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Hypocapnia and Sustained Hypoxia Blunt Ventilation On Arrival at High Altitude

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Running Head: Blunting of ventilatory response to high altitude

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ABSTRACT

Hypoxia at high altitude stimulates ventilation but inhibitory influences limit the ventilatory response. Possible inhibitory influences include hypocapnia and depression of ventilation during sustained hypoxia. Our approach was to compare hypoxic ventilatory responses at low altitude with ventilation at high altitude. In 12 subjects we compared responses to acute (<10 min) isocapnic hypoxia, acute poikilocapnic (no CO_2 added) hypoxia and sustained (30 min) hypoxia in Denver, 1600 M, with ventilations measured on each of 5 days on Pikes Peak, 4300 M. On Pikes Peak day 1 ventilation (V_E=10.0 1/min, $Sa0_2$=82%) was less than predicted by either acute isocapnic or poikilocapnic tests. However sustained poikilocapnic hypoxia ($Sa0_2$ =82%) in Denver yielded ventilation similar to that on Pikes Peak day 1. By Pikes Peak days 4 and 5, end-tidal $PC0_2$, pHa, and arterial oxygen saturation approached plateaus, and ventilation (12.4 1/min) was as predicted by the acute isocapnic test. Thus the combination of hypocapnia and sustained hypoxia may have blunted the ventilatory increase on Pikes Peak day 1, but apparently not after 4 or 5 days of acclimatization.

INTRODUCTION

Increased ventilation is important for persons going to high altitude (7,10) but the relative roles of factors which influence the ventilation are not clear as discussed in a recent authoritative review (4). In attempting to investigate this problem we assumed that hypoxia is the primary stimulus for increasing ventilation at high altitude (4,8,16). If so, then a measure of ventilatory response to hypoxia at low altitude should relate to ventilation at high altitude. However the ventilatory response to high altitude might be inhibited by hypocapnia (and alkalosis) which begin on exposure (4). A measure of the inhibitory effect could be obtained at low altitude by comparing the ventilatory response to isocapnic hypoxia with the response to hypoxia in the presence of falling CO_2. We termed the response without CO_2 addition the poikilocapnic hypoxic response, (from the Greek poikilos, meaning varied) (12). Another factor which might attenuate the increase in ventilation at high altitude is the depression of the acute hypoxic ventilatory response which is observed when hypoxia is sustained (5,17). To evaluate this effect we compared the acute hypoxic response measured for a few minutes with the response to 30 minutes of isocapnic and poikilocapnic hypoxia.

The results indicated that ventilatory response during early high altitude exposure was due to the stimulating effects of hypoxia in combination with inhibition by hypocapnia and by time dependent depressant effects. Subsequently at high altitude, ventilation rose and stabilized at values attained during acute isocapnic hypoxia.

Thus, ventilatory measurements at low altitude of the response to the stimulus of hypoxia in combination with inhibition by hypocapnia and by sustained hypoxia permits estimation of ventilation on arrival at high altitude. With continued exposure, these inhibitory influences appear to be offset. This approach provides insight into the relative roles of factors influencing ventilation at high altitude.

METHODS

Twelve healthy male volunteers, age 22 to 34 years, participated in the present study with their informed consent. They were residents of Denver, Colorado, elevation 1600 M, and were subjects 1-12 of a previous report (12) where their individual characteristics are reported. Resting low altitude tests were performed on two separate days in Denver, Colorado, as previously described (12). Briefly, the subjects were studied after fasting for 4 hours or more and after resting semi-recumbent for at least 20 minutes. Measurements at rest during room air breathing included expired minute volume (by hot-film flowmeter) respiratory frequency, tidal volume, end-tidal PO_2 (by fuel cell oxygen analyzer), end-tidal PCO_2 (by capnograph CO_2 analyzer), arterial oxygen saturation (by ear oximeter), and heart rate. Measurements were printed out as 30 second averages by a computer system as previously described. The flowmeter was calibrated against a Tissot spirometer and the analyzers were calibrated after each subject with gases previously analyzed by the Scholander technique. The computer system was used during room air breathing to indicate that ventilation was stable. Values of ventilation reported here were measured on 3-minute collections using a Tissot spirometer both in Denver and on Pikes Peak.

On a given day in Denver, ventilation was measured during quiet, room air breathing and, on alternate days, during isocapnic or poikilocapnic hypoxia. During room air breathing, a sample of arterialized venous blood was withdrawn from a heated hand vein for analysis of CO_2 tension and pH. The ventilatory response to isocapnic hypoxia was measured using the computer system. Progressive hypoxia was induced by adding nitrogen to the inspired air over a 7 to 10 minute period and was terminated when the end-tidal PO_2 reached 40 mmHg. End-tidal PCO_2 was maintained at the resting value by adding 100% CO_2 to the inspired gas. The response to poikilocapnic hypoxia was measured following the

same procedure except that no CO_2 was added to the inspired gas. Measurements of ventilatory response to isocapnic and poikilocapnic hypoxia were performed in random order and in duplicate or until the resulting values of ventilatory response agreed to within 50% of the smaller value. For the purposes of the present report, the hypoxic ventilatory responses were analyzed by relating ventilation ($\dot{V}_E$) to arterial oxygen saturation ($Sa0_2$).

