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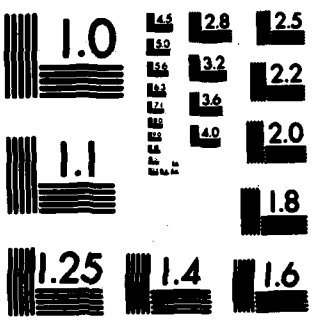

PULMONARY ADAPTATION TO HIGH ALTITUDE

ANNUAL PROGRESS REPORT

Jerome A. Dempsey, Ph.D.

November 1984

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, MD 21701

Contract No. DAMD 17-82-C-2259

University of Wisconsin
Madison, Wisconsin 53706

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Example: The subject "Solid Rocket Motors" is Field 21, Group 08, Subgroup 2 (page 32, AD-624 000).

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Annual Progress Report

1 August 1983 - 13 November 1984

Studies completed during contract year 07 were aimed at defining: a) the role of the carotid bodies in ventilatory acclimztization to chronic hypoxia of varying severity; b) the effects of acute or chronic hypoxia on respiratory muscle metabolism; c) the effect of changes in pulmonary mechanics on periodic breathing during sleep in hypoxia; and d) the effects of heavy exercise--in normoxia and hypoxia--on chest wall mechanics and (in turn) on the control of ventilation and gas exchange (in humans). In general we made satisfactory progress in this the initial year of the contract. The animal studies concerned with chronic hypoxia (goats) and muscle metabolism (rats) are now complete; one human study concerned with exercise is complete and most of the methods are in place or nearly so for the remaining human studies; and the human studies of periodic breathing in hypoxic sleep are underway.

Brief Summary of Progress to Date

Aim 1: The Role of the carotid bodies in ventilatory acclimatization to chronic hypoxia of varying severity.

We studied intact and carotid body denervated goats at two levels of severity of acute and chronic hypoxia. A preliminary report has been given of the data at the 1984 American Physiological Society fall meeting (Smith, et al, 1984). We carefully documented the completeness of carotid body denervation (CBX) through the use of acute hypoxia, hyperoxia, Na Cyanide and dopamine and accepted only those animals who showed consistent responses--or a lack of response--to all of the

criteria. Initial and CBX animals were exposed to identical levels of arterial hypoxemia--PaO_2 40-45 mmHg or PaO_2 28-35 mmHg, the latter severe level being chosen because it would cause cerebral metabolic acidosis (as we had previously shown in rats). The essential data in the study is shown in Fig. 1 and 2--clearly carotid bodies were essential to achieve a significant ventilatory acclimatization to hypoxia--indeed to achieve any ventilatory response to acute or chronic hypoxia of any severity. Also note the marked differences in response to acute reoxygenation in the intact vs denervated animal. These data also suggest that cerebral metabolic acidosis perse--at least that produced by hypoxia--does not stimulate ventilation. These comprehensive data provide strong support for the earlier data of Forster and Bisgard that CBX prevents ventilatory acclimatization to chronic hypoxia. We have no obvious explanation for the conflicting data of Steinbrook et al (1983) on this topic.

Aim 2--Does acute or chronic hypoxia effect respiratory muscle metabolism?

We used rats exposed for 3 weeks to 6600 m altitude. The animals showed a marked and sustained hyperventilation in this severe hypoxia; but showed no significant change in mitochondrial enzymes (citrate synthase activity) in their limb skeletal muscle or in their diaphragms. Analagous to this negative effect of chronic hypoxia we also showed no effect of chronic physical training on aerobic capacity of the diaphragm. During very heavy exercise we showed that the rat's diaphragm showed no significant glycogen depletion or lactate production, at the same time that leg locomotor muscles were showing marked anaerobic glycolysis. Thus--enzymatically-the diaphragm seems to

be much more like cardiac muscle than it does like limb locomotor muscle. However if the respiratory muscles are really "loaded" by the condition of heavy prolonged exercise in acute hypoxia (4300 m or PaO_2 40-50 mmHg) we did see a clear glycogen depletion. The inference here is that this combination of exercise in hypoxia might well produce respiratory muscle fatigue--and we will follow up on this possibility in the exercising human. These rat data were presented at FASEB (Fregosi and Dempsey, 1984) and the first study concerned with acid-base status in exercising rats was recently published (Fregosi and Dempsey 1984).

