AD-A130 827 INCREASED METABOLISM AND DEAD SPACE AS COMPONENTS OF VENTILATION AT HIGH ALTITUDE(U) COLORADO UNIV HEALTH SCIENCES CENTER DENVER S Y HUANG ET AL. 12 JUL 83 1/1

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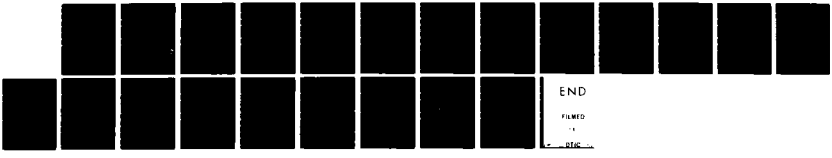

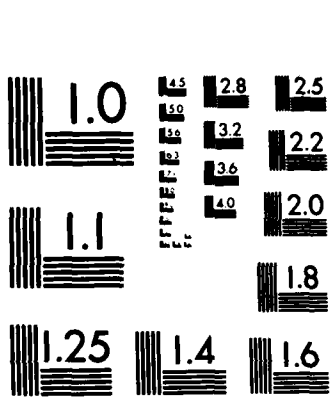

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Ventilatory acclimatization to high altitude results in alveolar hyperventilation, which is an increase in alveolar ventilation per unit of CO_2 production and is associated with a fall in the PCO_2. A measurement frequently made during acclimatization to high altitude is the total volume of air expired per minute, the minute ventilation. However, the relation of total to alveolar ventilation and the influence of CO_2 production on the latter at high altitude is unclear. We sought to determine the contribution of changes in metabolism and in dead space ventilation to the

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increase in minute ventilation observed with ascent and during exposure to high altitude. In 12 healthy male subjects taken from Denver, Colorado (1600 M) to Pikes Peak, Colorado (4300 M) for 5 days, resting minute ventilation increased from low to high altitude (+35% by day 5) and arterialized venous PCO_2 fell. Resting metabolic rate ($\dot{V}CO_2$) increased 16% by day 5 and could account for approximately half of the increase in minute ventilation. The increases in ventilation on days 1, 2 and 4 were positively correlated with increased CO_2 production; they were not correlated with arterial oxygen saturation on any day. During exercise at high altitude, minute ventilation rose above low altitude values but less than 10% of the increase in ventilation could be attributed to increased CO_2 production. Dead space ventilation at high altitude was the same as at low altitude in resting subjects. However, during exercise dead space volume and respiratory frequency increased. The resulting increase in dead space ventilation paralleled the increase in total ventilation and accounted for approximately 30% of it. Thus an increase in metabolism at rest and dead space ventilation during exercise may be important contributors to the increases in resting and exercise ventilations observed at high altitude.

Increased Metabolism and Dead Space as Components of Ventilation at High Altitude

S.Y. Huang[1]*, J.K. Alexander[2], R.F. Grover[1], J.T. Maher[3], R.E. McCullough[1], R.G. McCullough[1], L.G. Moore[1,4], J.V. Weil[1], J.B. Sampson[3] and J.T. Reeves[1]

Running Head: Metabolism and Ventilatory Dead Space at High Altitude

[1]University of Colorado Health Sciences Center, Cardiovascular Pulmonary Research Laboratory, Denver, CO 80262

[2]Baylor University, Houston, TX

[3]United States Army Research Institute of Environmental Medicine, Natick, MA

[4]University of Colorado - Denver Campus, Department of Anthropology, Denver, CO

*Visiting Scholar, Shanghai Institute of Physiology, Academia Sinica, Shanghai, China

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Correspondence: J.T. Reeves, M.D.
CVP Research Laboratory
4200 E. Ninth Avenue, B133
Denver, CO 80262 (303)394-8103

