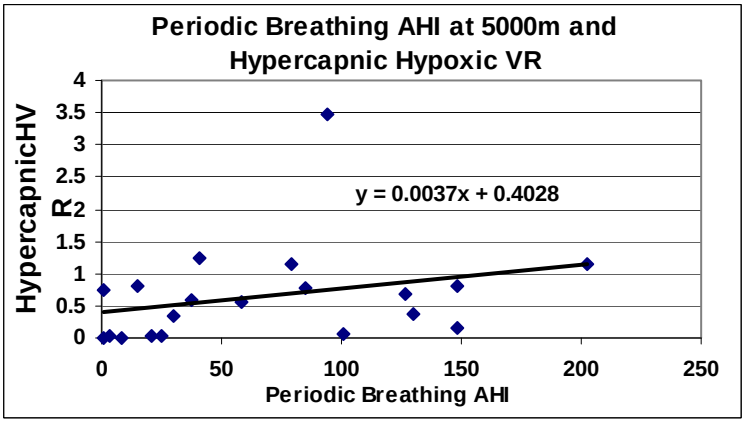
The subjects' ventilatory responses to hypercapnic hypoxia were plotted against the periodic breathing apnea/hypopnea indices at 3900m. There was no significant relationship found (correlation = 0.14).

4.4.10 k



The subjects' ventilatory responses to hypercapnic hypoxia were plotted against the periodic breathing apnea/hypopnea indices at 4200m. There was no significant relationship found (correlation = -0.01).

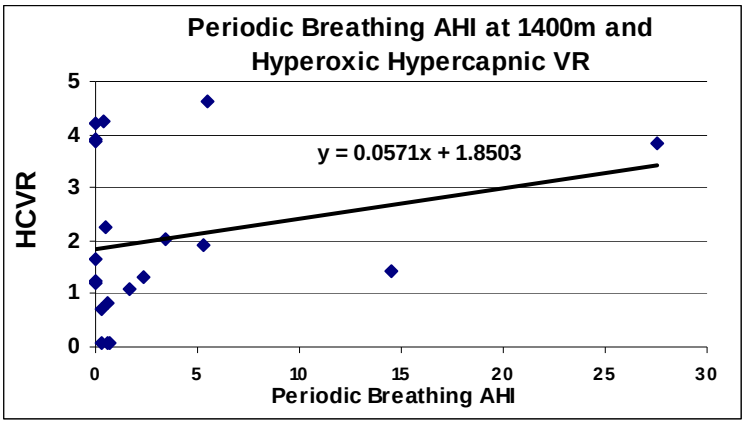
4.4.10 l



The subjects' ventilatory responses to hypercapnic hypoxia were plotted against the periodic breathing apnea/hypopnea indices at 5000m. There was no significant relationship found (correlation = 0.28).

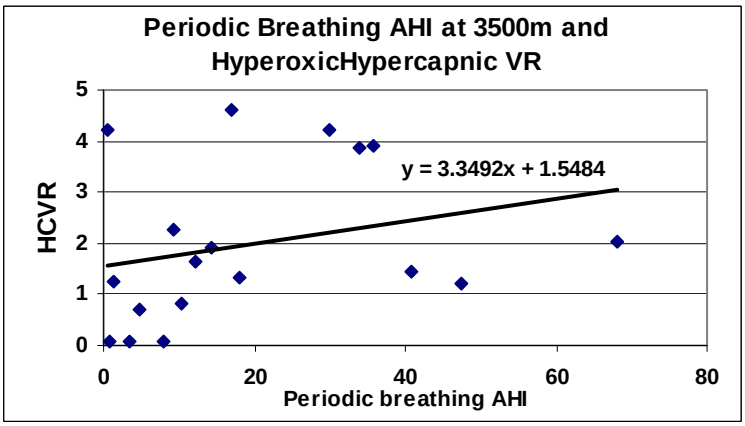
Figures 4.4.10m-q Hypercapnic (Hyperoxic) Ventilatory Responses and Periodic Breathing Indices at High Altitude

4.4.10 m



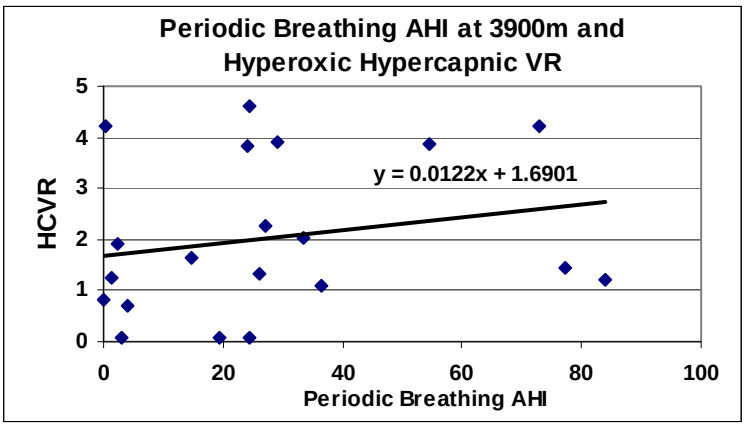
The subjects' ventilatory responses to (hyperoxic)hypercapnia were plotted against the periodic breathing apnea/hypopnea indices at 1400m. There was no significant relationship found (correlation = 0.25).

4.4.10 n



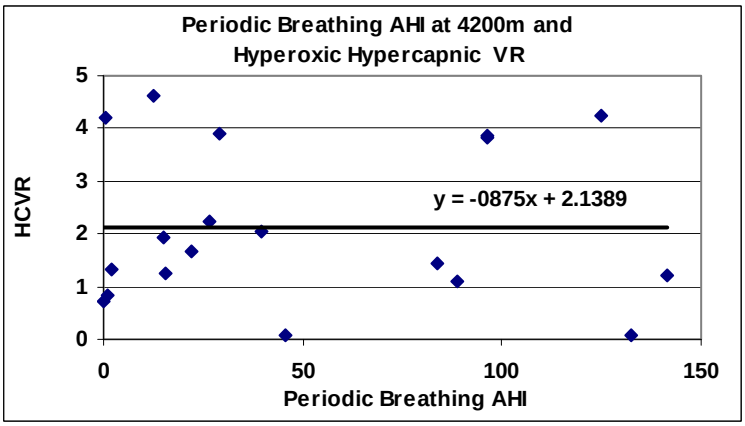
The subjects' ventilatory responses to (hyperoxic)hypercapnia were plotted against the periodic breathing apnea/hypopnea indices at 3500m. There was no significant relationship found (correlation = 0.25).

4.4.10 o



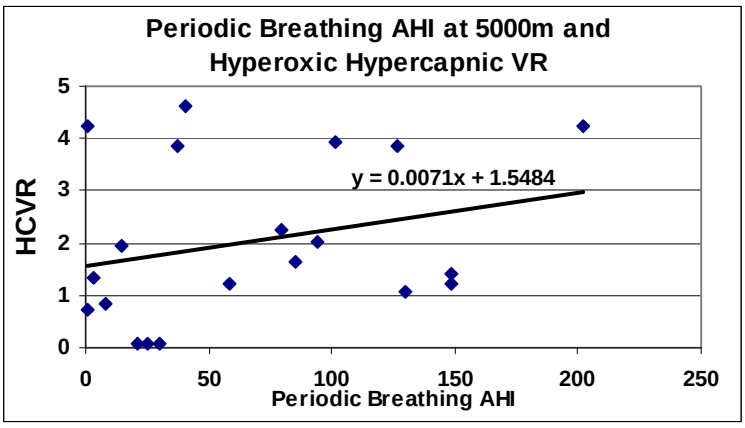
The subjects' ventilatory responses to (hyperoxic) hypercapnia were plotted against the periodic breathing apnea/hypopnea indices at 3900m. There was no significant relationship found (correlation = 0.21).

4.4.10 p



The subjects' ventilatory responses to (hyperoxic) hypercapnia were plotted against the periodic breathing apnea/hypopnea indices at 4200m. There was no significant relationship found (correlation = -0.003).

4.4.10 q



The subjects' ventilatory responses to (hyperoxic) hypercapnia were plotted against the periodic breathing apnea/hypopnea indices at 5000m. There was no significant relationship found (correlation = 0.28).

4.4.11 Ventilatory Responses to Hypoxia and Hypercapnia, Sleeping Oxygen Saturation and Arterial Blood Gases.

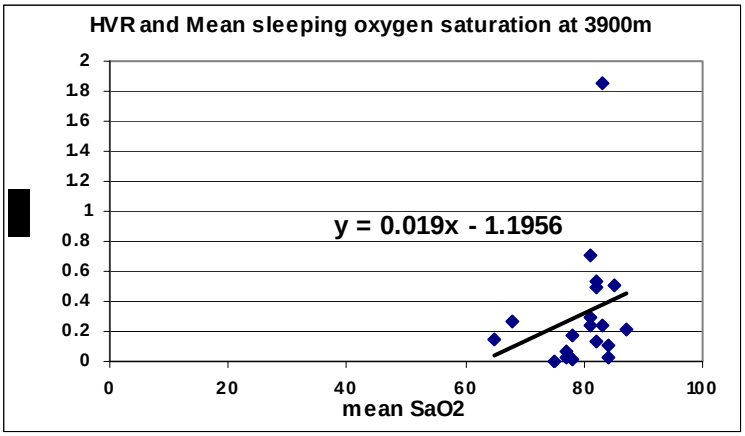
There were few relationships found between ventilatory responses and the sleeping oxygen saturation or arterial blood gases.

When analysing the relationship between ventilatory responses (VR) to hypoxia and hypercapnia and the sleeping mean and minimum oxygen saturation (SaO_2) positive relationships were found between the mean SaO_2 at 3900m and the eucapnic hypoxic VR (correlation = 0.46, p = 0.05) and the hypercapnic hypoxic VR (correlation = 0.52, p = 0.02).

There were no other significant relationships between any ventilatory responses and sleeping SaO_2 at any altitude.

