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19. ABSTRACT (Continue on reverse if necessary and identify by block number) This study addressed the issue as to how exposure and subsequent acclimatization to high altitude influences ventilatory control during wakefulness and sleep and considers the potential implications of such changes for adjustment to high altitude. Specifically, it has been known for some time that during several days exposure to high altitude there occurs a steady, progressive rise in ventilation, the origins of which have been the subject of extensive controversy. Under these same conditions, it is also known that sleep disturbance associated with periodic breathing is common. To further investigate these issues, we studied six healthy males at sea level and on nights 1, 4, and 7, after arrival at high altitude (14,110 feet). During wakefulness, ventilation and the ventilatory responses to hypoxia and hypercapnia were measured, and during both non-rapid-eye-movement and rapid-eye-movement sleep, ventilation, ventilatory pattern and hypercapnic ventilatory response were measured. We found that the hypoxic ventilatory response was similar to sea-level values on arrival at altitude, but increased steadily with acclimatization increasing (over)						
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19. (continued) nearly three-fold by 7 days. The slope of the hypercapnic response increased on initial arrival at high altitude and showed little further increase with acclimatization, although the position of the response shifted steadily to the left (lower PCO<sub>2</sub> values). Sleep-induced decrements in both ventilation and CO<sub>2</sub> responsiveness at altitude were comparable to those observed at sea level. The course and extent of acclimatization-related changes in ventilation was similar during wakefulness and sleep. Finally, the extent of periodic breathing during sleep at high altitude was highly variable among the subjects and tended to occur more frequently in individuals with higher ventilatory responses to both hypoxia and hypercapnia. The results indicate that ventilatory acclimatization to high altitude is closely associated with an increase in the ventilatory response to hypoxia, that acclimatization is preserved in sleep and that heightened ventilatory responsiveness may contribute to the development of periodic breathing and sleep disturbance at high altitude.



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APNEIC THRESHOLD

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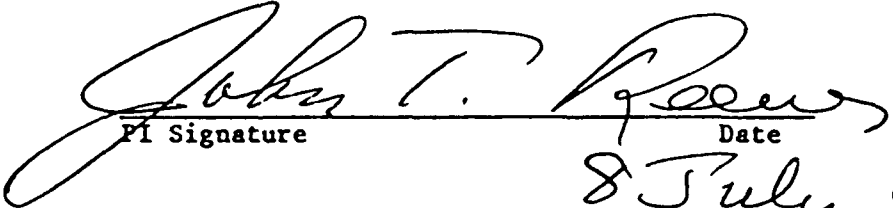
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APPENDIX

## Publications:

Fulco C.S., P.B. Rock, J.T. Reeves, L.A. Trad, P.M. Young, A. Cymerman. Effects of propranolol on acute mountain sickness (AMS) and well-being at 4,300 meters of altitude. *Aviat. Space Environ. Med.* 1989; 60:679-83.

Fulco CS, A. Cymerman, J.T. Reeves, P.B. Rock, L.A. Trad, P.M. Young. Propranolol and the compensatory circulatory responses to orthostasis at high altitude. *Aviat. Space Environ. Med.* 1989; 60:1049-55.

Huang, S.Y., L.G. Moore, R.E. McCullough, R.G. McCullough, A.J. Micco, C. Fulco, A. Cymerman, M. Manco-Johnson, J.V. Weil, J.T. Reeves. Internal carotid and vertebral arterial flow velocity in men at high altitude. *J. Appl. Physiol.* 1987; 63(1):395-400.

Moore, L.G., A. Cymerman, S-Y. Huang, R.E. McCullough, R.G. McCullough, P.B. Rock, A. Young, P. Young, J.V. Weil, J.T. Reeves. Propranolol blocks metabolic rate increase but not ventilatory acclimatization to 4300 m. *Respiratory Physiology* 1987; 70:195-205.