ABSTRACT

Ventilatory acclimatization to high altitude results in alveolar hyperventilation, which is an increase in alveolar ventilation per unit of CO_2 production and is associated with a fall in the PCO_2. A measurement frequently made during acclimatization to high altitude is the total volume of air expired per minute, the minute ventilation. However, the relation of total to alveolar ventilation and the influence of CO_2 production on the latter at high altitude is unclear. We sought to determine the contribution of changes in metabolism and in dead space ventilation to the increase in minute ventilation observed with ascent and during exposure to high altitude. In 12 healthy male subjects taken from Denver, Colorado (1600 M) to Pikes Peak, Colorado (4300 M) for 5 days, resting minute ventilation increased from low to high altitude (+35% by day 5) and arterialized venous PCO_2 fell. Resting metabolic rate ($\dot{V}CO_2$) increased 16% by day 5 and could account for approximately half of the increase in minute ventilation. The increases in ventilation on days 1, 2 and 4 were positively correlated with increased CO_2 production; they were not correlated with arterial oxygen saturation on any day. During exercise at high altitude, minute ventilation rose above low altitude values but less than 10% of the increase in ventilation could be attributed to increased CO_2 production. Dead space ventilation at high altitude was the same as at low altitude in resting subjects. However, during exercise dead space volume and respiratory frequency increased. The resulting increase in dead space ventilation paralleled the increase in total ventilation and accounted for approximately 30% of it. Thus an increase in metabolism at rest and dead space ventilation during exercise may be important contributors to the increases in resting and exercise ventilations observed at high altitude.

INTRODUCTION

Ventilatory acclimatization to high altitude produces an increase with time in minute ventilation (12) and an associated fall in arterial PCO_2. For the purposes of this report, acclimatization is the increase in alveolar ventilation per unit of CO_2 production, i.e. alveolar hyperventilation. Minute ventilation is the sum of alveolar ventilation plus dead space ventilation. Alveolar ventilation at rest and during exercise is linked to metabolic rate, particularly to carbon dioxide production (15,16). Increased metabolism has been reported at high altitudes (6,7,9,13) but it is not consistently found (7) nor is it clear how an increase in metabolism at high altitude relates to the increase in ventilation. If metabolism at high altitude is increased, then the increase in alveolar ventilation would reflect both the increase in metabolism and the acclimatization process. Dead space ventilation is the product of dead space volume and respiratory frequency. Dead space volume in turn is related to tidal volume (1,10) which could change at high altitude. We are not aware of reports which examine dead space ventilation both at rest and during exercise at high altitude.

We wondered if the increase in minute ventilation at high altitude was influenced by metabolism and by dead space ventilation. To answer this question we measured minute ventilation and two of its determinants, alveolar ventilation and metabolic rate, at rest and during exercise in 12 healthy men at low altitude in Denver at 1600 M and during 5 days on Pikes Peak, Colorado at 4300 M elevation. We separated the influences of increased metabolic rate and dead space on the increase in minute ventilation to determine the magnitude of ventilatory acclimatization, i.e. alveolar hyperventilation. Results showed that an increase in resting metabolic rate and an increase in dead space ventilation during exercise were important contributors to the increase in minute ventilation observed at high altitude.

METHODS

The 12 healthy male subjects of the present study ranged in age from 22 to 34 years and were subjects 1 through 12 of a previous report (14). The methods of study at rest and a portion of the results for low altitude (14) and for high altitude (7) are given in those reports.

Briefly, resting measurements were made in Denver (1600 M) on 2 separate days. During air breathing a computer system (14) allowed continuous measurement of minute ventilation, end tidal O_2 and CO_2 tensions, arterial O_2 saturation, tidal volume, breathing frequency, O_2 consumption, CO_2 production, and heart rate. This system which produced real time computation of data was used to demonstrate that a steady state was present. After at least 5 minutes, or when the level of ventilation had reached stable values, expired gas was collected for 3 minutes in a Douglas bag for measurement of volume by a Tissot spirometer and O_2 uptake and CO_2 production. Arterialized venous blood was withdrawn from a heated hand for analysis of pH and PCO_2 (5). Also at 1600 M the ventilatory response to steady state exercise was measured while the subject pedalled a bicycle ergometer at a 450 kpm/min work load while breathing room air. He exercised for a 5 minute warm up after which ventilation and gas exchange were monitored by the computer system for 3 minutes. Then a Tissot collection of the expired air was made for measurement of ventilation, O_2 uptake and CO_2 production. Unless otherwise specified, reported measurements of ventilation were made using the Tissot spirometer. Analysis of the gas for calculation of oxygen consumption and CO_2 production was by Scholander in Denver and by O_2 fuel cell and CO_2 capnograph on Pikes Peak. To validate the use of O_2 fuel cell and CO_2 capnograph gas analysis on Pikes Peak, duplicate gas samples were analyzed by Scholander and by O_2 fuel cell and CO_2 capnograph in Denver. Results by fuel cell agreed to within .08±.02% O_2 (n=7) and by capnograph to within .05±.02% CO_2 (n=5) of Scholander values.