Aime 3--What is the effect of changes in pulmonary mechanics on periodic breathing during sleep in hypoxia in humans.

These studies have just begun. The methods for measuring EMG of the diaphragm and lung and chest wall mechanics during sleep have been completed and two sleep studies have been completed. Thus far the data show that the development of periodic breathing in hypoxic sleep also causes substantial narrowing of the upper (extra-thoracic) airway--perhaps leading to obstructive sleep apnea. Most of the data from our studies which led to the current sleep studies have now been published (Bersenbrugge et al, 1983, '84, '84; Dempsey et al, 1984).

Aim 4--What are the effects of heavy exercise--in normoxia and hypoxia--on chest wall mechanics and (in turn) on the control of ventilation and gas exchange (in humans).

Three studies--one complete and the other two ongoing--are directed at this question.

(a) First, we determined that a significant "impedance" to air-flow did indeed exist during moderate and heavy exercise. Further, by using transient responses of diaphragmatic EMG and trans-diaphragmatic

pressure (Pdi) to changes in inspired gas density (i.e., loading and "unloading") we showed that this impedance encountered during the physiologic state of air-breathing exercise caused a significant augmentation of inspiratory neural drive and presented a significant inhibition to exercise hyperpnea. Indeed, if this "extra" mechanical impedance was not present (as in He:O_2 breathing), inspiratory flow rate increased one for one with increasing neural drive during progressive exercise and hypocapnia--rather than iso-capnia-- prevailed. These data have been presented at FASEB and are currently undergoing review (Hussain, Pardy and Dempsey, 1984).

(b) We are currently about 3/4 of the way through a study to determine the effect of "chest wall mechanics" on endurance exercise performance. To this end we are comparing the effects of air vs. He:O_2 vs hyperoxia on endurance exercise time and on ventilatory muscle endurance in highly trained young males. Hypoxia will eventually be added to this protocol.

(c) We are just underway with a study of respiratory muscle recruitment patterns during exercise with special attention to the importance of abdominal (expiratory) muscle recruitment to the generation of pressure for the subsequent inspiration. We expect this type of recruitment to be especially critical to ventilatory control--and to the avoidance of diaphragmatic fatigue--in hypoxic exercise. Much of our exercise data supported by previous years contracts and this year's contract are now published or in press (Dempsey et al., J Physiol, 1984; Dempsey and Fregosi, 1984; Dempsey, Vidruk and Mitchell, 1984).

Publications supported all or in part by Contract No. DAMD 17-82-C-2259.
Contract Year 07 (Dec. 1983 - Nov. 5, 1984).

Manuscripts Published or in Press

1. Bersenbrugge, A., J. Dempsey, C. Iber, J. Skatrud, and P. Wilson. Mechanisms of hypoxia-induced periodic breathing during sleep in humans. J. Physiol. (London) 343:507-524, 1983.

2. Berssenbrugge, A., J. Dempsey, and J. Skatrud. Hypoxic Versus Hypocapnic Effects on Periodic Breathing During Sleep. In: High Altitude and Man, American Physiological Society, 115-127, 1984.

3. Berssenbrugge, A., J. Dempsey and J. Skatrud. Effects of sleep state on ventilatory acclimatization to chronic hypoxia. J. Appl. Physiol. 57:1089-1096, 1984.

4. Dempsey, J.A. Ventilatory control during sleep in hypoxia: Overview. Hypoxia Symposium III, Banff, Canada, January 1983 (J. Sutton and C. Houston, editors). Progress in Clinical and Biological Reserach, Vol. 136:61-64, 1984.

5. Dempsey, J., J. Skatrud and A. Berssenbrugge. Sleep in hypoxia. In: Contemporary Issues in Pulmonary Disease, editors N. Edelman and N. Cherniack (in press).

6. Dempsey, J. "Regulation of pulmonary control systems during exercise: 1984", Symposium on Biological Regulation During Exercise at FASEB National Meeting, St. Louis, April 1984 (in press, Fed. Proc.).