Moore, L.G., A. Cymerman, S-Y. Huang, R.E. McCullough, R.G. McCullough, P.B. Rock, A. Young, P.M. Young, D. Bloedow, J.V. Weil, J.T. Reeves. Propranolol does not impair exercise oxygen uptake in normal men at high altitude. *J. Appl. Physiol.* 1986; 61(5):1935-1941.

White D.P., K. Gleeson, C.K. Pickett, A.M. Rannels, A. Cymerman, and J.V. Weil. Altitude acclimatization: influence on periodic breathing and chemo-responsiveness during sleep. *J. Appl. Physiol.* 1987; 63(1):401-412.

## INTRODUCTION

It is well known that ascent to high altitude triggers a rise in ventilation which seems to carry an adaptive advantage by reducing the impact of environmental oxygen deficiency on the extent of arterial oxygenation. The temporal characteristics of this increase in ventilation suggest at least two phases, perhaps corresponding to two processes, with an initial virtually immediate rise in ventilation and a slower, progressive increase over several days. The latter is often referred to as ventilatory acclimatization to high altitude. Although the characteristics of the ventilatory response to high altitude are well described, little is known about its mechanism. In addition, it seems likely that the increased ventilation following altitude ascent has both the adaptive attributes alluded to above but may also present some problems in adaptation to altitude. This arises through the consideration that changes in the stimuli to breathing and the drives or sensitivity to those stimuli may contribute to development of periodic breathing during sleep which is common at high altitude. *This is associated with frequent awakenings from sleep and may contribute to difficulties sleeping which constitute one of the more frequent symptoms associated with altitude ascent.*

## BODY

In order to shed light on mechanisms which might be involved in the changes of breathing during both wakefulness and sleep which follow altitude ascent, we undertook this study to characterize the changes in the ventilatory responsiveness to hypoxia and hypercapnia in human subjects before, and for several days after, arrival at high altitude. Measurements were made during both wakefulness and sleep, and we sought to examine acclimatization-associated effects on the ventilatory response to acute hypoxia which had not been well described. We reasoned that increasing ventilation at high altitude might represent a progressive sensitization to the hypoxic stimulus, i.e., an increase in hypoxic ventilatory response. We also sought to better delineate altitude effects on the ventilatory responsiveness to hypercapnia. Although previous studies had indicated that the

hypercapnic ventilatory response curve is shifted to the left at high altitude, the effect of altitude acclimatization on the slope of this response is less clear. Acute hypoxia is known to increase the slope of the response, but whether there are subsequent progressive increases during acclimatization is unknown.

Measurements of ventilatory responses during both sleep and wakefulness presented the opportunity to determine whether altitude-induced changes in ventilatory drive observed during wakefulness parallel or differ from findings during sleep. Further, we sought to measure the extent of periodic breathing in sleep and determine how this might relate to ventilatory drives prior to and following altitude ascent. It is now clear that chemical drive is of special importance in sustaining rhythmic breathing during sleep -- to a substantially greater extent than during wakefulness -- and that  $PCO_2$  may be of a special importance in this regard. Accordingly, we hypothesized that high ventilatory drives might lead to greater hyperventilation and hypocapnia with resulting apnea.

To explore these issues, we studied six healthy male subjects *under baseline conditions at sea level and subsequently at altitude during wakefulness and sleep on nights 1, 4 and 7 at the U.S. Army Medical Research Laboratory on Pikes Peak (14,110 feet)*. Studies during wakefulness indicated that the usual progressive increase in ventilation which occurs over several days following ascent was attributable largely to an increase in respiratory frequency with little change in tidal volume and was closely associated with a major progressive increase in the steepness of the relationship of increased ventilation to decreases in arterial oxygen saturation. In other words, the process of ventilatory acclimatization to high altitude was associated with a progressive and substantial increase in the acutely measured ventilatory response to hypoxia which increased two and one-half fold from over sea level values by day 7 at altitude. In contrast, the hypercapnic ventilatory response increased immediately on initial ascent but showed no further increase with acclimatization. This is commensurate with the well-known potentiating effect of hypoxia on the hypercapnic response. In contrast to the