Measurements of ventilation at rest and during exercise at high altitude were conducted in the U.S. Army Medical Laboratory facility on the summit of Pikes Peak, Colorado, elevation 4300 M. Measurements on Pikes Peak were made within 6 hours of beginning ascent and daily for a total 5 day stay. Resting measurements of ventilation, end-tidal PCO_2 and PO_2, oxygen uptake and CO_2 production were made after the subjects had fasted for at least 4 hours and had been recumbent for 20 minutes. On days 1, 3, and 5 arterialized venous blood was withdrawn for determination of PCO_2 and pH. The ventilation measurements were also made each day during steady state exercise of the same intensity (450 kpm/min) and duration as at 1600 M. $PaCO_2$ and pHa were measured during exercise on days 1, 3, and 5.

The components of ventilation examined in the present report were calculated by standard formulae:

The alveolar ventilation ($\dot{V}_A$, BTPS, l/min) was calculated:

$$\dot{V}_A = \frac{\dot{V}CO_2}{PaCO_2} \times 0.863$$

where $\dot{V}CO_2$ was carbon dioxide production in ml/min STPD and $PaCO_2$ was the arterialized venous blood PCO_2 mmHg.

The physiological dead space ventilation ($\dot{V}_D$, BTPS, l/min) was:

$$\dot{V}_D = \dot{V}_E - \dot{V}_A$$

where $\dot{V}_E$ was minute ventilation BTPS in l/min.

The physiological dead space volume (V_D, BTPS) was calculated

$$V_D = \dot{V}_D / f$$

where f was the respiratory frequency.

Means ± SE are reported in the tables, figures and text. Comparisons between Denver and high altitude values were performed using analysis of variance with student Neuman Keuls multiple comparisons. Correlation of two variables was analyzed by regression analysis. The null hypothesis of no differences between times and of no relationship between variables was rejected when the two-tailed probability was $< .05$.

RESULTS

Minute ventilation increased with ascent and during the course of exposure to high altitude both at rest and exercise (Table 1). At rest, the oxygen consumption and CO_2 production increased with ascent. At rest, the level of O_2 consumption and CO_2 production measured each day correlated positively with the level of minute ventilation (Figure 1). The level of O_2 consumption but not CO_2 production correlated with minute ventilation during exercise (Figure 1). The magnitude of the increase in resting minute ventilation from Denver to Pikes Peak was related ($p<.05$) among individual subjects to change in CO_2 production on days 1, 2 and 4. The increase in ventilation did not relate to arterial O_2 saturation on any Pikes Peak day. These findings are illustrated for Pikes Peak day 1, Figure 2.

The contribution of increased metabolism to the increase in minute ventilation was calculated as the average increase in $\dot{V}O_2$ or $\dot{V}CO_2$ divided by the average increase in minute ventilation. At rest for the 5 days on Pikes Peak, the average O_2 consumption increased 17±3% and CO_2 production increased 16±3% above Denver values whereas ventilation increased 26%±11%. Thus, increased CO_2 production or increased O_2 consumption could account for 62% (16/26 or 17/26) of the increase from low to high altitude observed in resting ventilation. During exercise, measurements of O_2 consumption and CO_2 production were not consistently higher on Pikes Peak than at Denver (Table 1). For the 5 days on Pikes Peak, the increase in O_2 consumption and CO_2 production averaged 6±1% and 3±1% above Denver values whereas ventilation increased 38±11%. Thus, increased

O_2 consumption and CO_2 production during exercise at high altitude could account for 16% (6/38) and 8% (3/38) respectively of the increase in ventilation observed. On a daily basis estimates of the proportion of the increase in ventilation at high altitude attributable to rises in CO_2 production were consistently greater at rest than at exercise (Figure 3).

Resting dead space volume and respiratory frequency on Pikes Peak were not greater than in Denver (Table 1). Hence, dead space ventilation at rest was unchanged (Figure 4). During exercise, dead space volume on day 5, respiratory frequency on days 1, 3, 4 and 5, and their product, dead space ventilation, were greater on Pikes Peak than in Denver (Figure 4, Table 1). Dead space to tidal volume ratio was not increased. The average increase in dead space ventilation on Pikes Peak (+4.1± l/min btps) could account for 29% (4.1/14.1=29%) of the average increase in ventilation observed from low to high altitude (Figure 4).