7. Dempsey, J.S., P.G. Hanson and K. Henderson. Exercise-induced arterial hypoxaemia in healthy humans at sea level. J. Physiol. (London) (1984) 355:161-175.

8. Fregosi, R. and J. Dempsey. Regulation of arterial acid-base status in the exercising rat. J. Appl. Physiol. 57:396-402, 1984.

9. Dempsey, J., and R. Fregosi. "Adaptability of the pulmonary system to increased metabolic demand". Am. J. Cardiology (in press).

Abstracts

1. Hussain, S.N.A., R.L. Pardy and J. Dempsey. "Pulmonary impedance as a determinant of inspiratory neural drive during exercise. Fed. Proc. 43:1412, 1984.

2. Fregosi, R., H.S. Hoff and J.A. Dempsey. "Effects of short-term exercise on locomotor and diaphragm muscle metabolism." Fed. Proc. 43:3590, 1984.

3. Smith, C., et al. "Carotid bodies are required for ventilatory acclimitization to moderate and severe hypoxia". Physiologist 27:13-4, 1984. Military Significance

Fig. 1. Changes in arterial PO_2 during exposure to moderate hypoxia and severe hypoxia. ● ○ = intact goats; ▲ △ = CBX goats. Open symbols = 10-30 mins of restoration of normoxia following hypoxic exposure. --- indicates confidence limits of sea-level control values obtained during a separate day.