The relationship was linear and fit the equation:

$$\dot{V}_E = b\ (Sa0_2) - \text{intercept},$$

where b was the slope, $\Delta\dot{V}_E/\Delta\, Sa0_2$ (8). We scaled $Sa0_2$ on the abscissa from high to low so that the slope $\Delta\dot{V}_E/\Delta\, Sa0_2$, appeared positive and we report it as a positive number.

Testing at high altitude was performed at the United States Army Medical Laboratory facility on the summit of Pikes Peak, Colorado, elevation 4300 m. The subjects were taken by car within 2 hours from Denver to Pikes Peak where they sojourned for 5 days. Resting ventilatory measurements were completed on the first day not earlier than 2 hours nor later than 6 hours after beginning the 1 hour ascent of the mountain. The resting ventilatory measurements were done daily as in Denver with the subjects fasting for at least 4 hours and having rested semi-recumbent for at least 20 minutes. On days 1, 3 and 5 arterialized venous blood was withdrawn for determination of PCO_2 and pH.

Measurements of ventilatory response during prolonged (30 minutes) hypoxia were done in 9 subjects who were available 8 months following the high altitude sojourn. Subjects had remained in the Denver area during the interim period. Each subject was studied as before in the rested, fasted condition. Measurements of ventilation, end-tidal CO_2, end-tidal 0_2, and $Sa0_2$ were made using the computer system described above. After 10 minutes of room air breathing, the P_A0_2 was lowered abruptly to approximately 45 mmHg and maintained

at that level for 30 minutes by adjusting the nitrogen content of the inspired air. At the end of 30 minutes the subject was returned to room air breathing and measurements were made for an additional 5 to 10 minutes. Measurements during 30 minutes of hypoxia were made twice, once with CO_2 added to the inspired air to maintain isocapnia, and once without adding CO_2, poikilocapnia. In alternate subjects the isocapnic test was followed by the poikilocapnic test and in the other subjects, the sequence was reversed.

Values are reported as mean ± one standard error. Correlation between pairs of variables was computed by linear regression techniques. Comparison between two or more mean values were performed with analysis of variance using Student Neuman Keuls multiple comparisons. The null hypothesis of no relationship between variables or differences between groups was rejected when the two-tailed probability $<.05$.

RESULTS

For the group, ventilation increased with ascent, rose progressively on Pikes Peak days 1-4 and approached a plateau on days 4 and 5 (Figure 1). The end-tidal PCO_2 fell abruptly on Pikes Peak day 1 and then fell more slowly. Arterialized pH showed a progressive rise above the Denver value on days 1 and 3 but rose no further on day 5. The arterial oxygen saturation fell abruptly on Pikes Peak day 1 and then rose to values which remained stable after day 3 (Figure 1). Thus the measures of ventilation changed rapidly with ascent and during the early days of the Pikes Peak sojourn but approached a plateau by days 4 and 5.

The levels of ventilation and arterial oxygen saturation observed on Pikes Peak were compared to those achieved during acute isocapnic hypoxia as measured in Denver. The acute ventilatory response in Denver, measured by the slope of ventilation (response) versus arterial oxygen saturation (stimulus) or $\Delta \dot{V}_E / \Delta Sa0_2$, averaged .52±.34 l/min/% (Figure 2, top). On Pikes Peak day 1,

at the level of arterial oxygen saturation observed, the ventilation was less than expected from the acute isocapnic hypoxic ventilatory response curve measured in Denver. However, by days 4 and 5 the values of ventilation lay quite near the acute hypoxic ventilatory response curve. On days 4 and 5, the levels of ventilation among the individual subjects correlated positively with their ventilatory responses to acute isocapnic hypoxia as measured in Denver (illustrated for day 4, figure 3, lefthand panel). Correlation was also found on day 2, but not on days 1 or 3 (Table 1).

We considered two factors which could have caused the ventilation on Pikes Peak day 1 to be below the value predicted from the acute isocapnic hypoxic response in Denver. First, the level of ventilation observed during acute tests is known to decrease when hypoxia is sustained (5,17) and this could contribute to the decrease in ventilation on day 1. In the 9 subjects given 30 minutes of sustained isocapnic hypoxia, the ventilation rose within 5 to 10 minutes to a maximum which was not maintained. However, ventilation after 30 minutes of sustained hypoxia remained above the normoxic levels and the levels observed on Pikes Peak day 1 (Figure 4).

A second factor considered was that hypocapnic alkalosis on Pikes Peak day 1 could have blunted the ventilatory response to an equal degree of hypoxia. The acute response of ventilaton to poikilocapnic hypoxia was less than that observed during isocapnic hypoxia (Figure 2). However, the ventilation on Pikes Peak day 1 at the observed CaO_2 was still less than that expected from the acute poikilocapnic hypoxic response measured in Denver. Also the ventilatory responses to acute poikilocapnic hypoxia among individual subjects did not correlate with ventilation on Pikes Peak day 1 (Table 1). A correlation was observed on day 2, but not on days 3, 4 (Figure 3, righthand panel) or 5.