absence of subsequent change in slope of the hypercapnic response during acclimatization, there was a progressive leftward shift in position of this curve which probably reflected the effect of progressively decreasing serum bicarbonate concentration. Measurements during sleep indicated that the influence of sleep on ventilation and its control at altitude was largely algebraic or subtractive, producing a decrement in ventilation and in the hypercapnic ventilatory response of similar proportions at both low and high-altitude. Viewed another way, ventilation and the hypercapnic response, although less during sleep, showed progressive augmentation during altitude acclimatization similar to measurements in wakefulness. Finally, periodic breathing during sleep at high altitude was prominent in some subjects and not in others but occurred most frequently in individuals with relatively high ventilatory responses to both hypoxia and hypercapnia.

#### CONCLUSIONS

These findings led to several important conclusions regarding ventilatory adjustment to high altitude. First, is that there is an impressive potentiation of the ventilatory sensitivity to hypoxia following ascent to high altitude, suggesting that a progressive increase in hypoxic sensitivity of ventilation could be a critically important factor in the progressive rise of ventilation seen during acclimatization which may be an important mechanism of this well described, but poorly understood, phenomenon. The changes in hypoxic ventilatory response were of substantial magnitude and closely related to increases in resting ventilation. This augmentation of hypoxic sensitivity may be an important feature of adaptation to hypoxia. It is noteworthy that this change may be relatively specific for hypoxia in that no parallel changes were observed for the ventilatory response to hypercapnia. It was also evident that these changes in basal ventilatory control during acclimatization ran parallel during wakefulness and sleep, indicating that the fundamental adjustments during altitude acclimatization are state-independent and may not involve higher central nervous system function (i.e., are



independent of consciousness). Finally, the positive association of periodic breathing during sleep at altitude with relatively high ventilatory response to hypoxia or hypercapnia suggest that periodic breathing under such circumstances constitutes a form of post-hyperventilation apnea wherein transient hypoventilation produces a fall in oxygen tension and rise in carbon dioxide tension which produces a brisk ventilatory response and overshoot in individuals with high hypoxic and hypercapnic sensitivity, leads to a subsequent rise in oxygen tension and fall in carbon dioxide tension to levels insufficient to stimulate rhythmic breathing during sleep with resulting respiratory pause which re-initiates the cycle. On balance, these results should prove helpful in improving understanding of the factors which contribute to improved ventilation, oxygenation and function during wakefulness at high altitude and to factors which lead to periodic breathing with consequent sleep fragmentation or deprivation. Both elements could have important implications for military function at high altitude.

Considerable investigation in addition to the work on sleep was done with the partial support of this contract. The efficiency of an high altitude expedition can be enhanced by combining several protocols as long as they complement each other without interfering. This was, in fact, successfully accomplished in these studies which were carried out in the summer of 1985.

The soldiers who participated in the sleep studies also had a separate evaluation by noninvasive Doppler methodology of their brain blood flow (Huang et al., Internal carotid and vertebral arterial flow velocity in men at high altitude. *J. Appl. Physiol.* 63:395-400, 1987). Thus, we monitored their internal carotid velocities and their vertebral arterial velocities. These studies could not be done at night, for fear of interfering with the sleep studies, but measurements were made awake during each day for the first several days at altitude. The results showed that the brain blood flow (both internal carotid and vertebral arteries) did not increase immediately on arrival at high altitude but rather reached a peak at about two days of stay. The flows then declined

toward the sea level values over the next several days. Such a study had not been done previously, and the results raised the question of the mechanisms for the pattern of responses. Further, one can consider that inappropriately low cerebral oxygen delivery during the first nights at altitude (before flow adaptation has occurred) could contribute to sleep disturbance and to AMS.

Also, in the summer of 1985 some 14 soldiers from the test subject platoon were taken to the summit of Pikes Peak to the Maher Memorial Laboratory. Half of these were on propranolol and half were controls who received placebo. The placebo group were the subjects who participated in the sleep protocol, the primary objective of the contract. The propranolol studies, however, were ground-breaking studies because this represented the first time beta blocked subjects were taken to altitude for prolonged study.