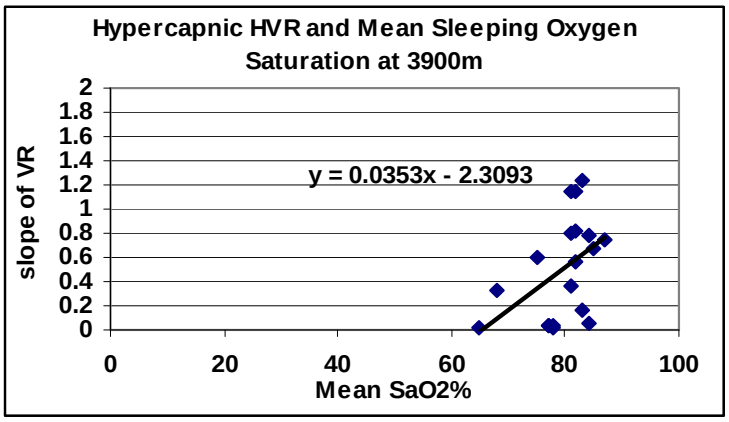
Figure 4.4.11a Relationship between the Ventilatory Responses to Eucapnic

Hypoxia and Sleeping Oxygen at 3900m.



The ventilatory responses to eucapnic hypoxia tested at sea level in nineteen subjects was plotted against the mean sleeping oxygen saturation. A positive relationship was found only at 3900m with the correlation 0.46 (p = 0.05).

Figure 4.4.11b Relationship between the Ventilatory Responses to Hypercapnic Hypoxia and Sleeping Oxygen at 3900m.



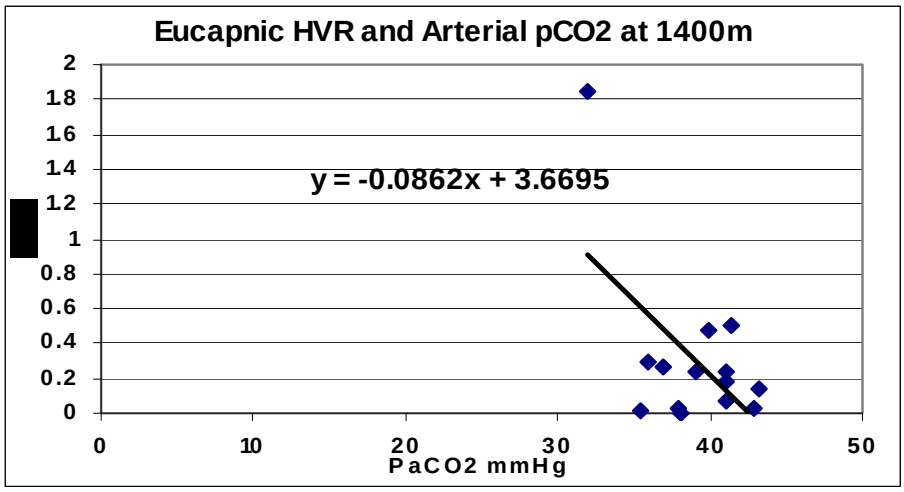
The ventilatory responses to hypercapnic hypoxia, tested at sea level in nineteen subjects, was plotted against the mean sleeping oxygen saturations. A positive relationship was found only at 3900m with the correlation 0.52 (p = 0.02).

There were few relationships between arterial blood gases and ventilatory responses. There was no significant relationship between eucapnic hypoxic ventilatory response (HVR), the hypercapnic HVR or the hyperoxic hypercapnic ventilatory response (HCVR) and arterial pO_2 at any altitude.

However, ventilatory responses to hypoxia and hypercapnia did appear to have a downwards effect on arterial carbon dioxide levels with consequent alkalosis, demonstrated by a higher pH. There were significant negative relationships between the eucapnic hypoxic VR and the hypercapnic hypoxic VR and arterial pCO_2 at two altitudes: eucapnic HVR and arterial pCO_2 were negatively correlated at 1400m (-0.57, $p = 0.03$) and the hypercapnic HVR and the arterial pCO_2 were negatively correlated at 4200m
(-0.55, p= 0 .04).

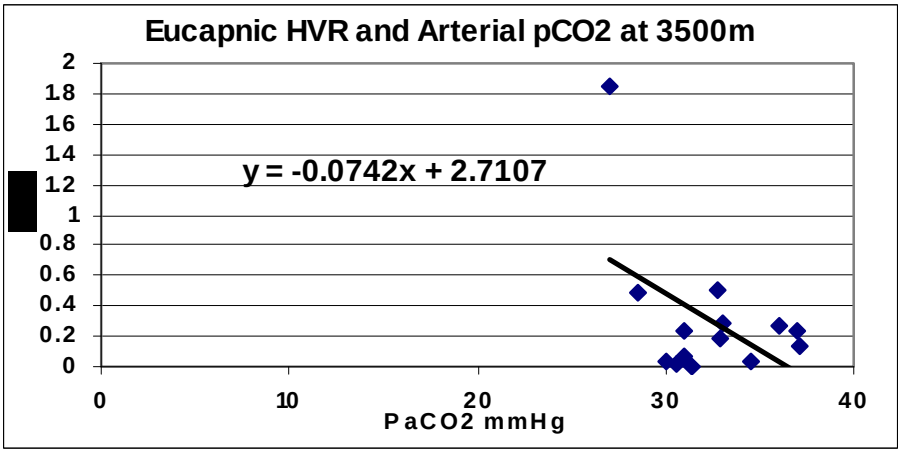
There was a trend towards a significantly negative correlation between the eucapnic HVR and the arterial CO2 at 3500m (-0.52, $p = 0.06$). There was also a trend towards a significantly negative relationship between the hyperoxic hypercapnic VR (HCVR) and arterial pCO_2 at 4200m (correlation = -0.51, $p = 0.06$).

Figure 4.4.11c Ventilatory Responses to Eucapnic Hypoxia and Arterial Carbon Dioxide at 1400m.



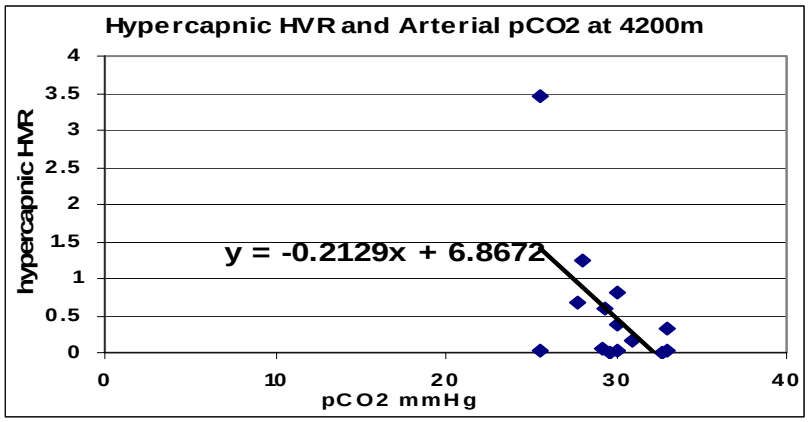
The ventilatory responses to eucapnic hypoxia, tested at sea level in nineteen subjects, were plotted against the arterial carbon dioxide measurements. A significantly negative relationship was found at 1400m (-0.57, p = 0.03).

Figure 4.4.11d Ventilatory Responses to Eucapnic Hypoxia and Arterial Carbon Dioxide at 3500m.



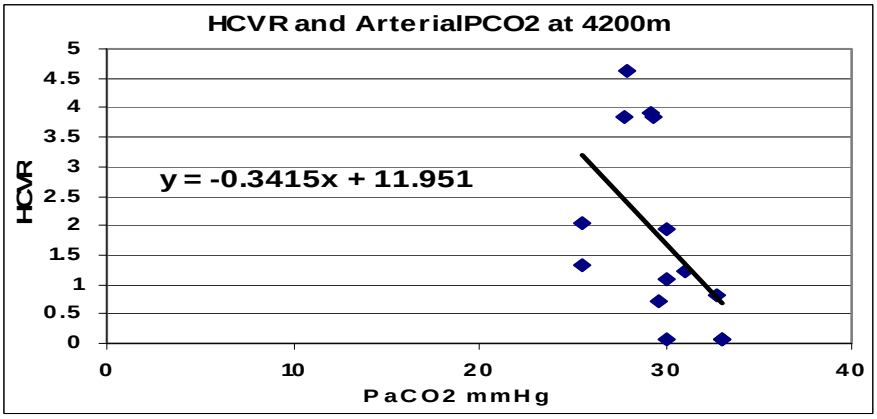
The ventilatory responses to eucapnic hypoxia, tested at sea level in nineteen subjects, were plotted against the arterial carbon dioxide measurements. A significantly negative relationship was found at 3500m (-0.52, p = 0.06).

Figure 4.4.11 e Ventilatory Responses to Hypercapnic Hypoxia and Arterial Carbon Dioxide at 4200m.



The ventilatory responses to eucapnic hypoxia, tested at sea level in nineteen subjects, were plotted against the arterial carbon dioxide measurements. A significantly negative relationship was found at 4200m (-0.55, p = 0.04).

Figure 4.4.11 f Ventilatory Responses to Hypercapnic (Hyperoxic) and Arterial Carbon Dioxide at 4200m.

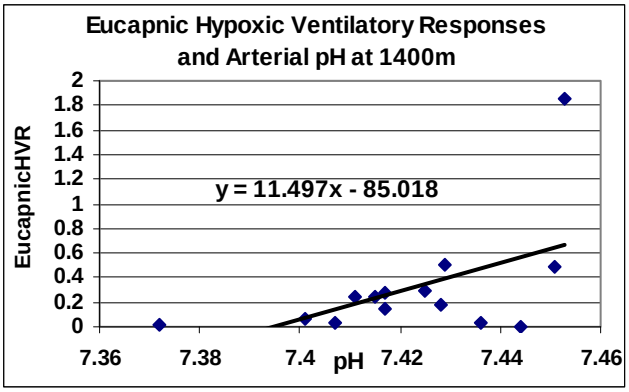


The ventilatory responses to eucapnic hypoxia, tested at sea level in nineteen subjects, were plotted against the arterial carbon dioxide measurements. A significantly negative relationship was found at 4200m (-0.51, p = 0.06).

There were positive relationships between eucapnic HVR and arterial pH at 1400m (correlation = 0.52, p = 0.06), 3500m (correlation = 0.67, p = 0.008) and 4200m (correlation = 0.52, p = 0.06), Figures 4.4.11g-i.