The alveolar ventilation per unit of CO_2 produced increased with ascent and during the course of exposure on Pikes Peak (Figure 5). The absolute alveolar ventilaton during exercise was greater during exercise than at rest but rest and exercise values were the same per unit of CO_2 production (Figure 5).

DISCUSSION

The main finding of the present study was that the increase in minute ventilation was not due to the acclimatization process alone, i.e., alveolar hyperventilation, but there were contributions from other factors. The two factors identified in this study were the increase in metabolic rate at rest and the increase in dead space during exercise.

Increased basal metabolic rate at high altitude has previously been described in men (though not necessarily in women (7)) after several days exposure (6,7) Although minute ventilation and metabolic requirements, particularly CO_2 production (14,15,16), are known to be closely linked at low altitude, the contribution of increased metabolism to the increased ventilation

at high altitude is not clear from previous reports. The increase in resting minute ventilation in our subjects was closely linked to an increase in metabolic rate, both when their relationship was considered within the group of subjects and over time. Our estimate was, that of the increase in resting ventilation on Pikes Peak, more than half (62%) could be attributed to an increased metabolism. Even if our estimates were high, the increase in resting metabolic rate on Pikes Peak suggested that increased metabolism at high altitude substantially contributed to the increase in minute ventilation. The mechanisms by which metabolic rate increases at high altiutde are not known but the possibilities include increased sympathetic activity secondary to hypoxia (2,11), increased glycolysis secondary to alkalosis (3), and an increase in the work of breathing. Because the subjects were housed in a warmed building, cold exposure was an unlikely explanation of the increase in metabolic rate on Pikes Peak.

During exercise, the metabolic requirements exceeded resting values but rose little at high compared to low altitude. Proportionately, the contribution of increased metabolism to increased ventilation during exercise at high altitude was less than at rest. Yet the absolute increase in total minute ventilation at high altitude during exercise was much greater for exercise than for rest, suggesting that some other factors were operating to increase exercise ventilation. One important factor appeared to be an increased dead space ventilation, resulting primarily from an increased dead space volume. Dead space volume increases with increased tidal volume (as has been reported) during muscular exercise at low altitude (1,10). In the present study during exercise at high altitude the progressive increase in dead space volume over the 5 days was accompanied by a progressive increase in tidal volume. Although the mechanism of the increase in dead space volume is not clear (4), the ratio dead space volume/tidal volume was little changed. The net result was that increases in dead sp . ventilation accounted for much of the increased minute ventilation during exercise at high altitude.

We considered that alveolar ventilation per unit of CO_2 production (which is inversely proportional to the PCO_2) would provide a relatively "pure" index of that part of ventilation which was related to acclimatization and which was free of influences from metabolic rate and dead space. The finding that the ratio of alveolar ventilation to CO_2 production and the values of PCO_2 were the same at rest and during exercise at high altitude suggested that the rate and magnitude of acclimatization was similar for these different metabolic states.

We concluded that metabolic factors contributed particularly at rest, and to a lesser extent during exercise, to the increased ventilation at high altitude. An increase in dead space was an important component of the increased minute ventilation during exercise at high altitude. We consider that the measurement of resting ventilation at high altitude remains useful for understanding the process of ventilatory acclimatization (8). However, both resting and exercising minute ventilation were influenced by factors other than the acclimatization process. Therefore, total ventilation is not a "pure" measure of the acclimatization process, and may be a rather insensitive tool for making inter-individual comparisons. At high altitude metabolic rate strongly influences ventilatory events. The mechanisms and implications of the increased metabolic rate remain to be investigated.

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Table 1. Resting and exercise respiratory and metabolic rate measurements at 1600 M and 4300 M (mean ± SE)