The propranolol administration was undertaken with some trepidation, because we feared that beta adrenergic blocked subjects would be at great risk for the development of acute mountain sickness. The beta sympathetics provide the first defense against hypoxia, we reasoned, and thus we must be prepared to deal with failure of adaptation and even frank illness in the propranolol-treated subjects.

However, such was not the case. In fact, the propranolol-treated subjects reported substantially less acute mountain sickness during days 1 and 2 than did the control subjects (Fulco CS et al., Effects of propranolol on acute mountain sickness [AMS] and well being at 4,300 meters of altitude. *Aviat. Space Environ Med.* 60:679-683, 1989.) Because these early days are the time of greatest risk for the disorder, we considered that AMS was reduced by beta blockade, and further one could surmise that excessive beta stimulation might contribute to AMS symptoms. This was further supported by the fact that the one subject who developed high-altitude pulmonary edema and had to be removed from the mountain, was in the control group and received the placebo, not propranolol.

We found also during this project that the propranolol-treated subjects showed normal ventilatory acclimatization to high altitude, confirming that ventilatory acclimatization was not under beta adrenergic control. We had expected this result. What we had not expected, however, was that the beta-blocked subjects had lower basal metabolic rates than did the unblocked subjects. (Moore, LG et al. Propranolol blocks metabolic rate increase but not ventilatory acclimatization to 4,300m. *Respiration Physiol.* 70:195-205, 1987.) It has been known for some time that ascent to high altitude is associated with increased metabolic rate. And further, this has been considered to contribute to the weight loss and general debility of troops at altitude. What had not been known was the mechanism for this increased metabolism. The results of this study suggested that the increased metabolism was, in fact, mediated by the sympathetic nervous system. Thus, the study made a major contribution to the understanding of this established physiological problem.

We had expected that the propranolol would markedly impair the exercise capacity of the subjects taking the drug. An additional surprise to come from the study was that no such impairment occurred (Moore et al., Propranolol does not impair exercise oxygen uptake in normal men at high altitude. *J. Appl. Physiol.* 61:1935-1941, 1986.) In fact, we found that propranolol impaired neither the maximal nor the submaximal oxygen uptake, even though the maximal heart rate was reduced from 176 to 135 beats/min. Presumably, the normal capacity to increase the stroke volume compensated for the loss of the rate increase with propranolol. The implication from these studies was that the beta adrenergic system was not really be as necessary for good exercise function at high altitude as we had assumed.

A further surprise was that the propranolol-treated subjects also tolerated orthostatic stress as well as did control subjects. Thus, we considered that the beta sympathetic system was not essential in the response of normal men to tilt.

The contract contributed to the first comprehensive examination of the sympathetic blood analyses over time at altitude. These studies (Young AJ et al., submitted) showed that the epinephrine levels under strictly basal conditions rose on arrival at 4,300m but then fell over time with acclimatization. The norepinephrine levels behaved in a different manner, and they rose over the first week of altitude residence and then reached a plateau which was substantially maintained for three weeks. Propranolol had no effect on these values.

Finally, the study showed for the first time that the administration of propranolol prevented the rise in exercise lactate that is normally observed on arrival at high altitude (Young, AJ et al., submitted). This strongly suggests that the lactate metabolism is under the control of the beta sympathetic system.

From the above, it is clear that the contract not only accomplished the primary mission and task to which it had committed itself, but also it provided substantial new information that is of potential use should troops be suddenly committed to high altitude. First, the study indicates those subjects who are likely to be at risk for sleep disturbance. Next, it has raised the important novel concern that a large beta sympathetic response is not necessarily beneficial and may, in fact, be detrimental. One wonders whether even small doses of beta blockers might be useful in preventing the early symptoms of AMS, while neither impairing ventilatory acclimatization nor impairing exercise performance.

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