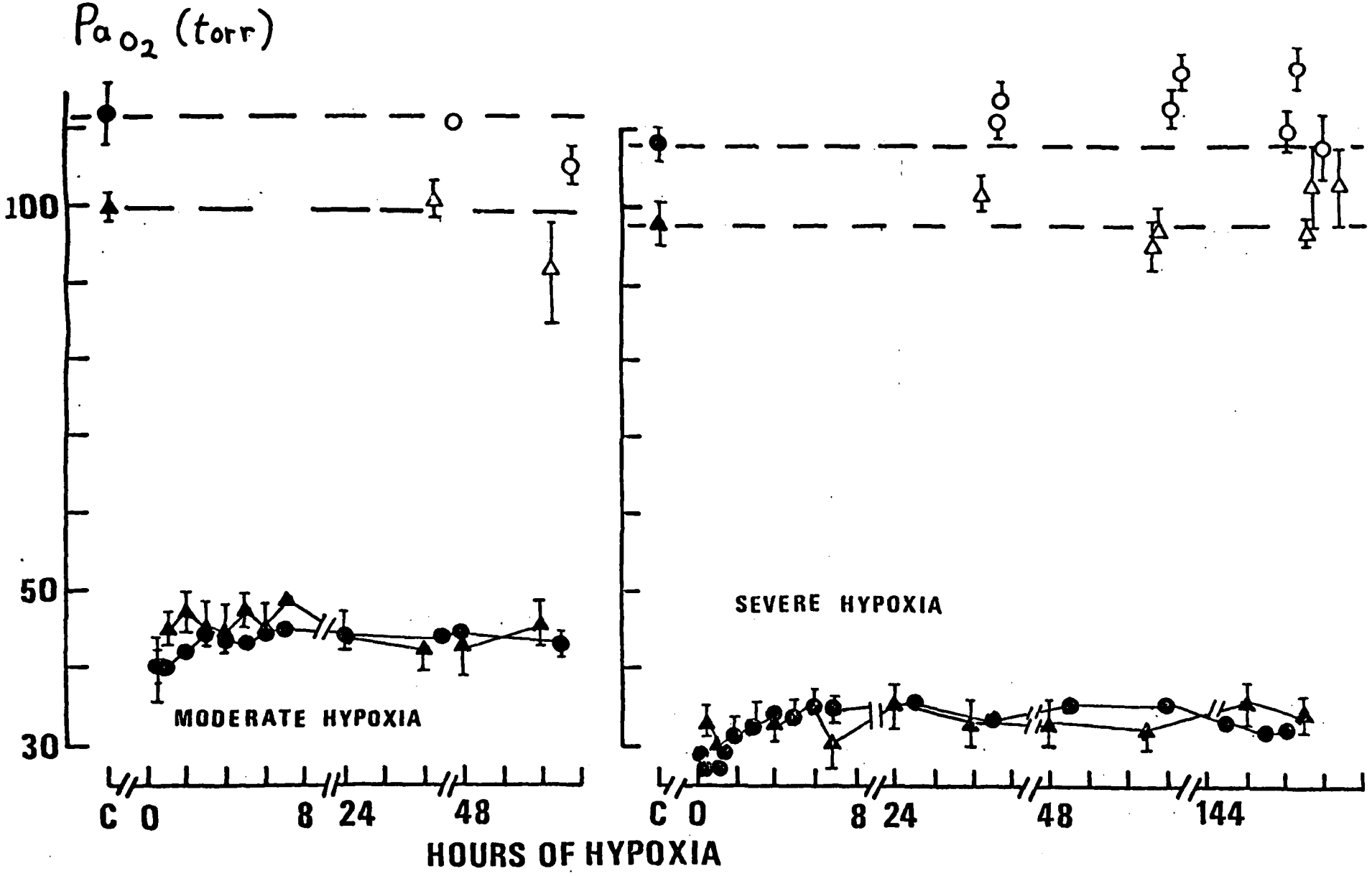
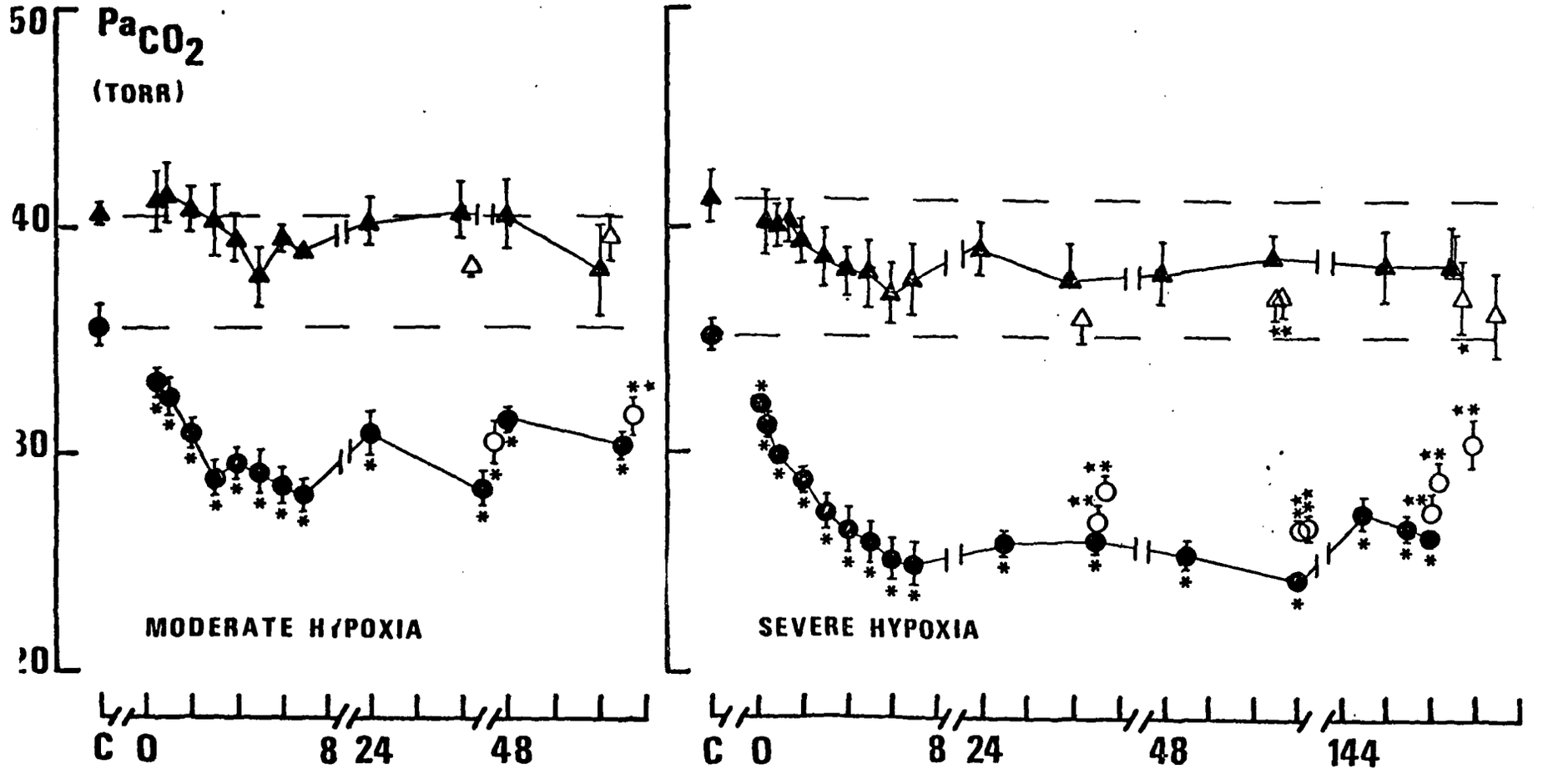