Measurements (n=12)	1600M	Days at 4300 M 1	2	3	4	5
			REST			
$\dot{V}_E$ 1/min, BTPS	9.2±.3	10.2±.5*	10.9±.6*	11.8±.4*	12.8±.8* (11)	12.4±.5*
f breaths/min	12.7±.9	14.4±1.4	13.7±1.4	15.1±1.5*	14.5±1.5 (11)	14.4±1.4
$\dot{V}A$ 1/min, BTPS	5.3±.2	6.4±.4* (11)		7.8±.4*		8.5±.4*
VD 1, BTPS	.31±.01	.27±.01 (11)		.28±.02		.28±.02
VD/VT	.42±.02	.37±.02 (11)		.34±.03*		.32±.02*
$PaCO_2$ Torr	36±.6	32±.8* (11)		29±.7*		26±.7*
$\dot{V}O_2$ 1/min, STPD	.26±.01	.30±.01*	.30±.01*	.31±.01*	.33±.02* (11)	.31±.01*
$\dot{V}CO_2$ 1/min, STPD	.22±.01	.24±.01	.25±.01	.26±.01*	.29±.02* (11)	.26±.01*
			EXERCISE			
$\dot{V}_E$ 1/min, BTPS	34.6±.6	43.3±1.1*	43.4±1.3*	48.3±1.7*	49.5±1.2*	54.6±2.8*
Breaths/min	20.8±1.3	24.7±1.5*	23.0±1.5	25.7±1.5*	25.4±1.8*	25.4±1.8*
$\dot{V}A$ 1/min BTPS	28.2±.5	34.4±.9* (8)		37.9±1.7* (11)		42.1±2.2*
VD 1 BTPS	.32±.03	.40±.03 (8)		.39±.03 (11)		.49±.05*
VD/VT	.19±.01	.21±.02 (8)		.24±.02 (11)		.23±.02
$PaCO_2$ Torr	36±.4	31±.7* (8)		28±.6* (11)		27±.9*
$\dot{V}O_2$ 1/min STPD	1.28±.02	1.35±.03	1.30±.03	1.36±.03*	1.32±.03	1.43±.04*
$\dot{V}CO_2$ 1/min STPD	1.18±.02	1.20±.03	1.17±.03	1.23±.03	1.18±.03	1.28±.05*

* Indicates that the values on Pikes Peak at 4300 M differ ($p<.05$) from those in Denver at 1600 M, by analysis of variance.

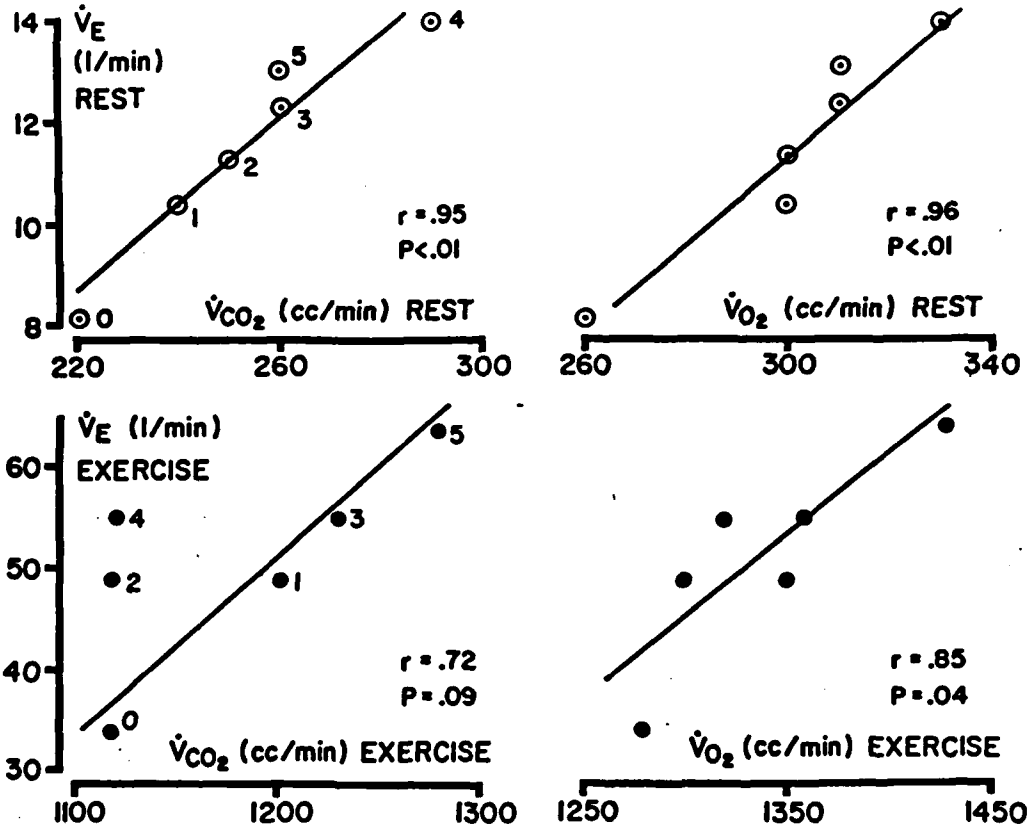
Figure 1 Minute ventilation as related to metabolic measurements (values from Table 1). TOP: Resting minute ventilation ($\dot{V}_E$, liters/min, BTPS) (open circles) increased with increasing CO_2 production ($\dot{V}CO_2$, left) and with increasing O_2 consumption ($\dot{V}O_2$, right). Indicated beside the points are the times the measurements were made, i.e. Denver measurement at 1600 M (D), and days 1, 2, 3, 4, and 5 at 4300 M on Pikes Peak. BOTTOM: Exercising minute ventilation (filled circles) vs. CO_2 production (left) and oxygen uptake (right). In this figure and in figure 4 measurements of $\dot{V}_E$ contained in the x and y axes must be independent to permit their comparison. Therefore $\dot{V}_E$ on the y axis was measured by the computer system whereas $\dot{V}_E$ for calculation of $\dot{V}CO_2$ and $\dot{V}O_2$ on the x axis was measured from a Tissot spirometer collection of expired air immediately after the computer measurement.