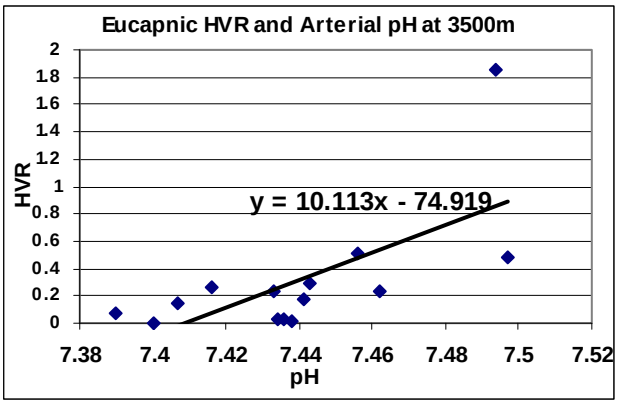
There were positive relationships between the hypercapnic HVR and the arterial pH at 1400m (correlation = 0.57, p = 0.03) and at 3500m (correlation = 0.71, p = 0.004), Figures 4.4.11j-k.

Figure 4.4.11 g Ventilatory Responses to Eucapnic Hypoxia (HRV) and Arterial pH at 1400m.



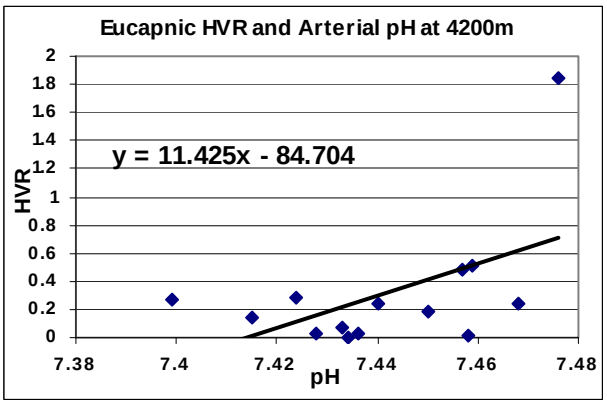
The eucapnic response to hypoxia, tested at sea level, in nineteen subjects had a positive relationship with the arterial pH at 1400m. (correlation = 0.52, p = 0.06).

Figure 4.4.11 h Ventilatory Responses to Eucapnic Hypoxia (HRV) and Arterial pH at 3500m.



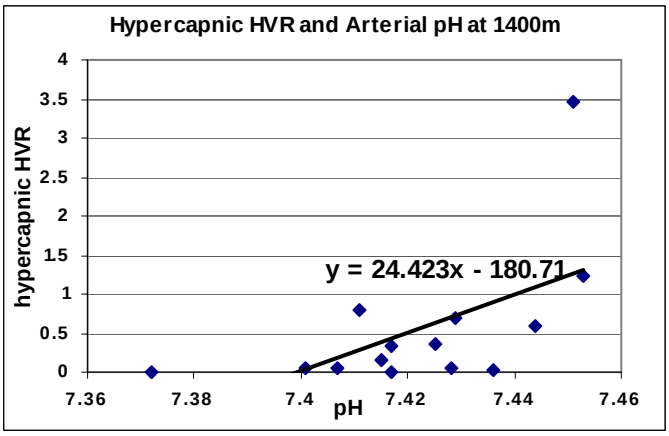
The eucapnic response to hypoxia, tested at sea level, in nineteen subjects had a positive relationship with the arterial pH at 3500m. (correlation = 0.67, p = 0.008).

Figure 4.4.11 i Ventilatory Responses to Eucapnic Hypoxia (HRV) and Arterial pH at 4200m.



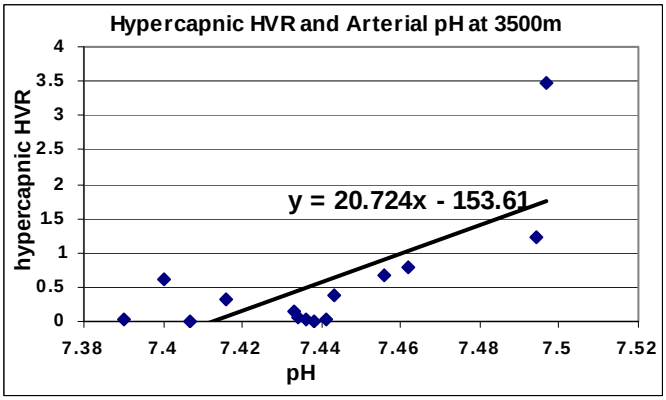
The eucapnic response to hypoxia, tested at sea level, in nineteen subjects had a positive relationship with the arterial pH at 4200m. (correlation = 0.52, p = 0.06).

Figure 4.4.11 j Ventilatory responses to Hypercapnic Hypoxia and Arterial pH at 1400m



The hypercapnic response to hypoxia, tested at sea level, in nineteen subjects had a positive relationship with the arterial pH at 1400m. (correlation = 0.57, p = 0.03).

Figure 4.4.11 k Ventilatory responses to Hypercapnic Hypoxia and Arterial pH at 3500m.



The hypercapnic response to hypoxia, tested at sea level, in nineteen subjects had a positive relationship with the arterial pH at 3500m. (correlation = 0.71, p = 0.004).

4.4.12 Relationship between Periodic Breathing Apneas/ Hypopneas, and their associated Arousal, with Sleep Oxygen Saturation.

Fewer than half the periodic breathing (PB) apneas and hypopneas resulted in arousal from sleep. This was expressed as the equation:

PB arousal index (PB AI)/PB apnea/hypopnea index (PB AHI) to give the ratio of PB apneas/hypopneas to PB arousal from sleep.

Arousal from sleep following apnea or hypopnea may increase ventilation during the hyperpneic phase of the PB cycle and hence increase oxygen saturation. However, there were no significant relationships between the PB AI/PB AHI ratio and sleeping mean or minimum SaO_2 at any altitude; nor were there any correlations between the PB AI/AHI ratio and sleeping mean or minimum SaO_2.

4.5 Discussion

This research examined the effects of high altitude on breathing during sleep and the effects on sleeping oxygen saturation and morning arterial blood gases. It also examined the relationship between the sea level ventilatory responses to hypoxia and hypercapnia and the development of periodic breathing, changes in arterial blood gases and sleeping oxygen saturation.

Results of blood gas analyses demonstrate the profound effect that increasing altitude had on the pO_2 and pCO_2, with the mean pO_2 falling from 95mmHg at sea level to below 80mmHg at even the lowest altitude of 1400m, thence to below 56mmHg for the next three altitudes and below 50mmHg at 5000m. The pCO_2 was similarly affected by even the lowest altitude, falling from a sea level mean of 42mmHg to 39mmHg, thence to the low 30s until 5000m, where it fell to 27mmHg. These results demonstrate the hypoxic effects of high altitude and the challenge to the respiratory control system that was presented to the subjects during their time in Nepal.

The most important finding from this research was that periodic breathing developed in the majority of our subjects with a wide variability in the amount of periodic breathing in the nineteen subjects. There was also intra-subject variability in some subjects, with PB developing at one or two altitudes only.

The dominant feature of breathing during sleep at high altitude was the development of periodic breathing. Most subjects developed periodic breathing at one or more

altitudes but three subjects did not develop periodic breathing at any altitude (AHI < 10/hour) with one subject having very low levels of PB (highest AHI 20/hour at 5000m, mean for all altitudes 10/hour). There was a wide individual variability in the periodic breathing apnea/hypopnea indices (PB AHI). PB was deemed to be present when the PB AHI was 20/hour or higher. Some subjects had very high PB AHI (e.g. 149/hour at 5000m in two subjects and from 101 – 130/hour in three other subjects) while some deemed to have PB had an AHI closer to 20/hour.

Ventilatory responses to hypoxia and hypercapnia, tested at sea level before the trek to high altitude, had very little relationship to the development of periodic breathing with the exception of a positive relationship between eucapnic HVR and the PB AHI at 3500m. When the subjects with PB at 3500m and higher (mean AHI 47/hour) were compared to those with low levels of PB (mean 6/hour) a significant difference was found in their HVR. Steeper HVR has been found in previous studies to be associated with PB at high altitude (Lahiri, 1983) so it was not surprising that the subjects with consistent and high levels of PB had a higher HVR than those who had low levels of PB. Thus it may be possible to predict who will develop periodic breathing at high altitude by performing ventilatory response testing at sea level.

There were no relationships between ventilatory responses and arterial pO_2 or sleeping SaO_2. The relationships that were found between VR and arterial blood gases were exclusively those of pCO_2 and pH i.e. lower pCO_2 and higher/more alkaline pH were correlated with each of the sea level ventilatory response tests at several altitudes.

This reflects an increase in ventilation driving down the CO2, with subsequent alkalosis, but not a higher pO_2.

The main shortcoming of this research was that, due to equipment availability, sleep studies were performed on either the first or second night at each new altitude which may have allowed a degree of acclimatisation to occur in those subjects who were studied on the second night. There were also a number of failures of the equipment, particularly at the highest altitude, where subjects slept while sleep was no longer being recorded. Although these studies were not used in the analysis, the missing sleep data have meant incomplete sets of studies at several altitudes being most pronounced at 5000m where only thirteen of nineteen studies were analysable due to short recording times.

The underlying physiological change at high altitude is hypobaric hypoxia. In turn the mechanism underlying the development of periodic breathing during sleep is alveolar hyperventilation, caused by hypoxia, and leading to a fall in P_{CO2} approaching or falling below the apneic threshold resulting in central hypopneas or apneas during sleep. With breathing cessation or reduction the arterial pO_2 falls, pCO_2 rises and hyperventilation is triggered; thus the cycle continues with repetitive apneas and/or hypopneas followed by hyperpnea. The hyperpneic part of the central apneic or hypopneic event consists of three to four breaths of high tidal volume in which the pO_2 rises and pCO_2 falls to near awake levels and it is thought that this helps to keep the pO_2 higher in those people who experience periodic breathing when asleep at high altitude. It has been suggested by West et al (1986) that periodic breathing during sleep at high altitude, with the severe desaturation that occurs, would be detrimental to

success at high altitude but this theory is not supported by the work of Ghazanshahi & Khoo (1993) who found in research using a computer model of respiratory gas exchange that periodic breathing with "2-4 large breaths that alternate with apnea produce the highest arterial oxygenation levels". Other studies conducted on human subjects at high altitude have not supported a link between either higher or lower mean SaO_2 in periodic breathing (Salvaggio et al., 1998; Normand et al., 1990) finding that the oxyhemoglobin saturation of periodic breathers was similar to those who did not develop periodic breathing. We did not find a difference in either the mean or minimum sleeping SaO_2 between periodic and non periodic breathers at high altitude; nor did we find any significant differences in the morning arterial blood gases between subjects with and without periodic breathing. The severe oxygen desaturation that occurs during PB is offset by the marked increase in SaO_2 after the hyperpneic phase of the PB cycle, thus producing a mean SaO_2 that does not differ from subjects who maintain steady ventilation during sleep.