Fig. 2. Changes in arterial PCO_2 during hypoxic exposure in intact and denervated goats. * signifies P<.01 change from sea-level control. See legend in Fig. 1 for symbols.



Military Significance

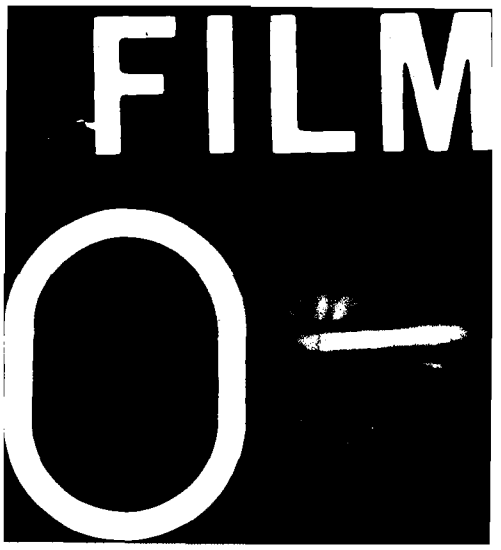
Our contract work is aimed at a better understanding of two physiological problems occurring in hypoxic environments which clearly affect the well-being and performance capabilities of the human sojourner at high altitudes. These problems are periodic breathing during sleep leading to loss of quality sleep and the resulting daytime hypersomnalence and fatigue; and the regulation of the ventilatory response and pulmonary gas exchange during exercise in hypoxia which are key determinants of exercise performance.

Our work on periodic breathing during hypoxic sleep provides the first comprehensive, quantitative description of this problem and provides the first definitive evidence detailing the major causes of periodicity and the reasons behind the beneficial effects of acute O_2 administration. Further, our more recent data suggests that acclimatization over a matter of a few days at high altitude may greatly alleviate periodic breathing during sleep. However, this remains a highly individual characteristic which we were unable to predict from available measurements. Indeed, the test of acute hypoxic ventilatory response--which is commonly used as a predictor of many facets of acclimatization--had no predictive value at all for the occurrence or severity of periodic breathing in hypoxic sleep.

Exercise capacity as determined by the pulmonary system in hypoxia and the debilitating symptoms of dyspnea which accompany exercise in hypoxia have been the subject of our investigations. Our work has detailed the critical limitations to oxygen transport presented by the failure of the lung's gas exchange and ventilatory control system and chest wall mechanics to respond adequately and/or efficiently to heavy work in hypoxic environments. Further, the baseline work in normoxic environments clearly shows the susceptibility of some highly fit individuals to these problems during exercise, thereby providing a basis for prediction of problems with high altitude exercise from measurements made at sea-level. We also showed the simple use of exercise tests in acute hypoxia--even using non-invasive measurements of arterial O_2 saturation--should provide excellent prediction of gas exchange "failure" at high altitudes. Our recent findings also strongly implicate a highly significant role for pulmonary and chest wall mechanics in the regulation of ventilation--and thus of gas exchange--during exercise--especially hypoxic exercise. We would predict with some confidence that the sea-level native with even "mild," asymptomatic airway disease (such as that due to chronic cigarette smoking or the mostly reversible airway disease of the otherwise healthy asthmatic) will have substantial problems in maintaining arterial oxygenation and/or avoiding extreme dyspnea during exercise at even mild elevations in altitude.

Facilities and Personnel

No changes were made in the past year.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