Figure 2 Relation of % change in ventilation, $\dot{V}_E$, from Denver to Pikes Peak day 1 to each of two potential regulators of ventilation, left, the percent change in CO_2 production ($\dot{V}CO_2$), and right, the arterial oxygen saturation (SaO_2). The change in ventilation related to the former and not the latter.

Figure 3 Resting (top) and exercising (bottom) minute ventilation ($\dot{V}_E$, BTPS) at Denver, 1600 M (D), and daily for 5 days at 4300 M. The shaded area estimates the ventilation attributed to increased CO_2 production. We assumed that ventilation at 1600 M was due to CO_2 production and that each day at 4300 M, ventilation attributable to CO_2 production was proportioned to the ratio $\dot{V}_E/\dot{V}CO_2$ observed at 1600 M.

Figure 4 Dead space ventilation ($\dot{V}D$, l/min, BTPS) during exercise (filled circles) exceeded that at rest (open circles) ($P<.05$) and increased with time at high altitude ($P<.01$).

Figure 5 Alveolar ventilation per unit of CO_2 production ($\dot{V}_A$ in l/min BTPS/$\dot{V}CO_2$ in cc/min, STPD) for rest (open circles) and exercise (filled circles) in Denver at 1600 M (D) and during 5 days on Pikes Peak (4300 M). There were no differences between rest and exercise in Denver or on Pikes Peak.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$\dot{V}_{CO_2}$ (cc/min) REST
r = .96
P<.01
$\dot{V}_{O_2}$ (cc/min) REST
$\dot{V}_E$ (l/min) EXERCISE
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P = .09