Respiratory events in REM sleep were quite different from PB, which was present almost exclusively in NREM sleep; these REM respiratory events occurred predominantly in phasic REM in which rapid eye movements, muscle twitches and disordered breathing normally occur. These REM events were called central hypopneas and apneas in this research; they did not occur in any pattern but tended to be of irregular length, unlike PB, and were associated with oxygen desaturation but not always arousal. Central hypopneas and apneas are common in phasic REM sleep and are associated with a degree of hypoventilation but, at sea level and in healthy individuals, are not associated with oxygen desaturation. At high altitude under

conditions of hypobaria these events lead to marked desaturation because of the position on the steeper part of the oxygen-dissociation curve present. These REM events occurred as frequently in subjects who had PB in NREM as those without PB in NREM. They seem to be simply a function of normal phasic REM phenomenon that result in marked desaturation due to the position on the steeper part of the oxygen-hemoglobin dissociation curve where oxygen readily dissociates from hemoglobin; at an altitude of 3500m the mean pO_2 of our subjects was 54 ± 8.5mmHg and this continued to fall with increasing altitude until by 5000m the mean pO_2 was 46.8 ±7.7mmHg. When the arterial pO_2 is below 60mmHg, oxygen dissociates more readily from hemoglobin so the REM sleep respiratory events (central hypopneas and apneas) would be expected to be associated with desaturation. In this research oxygen desaturation often exceeded 10% at altitudes 3500m and higher.

There was a minor degree of upper airway obstruction in several of the subjects, with obstructive apnea/hypopnea indices in sixteen subjects of 3-16/hour (mean 2.2 ± 3.8/hour) in NREM sleep and in twelve subjects with AHI 3-30/hour (mean 6.9 ± 6.1/hour) in REM sleep. This upper airway obstruction, and its related arousal from sleep, had virtually disappeared by 3500m; with a mean AHI 1.3 ± 2.8/hour in NREM, 1.3 ± 3.4/hour in REM, and remaining at these low levels for the rest of the trek. There was a reciprocal relationship between the obstructive AHI and the central (REM) and PB (NREM) AHI whereby as the obstructive AHI fell, the central/PB AHI rose with increasing altitude. This finding, that upper airway obstruction during sleep was resolved with increasing altitude, is in direct contrast to previous findings in which induced hypocapnic hypoxic periodic breathing produced upper airway

obstruction at the nadir of ventilatory drive in the PB cycle (Onal et al. 1986; Warner et al. 1987; Badr et al. 1997). This seeming resolution of upper airway obstruction at high altitude may be due to the non-linear output from the peripheral chemoreceptors, driving upper airway muscles harder than the diaphragm and other inspiratory respiratory muscles; while the development of central apneas is due to the hypocapnia that develops during increased ventilation at high altitude. Hypocapnia is a respiratory depressant and this may be the mechanism responsible for the marked decrease in upper airway obstruction at high altitude. Arterial pCO_2 levels fell from sea level values of 42 ± 3mmHg to 32 ± 3mmHg at 3500m and to 27 ± 4mmHg at 5000m. This degree of hypocapnia explains the occurrence of periodic breathing during sleep in most subjects.

The mean PB AHI in male and female subjects did not vary significantly from each other at altitudes 1400-4200m but more males than females developed PB at every altitude: at 3500m four male and one female developed PB, at 3900m eight male and four female subjects had PB, at 4200m seven male and three female had PB and at 5000m all ten male and five of the female subjects developed PB. This difference in PB is not reflected in sea level ventilatory responses in the male versus female subjects; there were no significant differences in the VR of each gender when compared to each other.

An interesting finding of our study was the marked difference between the periodic breathing AHI and the periodic breathing arousal index (AI); the AHI was at least twice the AI. This supports the findings from previous studies (Berssenbrugge et al.,

1983; Anholm et al., 1992; Khoo et al., 1996; Salvaggio et al., 1998) in which it was found that many periodic breathing cycles were not associated with arousals. This may go part way to explain why there were few complaints from most of our subjects about the quality of their sleep: despite having many hundreds of central apneas during a night's sleep the subjects seemed unaware of this disruption and did not report a bad night's sleep due to symptoms of periodic breathing e.g. waking gasping and difficulty initiating or maintaining sleep.

Arousal from sleep increases ventilation at the termination of each PB cycle and this might improve the oxygen saturation in subjects with a higher AI/AHI ratio. We did not find this effect however in our subjects; there was no difference in the mean or the minimum oxygen saturation in periodic breathers with high and low AI/AHI ratios.
It has been demonstrated that hypoxia is a poor stimulus to arousal from sleep; Berthon-Jones and Sullivan (1982) found that desaturation to as low as 70% caused arousal only around half the time. During PB in sleep at high altitude, the only stimulus to arousal is hypoxia; there is no stimulus to arousal from lung stretch receptors or upper airway receptors during PB.

It has been suggested that a steeper hypoxic ventilatory response predisposes people to periodic breathing at high altitude (West et al, 1986). The reasoning behind this theory is that those with a brisker response to hypoxia would have more hyperventilation in response to the hypobaric conditions and this would lower the arterial pCO_2 and induce more periodic breathing during sleep. We compared the three ventilatory responses (hypoxic, hypercapnic and hypercapnic/hypoxic) to the

periodic breathing indices for each altitude and found only one relationship i.e. eucapnic HVR and PB AHI at 3500m. Ventilatory responses may be altered by high altitude and further work on the changes that occur to ventilatory responses as altitude increases is needed to clarify the relationship (if one exists) between VR and periodic breathing.

Loop gain theory (Khoo et al, 1991) predicts that those with a loop gain closer to 1, i.e. higher gain, are more likely to develop periodic breathing. The reasoning behind the theory is that, when the corrective response to a disturbance is greater than the disturbance, self-sustaining oscillations will occur. The disturbance in the case of high altitude periodic breathing is the apnea, and the corrective response is the hyperpnea; if the hyperpnea is greater in magnitude, the arterial carbon dioxide level is driven lower and this results in further apnea followed by corrective hyperpnea and sustained oscillation i.e. periodic breathing.

It is logical that individuals with brisker ventilatory responses will have a greater corrective response but, in our research we found no relationship between ventilatory responses measured at sea level to the degree of periodic breathing at high altitude. Thus, loop gain may have more parameters than apnea and the hyperpnea that follows. Further work needs to be done in the area of high altitude periodic breathing to ascertain the mechanisms that contribute to its relationship with loop gain theory and ventilatory responses.

CHAPTER 5

ACUTE MOUNTAIN SICKNESS AND NON-INVASIVE VENTILATION DURING SLEEP

5.1 Introduction

Acute Mountain Sickness (AMS) is common in those who travel from near sea level to altitudes higher than 2500m (Coward 1906; Hackett et al. 1976; Ward et al. 1989; Shukitt-Hale et al. 1991) and can be a debilitating effect of high altitude which may require the administration of oxygen, respiratory stimulants such as acetazolamide or descent to lower altitude. The symptoms of AMS include headache, nausea, loss of appetite, breathlessness, dizziness, fatigue, weakness and disturbed sleep (Hansen et al. 1991; Carson et al. 1969; Sampson et al. 1983; Shukitt-Hale et al. 1991). Enrichment of room air with oxygen, by the use of concentrators, is known to eliminate AMS and improve the general well being of people working at high altitude (West 1995; Luks et al. 1998; Barash et al. 2001; McElroy 2000) thus it appears that the hypoxemia that occurs at high altitude is responsible for the development of AMS symptoms.

Hypobaric hypoxia, present at high altitude is likely to be the basis of AMS although the pathophysiologic mechanisms are poorly understood. The low barometric pressure at high altitude results in low inspired pO_2 and hence low alveolar pO_2 leading to oxygen deprivation.

Oxygen saturation during sleep at high altitude is known to be lower than awake

levels (West et al. 1986; Matsuyama et al. 1989) and the development of Acute Mountain Sickness (AMS) is related to lower oxygen saturation (SaO_2) during sleep (Erba et al. 2004; Burgess et al. 2004). AMS sufferers often awake after a poor night's sleep with a severe frontal headache. The severity of arterial oxygen desaturation (hypoxia) appears to be an important part of the development of AMS as the severity increases with increasing altitude as the arterial oxygen saturation falls. Correlations have been found between oxygen saturation at high altitude and AMS (Bircher et al, 1993; Roach et al, 1998). In the study by Roach et al, climbers were studied at Base Camp, at 4200m, and then had AMS symptoms assessed on return from their summit attempts; a lower SaO_2 at Base Camp correlated with subsequent AMS scores.

AMS is assessed using the Lake Louise scoring system (Roach et al, 1993) that was developed at the Lake Louise Hypoxia Symposium in 1991 and modified at the next Symposium in 1993. The Lake Louise Score (LLS) assesses the presence of AMS by a questionnaire; a score of 0-3 is given for each of the symptoms reported with "0" for no symptoms and "3" for severe, debilitating symptoms. Headache must be present to diagnose AMS with at least one of the following symptoms: loss of appetite, nausea, fatigue, weakness, dizziness/light-headedness and difficulty sleeping. Clinical assessment determines the presence of the following: change in mental status, ataxia and peripheral edema. The two scores (subjective/questionnaire and clinical assessment) are added to derive a total score and AMS is said to be present when the score is ≥ 3 in the presence of headache.

AMS can be avoided by ascending gradually, resting when early symptoms develop and allowing time for acclimatisation. It is recommended that no more than 300m should be ascended in one day when the altitude is above 3000m. Physical exercise is known to increase the risk of AMS (Roach et el. 2000) so a further recommendation is to have rest days every two to three days and to sleep for two nights at each altitude above 3000m before further ascent. Treatment of AMS includes symptomatic relief of headache with ibuprofen, paracetamol, codeine and caffeine.

Treatment and prevention by drugs such as acetazolamide have been shown to be effective. Acetazolamide causes acidosis by blocking carbonic anhydrase in the kidney and thus stimulates ventilation; it has been found to be an effective preventative when 125mgs are taken twice a day (Basnyat et al., 2003). Oxygen administration and descent to a lower altitude result in rapid recovery.