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r = .85
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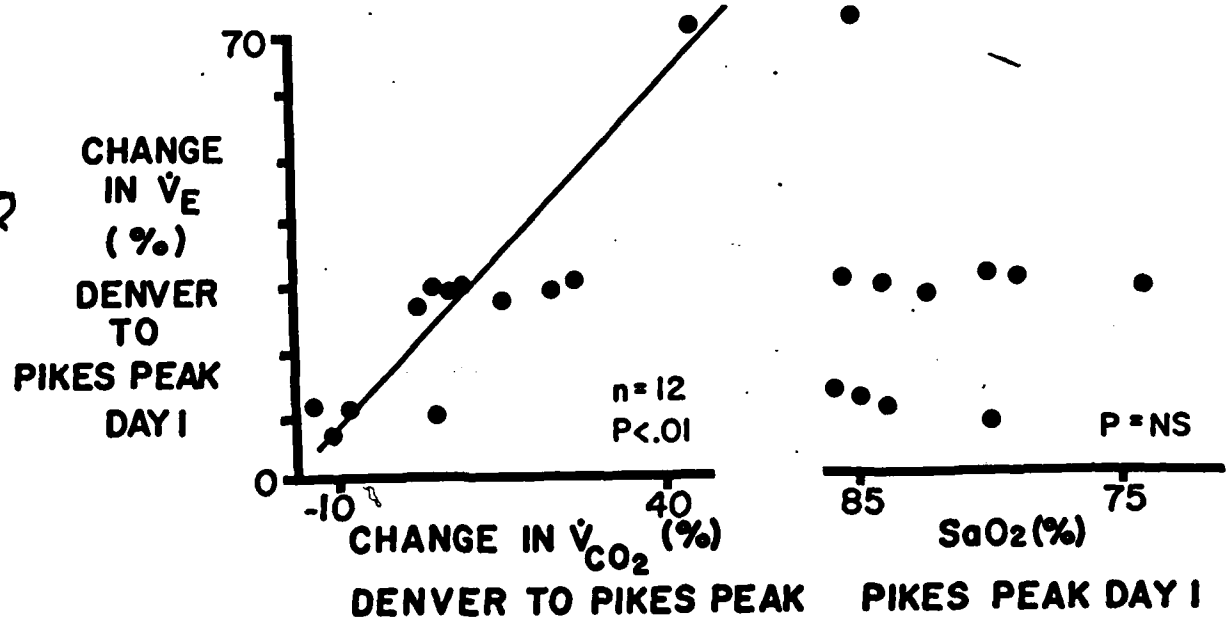
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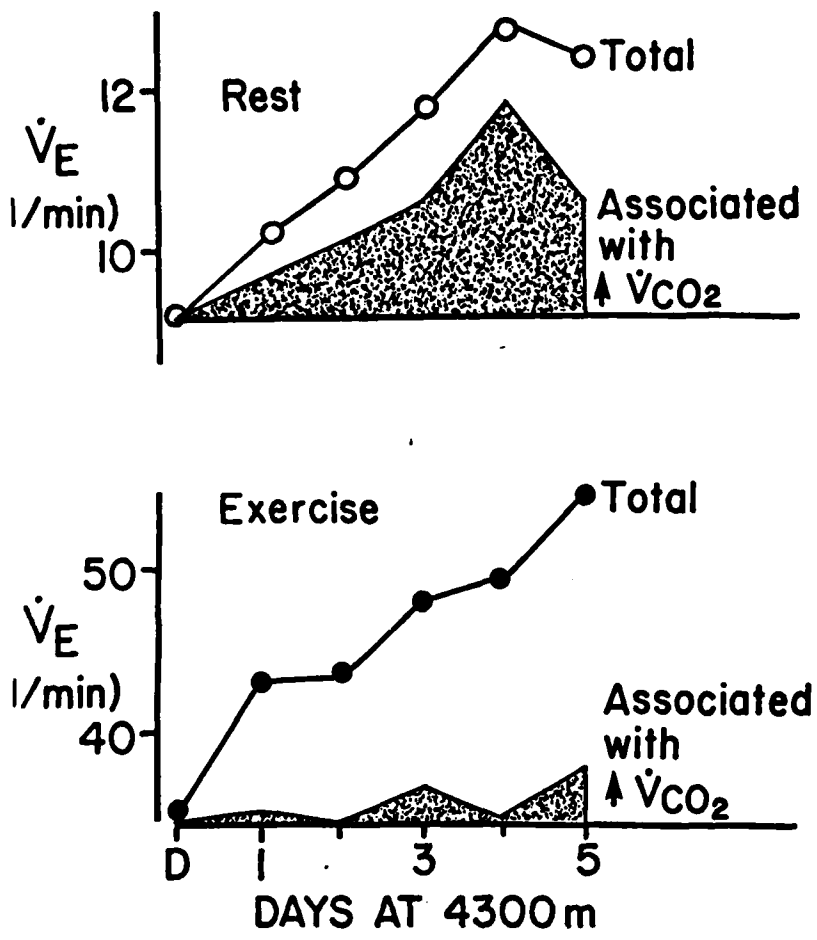
SaO_2 (%) PIKES PEAK DAY I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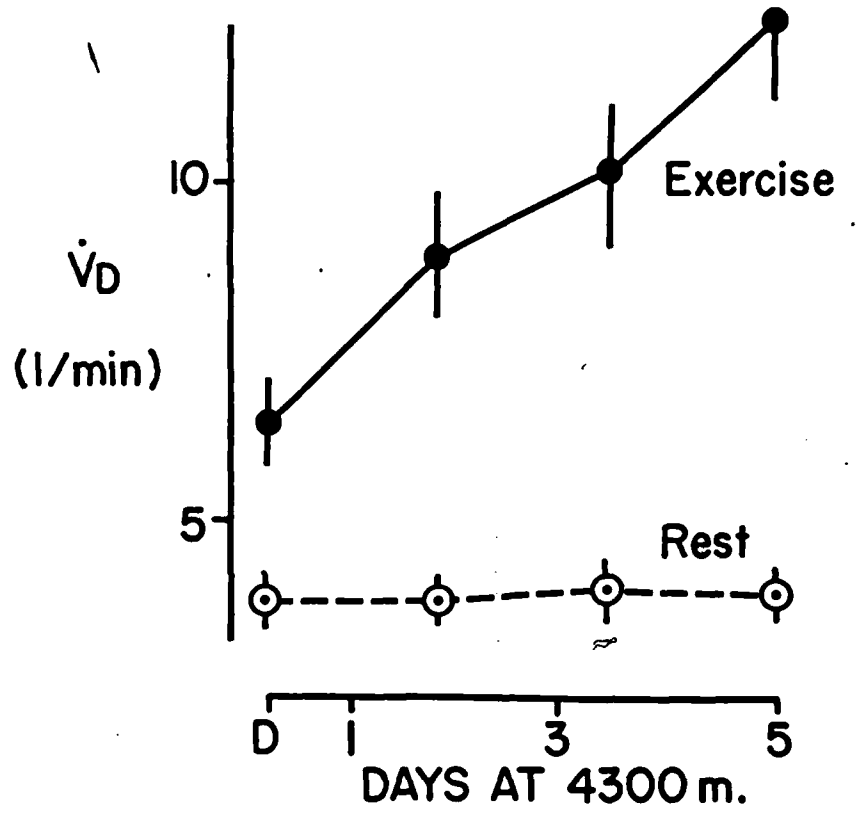
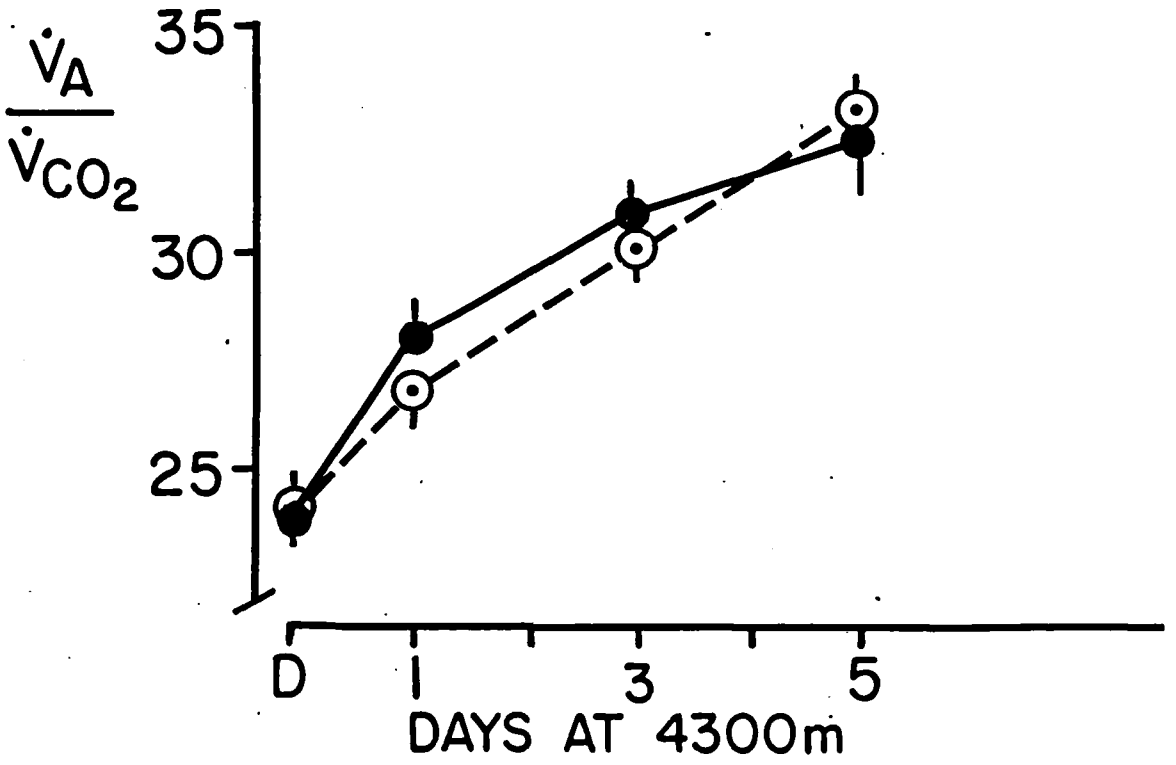
DAYS AT 4300 m

3


10
5
$\dot{V}_D$
(l/min)
Exercise
Rest
D
1
3
5
DAYS AT 4300 m.

4



5

The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of Volunteers in Research.

[illegible] above Denver values whereas ventilation increased 38±11%. Thus, increased

END

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