Research has shown that oxygen enrichment of room air by use of concentrators is a very useful method of eliminating AMS and improving the general well being of people working at high altitude (West JB, 1995; Luks AM et al, 1998; Barash et al, 2001); this comes as no surprise as AMS is due entirely to the hypoxia of high altitude.

Continuous positive airway pressure (CPAP) and end-expiratory positive airway pressure (EPAP) via face and nasal masks have been used at high altitude to improve oxygen saturation and the symptoms of AMS (Launay 2004; Oelz, 1983; Savourey et al. 1999; Schoene et al. 1985). However, these techniques were applied to subjects

when awake and, as far as is known, neither CPAP nor EPAP has been used in sleeping subjects at high altitude.

Non-invasive ventilation (NIV) has been used for long term ventilatory support since the polio epidemics of the 1950s (Collier and Offeldt 1954; Bach et al. 1987). Since the 1980s there has been a growth in the use of NIV using nasal masks; this growth is linked to the expansion in knowledge regarding the contribution of hypoventilation during sleep to the development of hypercapnic respiratory failure (Bye et al. 1990; Piper and Sullivan 1994; McNicholas 1997) and the successful use of NIV during sleep to improve daytime arterial blood gases (Bach et al. 1987; DiMarco et al. 1987; Ellis et al. 1987).

Tidal volume is increased by the use of NIV (Schönhofer et al., 1997; Diaz et al., 2002) due to positive pressure delivered during inspiration (inspiratory positive airway pressure/IPAP). During expiration airway pressure is maintained (end-expiratory positive airway pressure/EPAP) and this is known to prevent upper airway collapse (Piper and Sullivan, 1994), is thought to prevent passive alveoli collapse as well as recruitment of microatelectatic alveoli (Covelli et al., 1982., Duncan et al., 1987., Wayne, 1976) and has also been shown to reduce the work of breathing due to increased pulmonary compliance (Katz and Marks 1985., Naughton et al. 1995., Lenique et al. 1997).

5.2 Aims

The use of NIV at high altitude has not been trialled to prevent worsening oxygen desaturation during sleep. The aim of this research was therefore to use NIV during sleep at 3800m to assess sleeping oxygen saturation and the development of Acute Mountain Sickness.

5.3 Methods

5.3.1 Subjects

Seven normal, healthy, non smoking sea level-dwelling subjects (three female) were recruited from students of the University of California, San Diego. The mean age of the subjects was 23.6 ± 1.5 years and mean body mass index (BMI) 22.7 ± 1.8kgs/m^2. None of the female subjects was taking oral contraceptives. No subject had traveled to high altitude in the previous six months.

Each subject gave informed consent and the protocol was approved by the University of California, San Diego Human Research Protection Program.

Table 5.3.1 White Mountain Subjects

Subject	***Sex***	***Age (years)***	***Height (cms)***	***BMI (kg/m^2)***
1	M	23	190	26
2	M	23	170	24
3	M	21	184	23
4	M	25	170	23
5	F	23	172	20
6	F	25	166	21
7	F	23	164	22
Means ± SD		***23.3 ± 1.4***	***173.7 ± 9.6***	***22.7 ± 1.97***

Seven subjects were studied at sea level and at the Barcroft research station at 3800m at White Mountain. The subjects were students from the University of California, San Diego and were normal, healthy volunteers.

5.3.2 Measurements

Overnight sleep studies were performed at sea level in San Diego in each subject's home before departure to the high altitude location (White Mountain, California, USA) which is 3800m above sea level.

Sleep study equipment used at sea level and high altitude was the Compumedics (Melbourne, Australia) Siesta portable system.

Parameters measured were two electro-encephalograms (EEG) consisting of central and occipital leads (C3/A2 and O2/A1); two (right and left) electro-oculograms

(EOG); submental electro-myogram (EMG); two lead electro-cardiogram (ECG); chest and abdominal respiratory inductive plethysmography (RIP); anterior tibialis EMG; body position; nasal flow and oxyhaemoglobin saturation.

One subject was studied at 3800m using a limited channel device (Embletta™, Embla, Broomfield, CO, USA). This device measured nasal flow using oxygen cannula and a differential pressure transducer; respiratory movement using peizo bands; oxygen saturation with a finger probe and built-in oximeter.

5.3.3 Protocol and Equipment

Sleep studies were conducted at the subjects' homes in San Diego and on two consecutive nights at the high altitude location. Compumedics Siesta portable monitoring equipment was used to record sleep and breathing in seven subjects at sea level and in six subjects at 3800m. Embletta was used to measure breathing and SaO_2 in one subject at 3800m.

The subjects slept two nights at 3800m and did not ascend or descend to higher or lower altitudes between sleep studies.

On one of the nights at 3800m the subject slept while breathing room air and on the other with non-invasive positive pressure ventilation (NIPPV) via a face mask (ResMed Ultra Mirage Full Face Mask or Respironics Comfort Full Face Mask). The device used was the ResMed VPAP lll STA™ using spontaneous mode i.e. inspiration and expiration triggered by the subject. The VPAP device can deliver

inspiratory pressure of 4-30cms H_2O and expiratory pressure of 4-20cms. These pressures were adjusted for subject comfort in the evening before bed time with the inspiratory pressures being set at 9-12cms H_2O and the expiratory pressures at 4-6cms H_2O.

The order of the two sleep studies was randomised for each subject on the first night at 3800m by coin toss.

Sleep studies were performed using the same protocol and procedure as described in Chapter 3. Sleep staging and respiratory scoring were the same as described in Chapter 3.

5.3.4 Procedure: Sleep Studies

The procedure for sleep studies was the same as that described in Chapter 3.
Subjects were prepared for the sleep studies in the evening before retiring to bed for the night and recording was commenced when the subject was ready to sleep.

On the night when NIPPV was applied the mask was fitted in the evening and the most comfortable style of mask selected. The subject sat on a chair and breathed with the VPAP set on an inspiratory positive airway pressure (IPAP) of 6-12cms and the expiratory positive airway pressure (EPAP) of 4-6cms. The VPAP was then set to the most comfortable settings. The VPAP was set to spontaneous mode in which inspiratory pressure and expiratory pressure was triggered by the subject's breathing.

When NIPPV was not applied a nasal cannula was inserted to monitor airflow. Recording was ended in the morning when the subject awoke.

The sleep studies were downloaded from the memory card onto a laptop computer and then analysed to ensure adequate amount and quality of the data. The VPAP machine was also downloaded onto the laptop computer and this provided information on pressures, leak and time with mask on.

5.3.5 Procedure: Assessment of Acute Mountain Sickness

In order to detect the presence of AMS the Lake Louise questionnaire (Roach et al. 1993) was administered to each subject on the morning after the sleep study. There were two parts to the questionnaire: a self assessment and a clinical assessment (see appendix for complete questionnaire).

The subject was asked to respond to questions about headache, appetite and sleep quality and to give each symptom a score from zero (no symptoms) to 3 (severe symptom). Headache and at least one other symptom must be present for the diagnosis of AMS. A score of ≥ 3 is diagnostic AMS.

5.3.6 Sleep Stage, Arousal and Respiratory Scoring

Sleep stages and arousals were defined and analysed as described in Chapter 3. Respiratory events were defined and analysed as described in Chapter 4.

Some sleep studies failed during recording and therefore sleep architecture was examined in four subjects who had full polysomnography at sea level and two nights at 3800m and comparisons were made between the sea level, night without NIPPV and night with NIPPV.

Respiratory variables were examined in all seven subjects to compare periodic breathing and oxygen saturation during nights at sea level and at 3800m with and without NIPPV.

5.4 Results

5.4.1 Acute Mountain Sickness

Our subjects developed Acute Mountain Sickness (AMS) similar to the proportions found in previous studies (Maggiorini et al. 1990; Kayer et al. 1993; Hackett et al. 1976) i.e. 57% (four of seven subjects) developed AMS after a night's sleep at 3800m when not using non-invasive positive pressure ventilation (NIPPV). The other three subjects (43%) had no symptoms of AMS when sleeping without NIPPV. The Lake Louise Score in the four subjects with AMS were 4, 5, 7 and 7 while the three subjects who did not have AMS had Lake Louise scores 0, 0 and 0.

Table 5.4.1 Mean and Minimum oxyhemoglobin saturation, Lake Louise Acute Mountain Sickness score and order of night on which non-invasive positive pressure ventilation was used at 3800m.

Subject (sex)	Mean SaO_2% Off NIPPV	Mean SaO_2% On NIPPV	Min. SaO_2 Off NIPPV	Min. SaO_2 On NIPPV	LLS Off NIPPV	LLS On NIPPV	NIPPV 1st or 2nd night at 3800m
1 (m)	76	82	69	75	4	0	2
2 (m)	72	80	63	69	5	1	1
3 (m)	73	79	67	72	7	1	2
4 (m)	74	76	59	65	7	0	1
5 (f)	80	82	73	74	0	0	2
6 (f)	80	83	74	74	0	0	1
7 (f)	82	87	74	80	0	0	2
Mean ± SD	**76.7 ± 3.9**	**81.3 ± 3.5** ***p = 0.002***	**68.4 ± 5.8**	**72.7 ± 4.8** ***p = 0.005***	**3.3 ± 3.3**	**0.3 ± 0.5** ***p = 0.04***	

Due to equipment limitations the subjects used non-invasive positive pressure ventilation (NIPPV) either on the first or second night at 3800m and the order was randomised. There were no significant differences between the sleeping mean or minimum oxyhemoglobin saturation (SaO2) or the Lake Louise Acute Mountain Sickness score (LLS) between subjects who used NIPPV on the first or second night at high altitude. Both the mean and the minimum SaO_2 were significantly higher and the LLS significantly lower when NIPPV was used during sleep.

Table 5.4.2 Mean and Minimum sleeping oxyhemoglobin saturation in subjects using non-invasive positive pressure ventilation during sleep on the first or second night at 3800m

Subjects using NIPPV first night	mean SaO_2 off NIPPV	min. SaO_2 off NIPPV	mean SaO_2 on NIPPV	min.SaO_2 on NIPPV
2	72	63	80	69
4	74	59	76	65
6	80	74	83	74
Mean ± SD	75.3±4.2	65.3±7.8	79.7±3.5	69.3±4.5

Subjects using NIPPV second night	mean SaO_2 off NIPPV	min. SaO_2 off NIPPV	mean SaO_2 on NIPPV	min.SaO_2 on NIPPV
1	76	69	82	75
3	73	67	79	72
5	80	73	82	74
7	82	74	87	80
Mean ± SD	77.8±4.0	70.8±3.3	82.5±3.3	75.3±3.4
	ns	ns	ns	ns

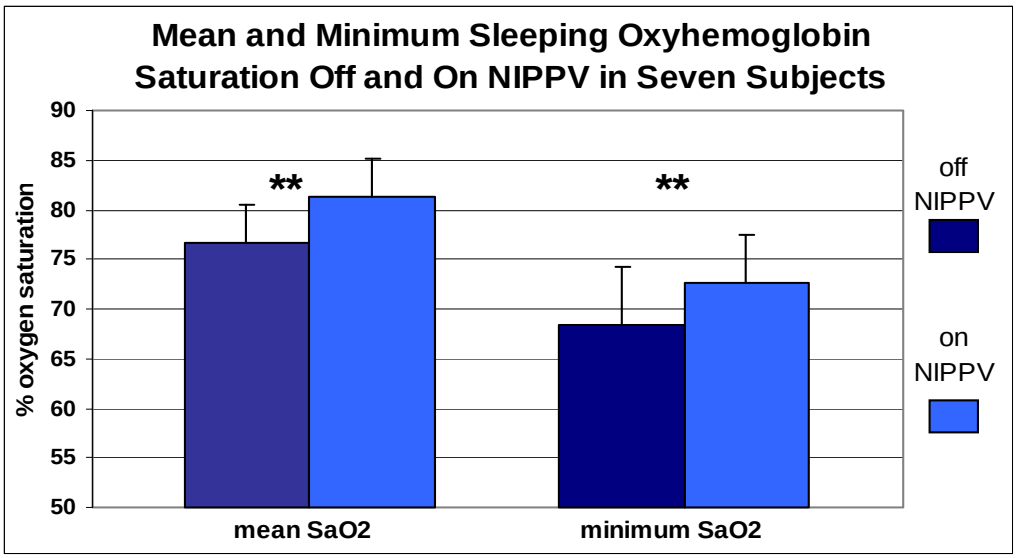
Due to equipment limitations the subjects used non-invasive positive pressure ventilation (NIPPV) either on the first or second night at 3800m and the order was randomised. There were no significant differences between the sleeping mean or minimum oxyhemoglobin saturation (SaO2) between subjects who used NIPPV on the first or second night at high altitude.

5.4.2 Mean and Minimum Sleeping Oxygen Saturation with and without Non-invasive Positive Pressure Ventilation at 3800m; NIPPV use on the first or second night at 3800m

The use of NIPPV during sleep at 3800m resulted in a significant improvement of both the mean and minimum sleeping oxygen saturation when compared to the night without NIPPV ($p = 0.003$ for mean and $p = 0.02$ for minimum.

Three subjects used NIPPV on their first night at high altitude and four subjects used NIPPV on their second night at high altitude. There were no differences in the mean or minimum oxygen saturation in these two groups either on, or off NIPPV.

Figure 5.4.2 Mean and Minimum Oxyhemoglobin Saturation during Sleep at 3800m with or without Non-invasive Positive Pressure Ventilation (NIPPV)

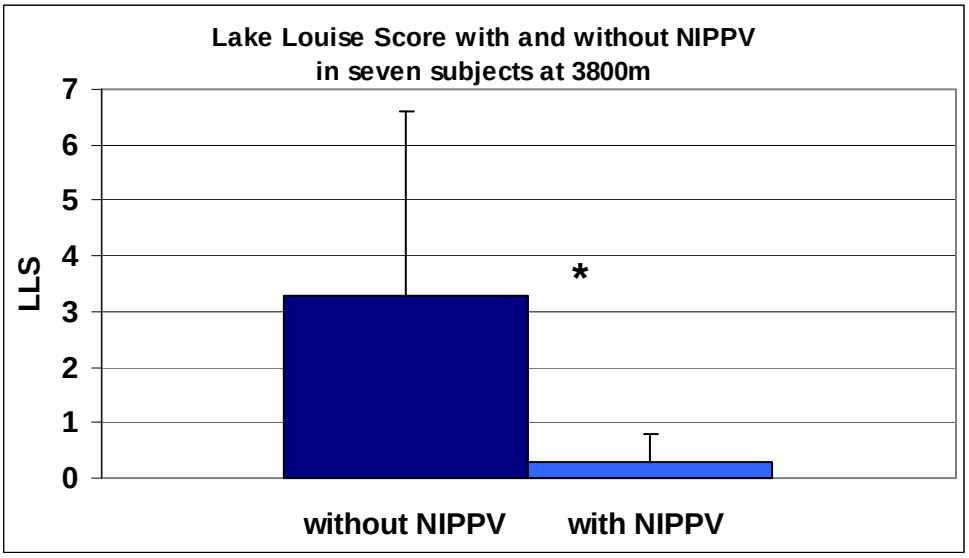


Non-invasive positive pressure ventilation (NIPPV) was used by seven subjects during one of two nights sleeping at 3800m. There was a significant improvement in both the mean and the minimum sleeping oxyhemoglobin saturation (SaO_2) when ventilation NIPPV was used during sleep at 3800m ($p = 0.002$ and 0.005 respectively).

5.4.3 Lake Louise Scores after a night sleeping with and without non- invasive positive pressure ventilation at 3800m

There was a significant improvement in the measure of Acute Mountain Sickness (Lake Louise Score) after a night of sleep using NIPPV. The LLS for the group after sleeping without NIPPV was 3 ± 3 (0,0,0,4,5,7,7) and after sleeping with NIPPV, 0.5 ± 0.3 (0,0,0,0,0,1,1) with NIPPV ($p = 0.03$).

Figure 5.4.3 Lake Louise Score (LLS) for Acute Mountain Sickness when sleeping with or without non-invasive positive pressure ventilation (NIPPV) during sleep at 3800m

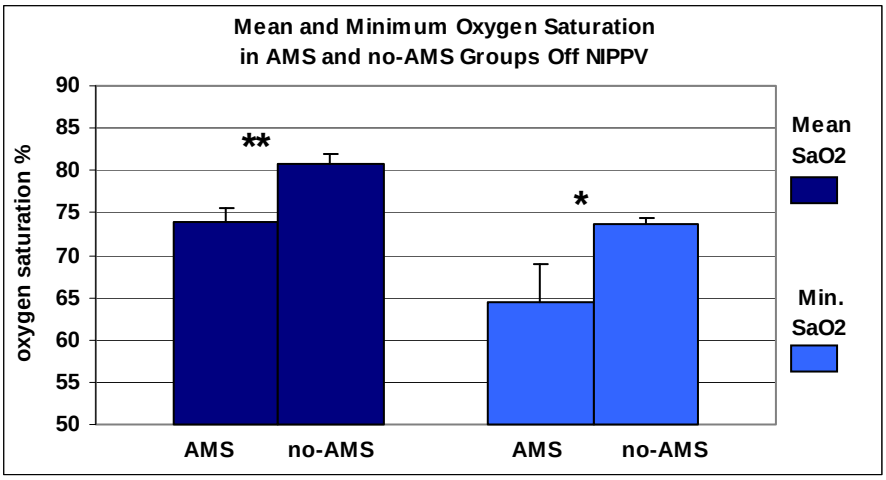


The Lake Louise questionnaire was administered to seven subjects in the morning, within an hour of waking, to evaluate the presence and severity of Acute Mountain Sickness (AMS). The Lake Louise score (LLS) was significantly lower i.e. fewer and less severe AMS symptoms, after a night during which non-invasive positive pressure ventilation (NIPPV) was used.

5.4.4 Mean and Minimum Sleeping Oxygen Saturation in Subjects with and without Acute Mountain Sickness

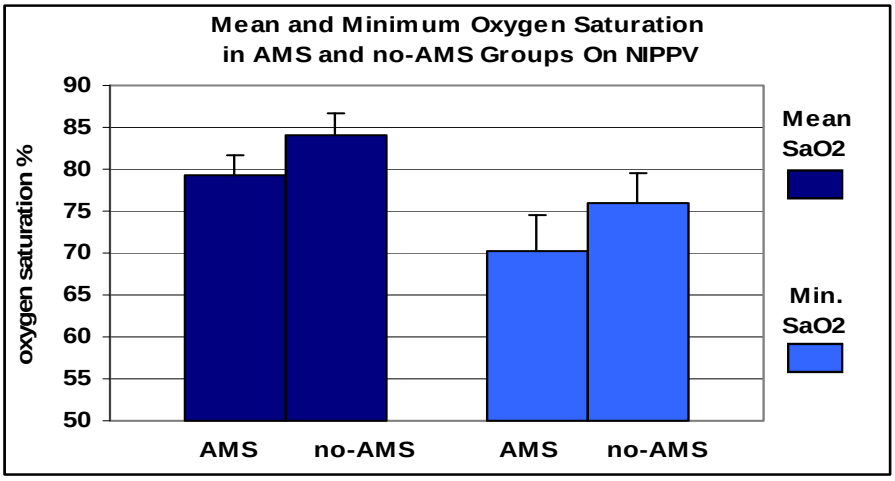
The four subjects who developed AMS after a night without NIPPV had significantly lower mean ($p = 0.002$) and minimum ($p = 0.02$) sleeping oxygen saturations than the three subjects who did not develop AMS after a night without NIPPV. However, when using NIPPV there were no significant differences between the two groups' sleeping oxygen saturations. Interestingly, the AMS group's mean and minimum SaO_2 ON NIPPV were not significantly different ($p > 0.1$) to the no-AMS group's mean and minimum SaO_2 OFF NIPPV.

Figure 5.4.4 a Mean and Minimum oxyhemoglobin saturation in subjects with or without Acute Mountain Sickness, during sleep at 3800m in which non-invasive positive pressure ventilation was not used



Subjects who developed Acute Mountain Sickness (AMS) had significantly lower mean and minimum oxyhemoglobin saturations (SaO_2) during sleep at 3800m in which non-invasive positive pressure ventilation (NIPPV) was not used ($p = 0.002$ and 0.02 respectively).

Figure 5.4.4 b Mean and Minimum oxyhemoglobin saturation in subjects with or without Acute Mountain Sickness, during sleep at 3800m in which non-invasive positive pressure ventilation was used



There were no significant differences between the sleeping oxyhemoglobin saturations (SaO2) in subjects with or without Acute Mountain Sickness (AMS) on the night at 3800m when non-invasive positive pressure ventilation (NIPPV) was used during sleep. However, the mean and minimum SaO_2 in AMS subjects when sleeping with NIPPV was similar to that of the subjects without AMS when sleeping without NIPPV.

5.4.5 Periodic Breathing during Sleep at 3800m

Six of the subjects developed periodic breathing (PB) in NREM sleep at 3800m when sleeping without NIPPV. One subject did not develop PB when sleeping with NIPPV (PB AHI < 2/hour). There was a wide range of periodic breathing in the six subjects with PB, with the highest AHI being 96/hour and the lowest 24/hour (mean 42 ± 32/hour). When NIPPV was used five subjects developed PB but the AHIs were lower. However this was not a significant difference ($p = 0.2$). The wide range in the PB AHI indices persisted in the five subjects with PB when using NIPPV, with the lowest AHI being 12/hour and the highest 53/hour (mean 24 ± 21/hour).

5.4.6 Sleep Architecture at Sea Level and at 3800m on or off Non-invasive Positive Pressure Ventilation

Full polysomnography was available for analysis on only four subjects.

Sleep architecture was disrupted on at 3800m compared to sea level and this was true for the nights when NIPPV was used and the nights when it was not used.

Total sleep time (TST) was significantly reduced compared to sea level on the nights when NIPPV was not used: TST was 322 ± 89 minutes at sea level and 213 ± 74 minutes at 3800m without NIPPV ($p = 0.05$). However, on the night that NIPPV was used, TST was not significantly different from sea level (219 ± 175 minutes). Sleep efficiency was reduced at 3800m when NIPPV was used: sleep efficiency was 88 ± 10% at sea level and only 58 ± 29% at 3800m when NIPPV was used ($p = 0.05$). Sleep efficiency when NIPPV was not used was 75 ± 23% (ns).

There were also some significant changes to sleep stages at 3800m both on the nights when NIPPV was used and on the nights it was not used.

The lightest sleep stage, Stage 1 non rapid eye movement (NREM) sleep, was increased significantly only on the night that NIPPV was not used: 11 ± 5 minutes of Stage 1 NREM sleep at sea level and 24 ± 13 minutes when NIPPV was not used ($p = 0.05$).

Slow wave sleep (SWS) was decreased on the nights that NIPPV was not used: 95 ± 43 minutes of SWS at sea level and 45 ± 28 minutes when NIPPV was not used ($p = 0.05$) and REM sleep was decreased both on the nights when NIPPV was used and on

the nights it was not used but reached significance only on the night without NIPPV; in fact two of the four subjects had no REM sleep when NIPPV was used and one subject had no REM sleep on the night when NIPPV was not used. The average REM sleep duration at sea level was 68 ± 39 minutes and only 18 ± 19 minutes without NIPPV ($p = 0.03$) and 22 ± 33 minutes when NIPPV was used ($p = 0.06$).

The total arousal index (number of arousals per hour of sleep) was increased at 3800m. At sea level the mean arousal index (AI) was 16 ± 5/hour and at 3800m when sleeping without NIPPV it was 36 ± 7/hour ($p = 0.001$) and 33 ± 14/hour when NIPPV was used ($p = 0.03$).

Table 5.4.6 Sleep architecture in four subjects studied at sea level and during two nights

Subject	TST	Sleep Efficiency	Sleep Latency	Stage 1 mins.	Stage 2 mins.	SWS mins.	REM mins.	Arousal index/hr	Periodic breathing/hr
Sea level									
1	255	94	13	15	129	73	51	20	0
2	362	97	23	3	130	158	72	11	0
3	429	87	12	14	212	84	119	13	0
4	242	74	21	10	142	64	28	21	0
Mean ± SD	**322 ± 89**	**88 ± 10**	**17 ± 6**	**11 ± 5**	**153 ± 40**	**95 ± 43**	**68 ± 39**	**16 ± 5**	**0 ± 0**
3800m off NIPPV									
1	293	92	9	31	169	51	43	32	33
2	237	92	4	8	149	60	22	35	30
3	117	43	46	20	95	3	0	30	47
4	203	72	7	38	94	65	6	46	96
Mean ± SD	**213 ± 74**	**75 ± 23**	**17 ± 20**	**24 ± 13**	**127 ± 38**	**45 ± 28**	**18 ± 19**	**36 ± 7**	**52 ± 31**
3800m on NIPPV									
1	150	64	30	9	96	30	16	29	26
2	429	88	26	11	237	112	70	18	25
3	20	19	37	10	10	0	0	33	0
4	276	59	9	37	160	80	0	52	53
Mean ± SD	**219 ± 175**	**58 ± 29**	**26 ± 12**	**17 ± 14**	**126 ± 96**	**48 ± 57**	**22 ± 33**	**33 ± 14**	**26 ± 22**

Sleep architecture was disrupted at 3800m. Total sleep time (TST) was decreased significantly on the nights when NIPPV was used (p = 0.05). Sleep efficiency was also reduced when non-invasive positive pressure ventilation (NIPPV) was used (p = 0.05). Sleep stages were disrupted by high altitude:
Stage 1 NREM sleep was increased on the nights when NIPPV was not used (p = 0.05); slow wave sleep was reduced at 3800m when NIPPV was not used (p = 0.05); REM sleep was reduced significantly when NIPPV was not used at 3800m (p = 0.03) and nearly reached significance when NIPPV was used (p = 0,06). The total arousal index was increased at high altitude both with (p = 0.001) and without NIPPV (p = 0.03).

5.5 Discussion

This research has demonstrated that sleeping at high altitude using a non-invasive positive pressure ventilator (NIPPV) improves sleeping oxygen saturation and alleviates or abolishes the symptoms of Acute Mountain Sickness (AMS).

Sleep was disrupted at 3800m on the nights when NIPPV was used and on the nights it was not used. Total sleep time, sleep efficiency and slow wave sleep were reduced and Stage 1 NREM was increased on the nights when NIPPV was used. REM sleep was reduced and the total arousal index was increased on both nights at 3800m.

AMS has been shown to be associated with a low mean sleeping SaO_2 (Burgess et al 2004; Erba et al 2004), therefore keeping the SaO_2 higher during sleep by the use of NIPPV during sleep effectively prevented AMS symptoms. This research also demonstrated that those subjects who developed AMS benefited more from the use of NIPPV during sleep i.e. AMS subjects demonstrated more improvement in their SaO_2 than the subjects who did not develop AMS. The mechanism of this improvement is likely to be increased tidal volume by the use of inspiratory positive pressure and by prevention of alveolor collapse and recruitment of microatelectatic alveoli by the use of expiratory positive pressure.

The major shortcoming of this research was that only seven subjects were studied. The power of the statistical analyses would be increased by studying a larger group. This was also an unblinded study, with no control e.g. sham NIPPV being used. However, the results, particularly for the AMS subjects, clearly demonstrate a strong

case for the use of positive pressure ventilation at high altitude to prevent and treat AMS. Our subjects found the mask and NIPPV uncomfortable and this may have affected their sleep quality; two subjects had no REM sleep while using NIPPV and some sleep values were reduced when NIPPV was used.

AMS is very common in people who rapidly ascend to high altitude. In our subjects 57% developed AMS with Lake Louise Scores from 4-7; this prevalence is in agreement with previous work on AMS e.g. Hackett et al, 1976 finding of 53% of trekkers at Pheriche in the Nepal Himalaya at an altitude of 4200m; Kayser et al, 1991, at 5400m in the Nepal Himalaya; and Maggiorini et al, 1990 with 41% in the Alps at altitudes from 2800m to 4559m.

Positive expiratory pressure has been used as a treatment and prevention for AMS in previous studies. Positive end-expiratory pressure (PEEP) is known to improve gas exchange and increase oxyhemoglobin saturation in pulmonary edema (Wayne K S., 1976) and at high altitude (Schoene et al, 1985; Larson, 1985) but it is also thought to increase the work of breathing, the risk of barotrauma, worsen concomitant cerebral edema by decreasing venous return (Oelz, 1983) and reduce cardiac output. The method used to deliver PEEP in the field at high altitude is via a tightly fitted face mask with a valve that allows inspiration at barometric pressure and expiration at increased pressure.

PEEP has also been used during ascent of Mont Blanc at 4810m (Launay et al., 2004), in hypobaric chamber experiments (Savourey et al., 1998; Savourey et al., 1999) and was found to reduce the incidence of AMS and improve oxyhemoglobin saturation.

Continuous positive airways pressure (CPAP) was used by a group studying its effect at Mount Cook (3205m) in New Zealand (Davis et al., 2002). Fourteen subjects ascended Mt Cook rapidly; the use of a specially designed CPAP machine that operated at low gas flows increased oxyhemoglobin saturation and decreased the respiratory rate with no apparent fall in cardiac output. Unfortunately this work was presented as an abstract only.

Non-invasive positive pressure ventilation (NIPPV) has not been used at high altitude to treat or prevent AMS. The mechanism by which NIPPV improves oxygen saturation is likely to be the increased tidal volume that is delivered by the positive airway pressure delivered during inspiration (IPAP) and by the prevention of passive collapse of the upper airway and alveoli during expiration by the delivery of a reduced, but still ≥4cms H_2O pressure. The difference between the inspiratory and expiratory pressures (swing) determines the amount of increased tidal volume. In our subjects we titrated the pressures in the evening before retiring for the night and set the VPAP machine on pressures that were tolerable and comfortable. In our subjects these pressures were 9-10cms H_2O for the IPAP setting and 4-5cms H_2O for the EPAP settings, giving a swing of 5cms H_2O. This represents a very small increase in tidal volume but, as can be seen from the improvement in sleeping SaO_2 when NIPPV was used, was sufficient to markedly reduce the symptoms of AMS. These findings

tend to reinforce the theory that AMS is more likely to develop in those people whose sleeping oxygen saturation is lower (Burgess et al, 2004; Erba et al, 2004). However, this was a small group and further research is needed to ascertain whether NIPPV is a viable and effective prevention or treatment for AMS.

There are several effective treatments and strategies for dealing with the development of symptoms of AMS. Rest is an effective strategy; two or more days spent at each new altitude above 3000m assists in the acclimatisation process. Oxygen administration rapidly resolves AMS, as does acute descent by as little as 300m but neither will assist acclimatisation. Medications can be used to stimulate breathing (e.g. acetazolamide) and treat headache (e.g. paracetamol, ibuprofen) but it is unwise to remain at high altitude and particularly to sleep at high altitude once AMS symptoms have become severe (Lake Louise Score >7) and do not respond to the recommended treatments and strategies. It is important to descend as quickly and as far as possible; this is not easily accomplished if the patient is very ill and unable to walk and there is no means of transportation; hence the importance of effective treatments available in the field.

There are several treatments that have been shown to be effective in treating AMS.
The portable hyperbaric chamber, or Gamow bag, is a zippered, rubberised canvas bag in which the patient can lie while an operator uses a foot pump to increase the air pressure inside the bag. It is an effective method of treating AMS (Kasic et al., 1989) but it can be a difficult task for the foot pump operator to maintain optimal pressure, as exercise at high altitude is quickly exhausting.

The results of this research into the use of positive pressure ventilation at high altitude support the theory that SaO_2 can be improved by increasing both inspiratory airway pressure, thus increasing tidal volume during sleep and expiratory airway pressure which may work by recruitment of microatelectatic alveoli, leading to improved gas exchange (Wayne 1976) and the prevention of collapse of the upper airway (Sullivan et al, 1981).

There is no published work to report NIPPV or CPAP use during sleep at high altitude to prevent the occurrence of AMS or treat AMS after it has developed. The findings from Erba et al 2004 and Burgess et al 2004, demonstrating the link between low nocturnal/sleeping oxyhemoglobin saturation and AMS, suggest that more research into the use of the above methods during sleep is needed.

More research is needed in this area to ascertain the feasibility of using positive airways pressure devices during sleep in the field in areas of high altitude.

In conclusion, this research demonstrated that the use of positive pressure ventilation, that delivers both positive inspiratory and expiratory pressures, during sleep at high altitude reduces or abolishes the symptoms of AMS. The mechanism is likely to be increased ventilation that maintains higher oxyhemoglobin saturation during sleep.

CHAPTER 6

SUMMARY

This research aimed to examine the effects on sleep, and breathing during sleep, of incremental increases in altitude from sea level to 5000m. We also aimed to determine the relationships, if any, between ventilatory responses to hypoxia and hypercapnia at sea level and the development of periodic breathing at high altitude. A further aim of the research was to investigate whether the use of non-invasive positive pressure ventilation during sleep at high altitude would improve the overnight, sleeping oxygen saturation and the symptoms of Acute Mountain Sickness that are known to be linked to a lower sleeping oxygen saturation at high altitude.

The most important finding from this research was that most sleep parameters were largely unaffected until the two highest altitudes. Our findings that Stage 1 NREM sleep was increased and slow wave sleep decreased at high altitude are in agreement with most previous findings. Stage 1 NREM sleep was increased in both duration and the percentage of total sleep at all altitudes from 3500m. Slow wave sleep was decreased in duration and percentage of total sleep from 3500m. However, unlike many previous reports of sleep at high altitude we found that total sleep time, sleep efficiency and REM sleep were unaffected by high altitude. These changes to Stage 1 NREM (the lightest sleep) and slow wave sleep (the deepest sleep) may explain reports from previous research that subjective sleep quality is poor at high altitude.

We did find a reduction in total sleep time and Stage 2 NREM sleep at the lowest altitude in Nepal (1400m) but this is most likely due to the changes in time between Australia and Nepal, changes to the circadian cycle of the individual subjects and the effects of long distance travel immediately prior to sleep studies being performed..

A further important finding from our study was that fewer than half the central apneas and hypopneas occurring in NREM sleep (periodic breathing) and REM sleep were associated with arousal from sleep. Although arousal from sleep due to central apneas and hypopneas increased significantly with increasing altitude, the total arousal index was similar to sea level values until the two highest altitudes. Higher total arousal indices were due to increasing arousal from central apneas and hypopneas, despite only half the central apneas and hypopneas terminating with arousal.

Cortical arousal (detected on the EEG) and autonomic arousal (detected from increased heart rate) were not present in over half the central events despite profound oxygen desaturation. Hypoxia is known to be a poor stimulus to arousal and at high altitude; hypocapnic hypoxia is the prevailing feature. Lung stretch receptors are not stimulated in the central apneas of PB as there is no increased lung volume, nor are upper airway receptors stimulated as there is no upper airway obstruction with its associated increased airflow resistance. The termination of apnea by a short period of hyperpnea appears to be a relatively passive return to breathing (compared to termination of obstructive apneas) mediated by the chemoreceptors and brought about by the drift downwards of arterial pO_2, the drift upwards of arterial pCO_2 and changes in $[H^+]$ in the region of the central chemoreceptor.

Chapter 6 Summary

Arterial blood gases sampled in fourteen of our subjects demonstrated the challenge to the respiratory control system by increasing altitude. The pO_2 at sea level was normal at around 95mmHg but even at the lowest altitude in Nepal i.e. 1400m, it was significantly decreased to 77mmHg and was in the low 50s at 3500m 3900m and 4200m reaching a nadir of 46mmHg by an altitude of 5000m. A brisk increase in ventilation resulted from this hypobaric hypoxia with the consequence being, in most subjects, periodic breathing during sleep. The effectiveness of the increased ventilation ensured that the pCO_2 was driven to low levels as altitude increased. At sea level the pCO_2 was normal at around 42mmHg but was significantly lower even at 1400m (39mmHg) then 32mmHg at 3500m and 29mmHg at the three highest altitudes. This level of pCO_2 obviously was below the apneic threshold for most of our subjects, but the pattern of periodic breathing was not consistent either in the group as a whole or, for some of the subjects, in the individual at the different altitudes during the trek. Half the subjects had PB at 3500m, increasing as altitude increased. Others had PB at only one altitude and it was not always the highest altitude that appeared to trigger PB; in some subjects the highest level of PB was at 3900m or 4200m then returned to lower PB indices at 5000m. This probably represents differing acclimatisation responses. However, acclimatisation to each altitude was not likely to have occurred, due to the short period of time spent at each altitude before ascending higher.

Hypoxia is known to be a poor stimulus to arousal from sleep in humans (Berthon-Jones & Sullivan, 1982) and this was confirmed in our subjects despite profound oxygen desaturation to below 65% in many instances. Failure to arouse from hypoxia

may have been exacerbated by the progressively higher arousal indices in our subjects; as altitude increased so did the total arousal index (predominantly due to central apneas and hypopneas). This sleep fragmentation may have contributed to a higher arousal threshold in our subjects. Previous research has found that even one night of sleep fragmentation can result in depression of the arousal threshold (Bowes et al, 1980, Stepanski et al, 1984, 1987, 2002) so increasing hypoxia did not result in increased ratio of arousal:desaturation events (central apneas & hypopneas). Hypoxic stimulus to arousal was most likely further depressed by the hypocapnia present in our subjects. Hypocapnia is known to cause a considerable reduction in the ventilatory response to hypoxia (Rebuck & Woodley, 1970, Weil et al, 1970) and was known to be present in fourteen of our subjects who had morning arterial blood gas analysis and can be extrapolated to include the entire group of nineteen subjects. It is thus likely that arousal was depressed by hypocapnia in our study.

The cognitive deficits present at high altitude are well known, both anecdotally and objectively (Tune 1964; Denison et al, 1966; McFarland 1969; Sharma et al. 1975; Fowler et al. 1982; Townes et al. 1984; Cavaletti et al. 1987; Fowler and Porlier 1987; Regard et al. 1989; Virues-Ortega et al, 2004). We assume that the high arousal index during sleep at high altitude may have contributed to this well known cognitive effect in our group of subjects. However, we did not measure cognitive function.

This large group of subjects has demonstrated the wide variety of ventilatory responses to increasing altitude. The changes in sleep and breathing and in levels of arterial oxygen appear not to be fully dependent on each individual's ventilatory

responses measured at sea level, as there was no relationship found between any parameter measured that could indicate an association in either sleep architecture, periodic breathing, sleeping oxygen saturation or arterial blood gases. Ventilatory responses are known to change during sleep at high altitude (White et al, 1987) but the magnitude of the change is probably not enough to explain the lack of a relationship between sea level ventilatory response testing performed during wakefulness and the development of periodic breathing, changes to sleep architecture or oxygen saturation during sleep.

The most important finding from our research conducted at White Mountain was that acute mountain sickness (AMS) symptoms were abolished by the use of non-invasive positive pressure ventilation (NIPPV) during sleep at 3800m. We assume that the positive pressure delivered during inspiration increased tidal volume and that pressure delivered during expiration resulted in the prevention of upper airway and alveoli collapse, the recruitment of microatelectatic alveoli; and these effects may have contributed to a higher sleeping mean and minimum oxygen saturation. AMS has been linked to low sleeping oxygen saturation (Burgess et al, 2004 and Erba et al, 2004) and it appears that by keeping the overnight SaO_2 a few percent higher effectively abolished AMS symptoms. The mechanisms for this result are not well understood and further research is needed to ascertain the mechanisms responsible for improvement in AMS and sleeping SaO_2.

In conclusion, we found fewer effects on sleep than those found by previous research into sleep at high altitude. Sleep architecture was altered, but less so than previous findings and this may have been due to our protocol in which incremental changes to

altitude occurred over a period of ten to eleven days, with vigorous exercise in between each new, higher altitude. Breathing during sleep and the development of periodic breathing in NREM and central apneas and hypopneas in REM sleep demonstrated a wide variety of changes. There was also a wide variety of oxygen saturations during sleep. None of these variables could be correlated to ventilatory responses, age or gender.

CHAPTER 7

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APPENDIX

The Lake Louise Scoring System for the Assessment of Acute Mountain Sickness. (Roach et al. 1993).

Subjects are asked about the presence and severity of the following:

Headache	0 none at all
	1 mild headache
	2 moderate headache
	3 severe headache, incapacitating
Gastrointestinal symptoms	0 good appetite
	1 poor appetite or nausea
	2 moderate nausea or vomiting
	3 severe, incapacitating nausea/vomiting
Fatigue and/or weakness	0 not tired or weak
	1 mild fatigue/weakness
	2 moderate fatigue/weakness
	3 severe fatigue/weakness
Dizziness/light headedness	0 none
	1 mild
	2 moderate
	3 severe, incapacitating

Difficulty sleeping	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

Clinical assessment: subjects are observed for the presence and severity of the following:

Change in mental status	0 no change
	1 lethargy/lassitude
	2 disorientated/confused
	3 stupor/semi consciousness
	4 coma
Ataxia (heel/toe walking)	0 none
	1 balancing manoeuvres
	2 steps off the line
	3 falls down
	4 unable to stand
Peripheral edema	0 none
	1 one location
	2 two or more locations