Ventilation during poikilocapnic hypoxia, like that during isocapnic hypoxia is not maintained during sustained hypoxic challenge (Figure 4). The fall in ventilation from peak response to 30 minutes of hypoxia was accompanied by a small, but significant increase in end-tidal PCO_2. Sustained poikilocapnic hypoxia combined the effects of time dependent decreases in hypoxic ventilation and of hypocapnia and produced ventilations not different from those measured on day 1 on Pikes Peak (10.8±1.5 vs 10.0±0.4 l/min btps, P=NS).

DISCUSSION

In the present study as ventilatory acclimatization to high altitude progressed, the average ventilation for the group of subjects approached levels observed during acute isocapnic hypoxia at low altitude. Not only was ventilation for the group predicted by the isocapnic hypoxic ventilatory response at low altitude but the rank order among individual subjects was preserved. In contrast, ventilation measured during the first three days at high altitude was lower than that predicted by the isocapnic hypoxic response at low altitude. Our data suggest that approximately half of this decrement was explained by the inhibitory effects of hypocapnia as estimated from the difference between the acute isocapnic and poikilocapnic hypoxic response slopes. The remaining half of the decrement appeared to be due to the decrease or "roll-off" of ventilation seen when hypoxia was prolonged as measured in the 30 minute isocapnic hypoxic test. When these two effects were combined in the sustained poikilocapnic test, ventilations nearly identical to those seen on day 1 at high altitude resulted.

The reduction in ventilation during the early phases of high altitude was expected given the inhibitory effects of alkalosis on ventilation (4). In this respect ascent to high altitude is a physiological dilemma in that hypoxia drives breathing but breathing results in hypocapnic alkalosis and reduces the ventilatory response. Reducing the extent of alkalosis with ammonium chloride

or acetazolamide typically leads to increases in alveolar ventilation following ascent (2). Subsequently, the process of ventilatory acclimatization seems to act as if it were reversing this attenuating effect of the persistent alkalosis seen in this and in numerous other studies recently reviewed (4). Previous reports also suggest that there is no apparent lessening of alkalosis in the cerebrospinal fluid which would account for the acclimatization phenomenon although indirect estimates indicate that cerebral interstitial pH may be falling during this period due perhaps to local generation of lactic acid (4,6).

The second component decreasing ventilation during early high altitude exposure appeared to be time-dependent depression of ventilation with sustained hypoxia. This depression occurred in our study within 30 minutes as has been reported by others (5,17,18). Further evidence for depression is seen in the paradoxical increase in ventilation which sometimes follows the administration of oxygen to high altitude natives and to persons with chronic mountain sickness (10,11). That the depression is most readily demonstrated when the hypoxia is very severe ($Pa0_2$ approaching 20 mmHg) suggests that hypoxia may be acting through depressant effects on the central nervous system (3,13). Alternatively, the depression of ventilation could be due to a decrease in metabolic rate. However, we observed that decreasing ventilation was accompanied by a rising P_ACO_2 during the sustained poikilocapnic hypoxic test which indicated that alveolar ventilation diminished per unit of metabolic rate. Thus, it appeared likely that the ventilatory depression observed after 30 minutes of sustained hypoxia at low altitude also ocurred during the early period of high altitude exposure and contributed to the determination of ventilation on Pikes Peak day 1.

Our statement that ventilatory acclimatization to altitude resulted in ventilations closely approaching those predicted by the acute isocapnic hypoxic ventilatory response must be qualified by the possibility that acclimatization

was not complete by days 4 and 5. Yet it would seem that this condition was nearly met. While several indices have been proposed for measuring acclimatization, we have taken this process to represent an increase in alveolar ventilation which is disproportionate to a rise in metabolic rate, i.e. true alveolar hyperventilation, and have taken the $PACO_2$ as the best measure of this. While the time required to complete the acclimatization process is quite variable both between and within species (1), the plateau in P_ACO_2 observed in our subjects by days 4 and 5 suggests that acclimatization was largely complete. Possibly, it was mere coincidence that the level of ventilation at high altitude rose to levels achieved during acute isocapnic hypoxia. We think not for two reasons. First, the similarity between high altitude ventilation and that predicted from the acute isocapnic response was true for the group as a whole on both days 4 and 5. Second, the similarity in the group data was also observed among individuals such that individuals with the highest isocapnic hypoxic ventilatory responses at low altitude achieved the highest high altitude ventilations while the persons with the lowest hypoxic responses had the lowest ventilations at high altitude.

Few other studies have attempted to relate hypoxic ventilatory response at low altitude to ventilation at high altitude. King and Robinson (9) found that the levels of ventilation at high altitude and isocapnic hypoxic ventilatory responses at low altitude were lower in a subgroup of subjects with symptoms of acute mountain sickness than in a subgroup without symptoms. Their study suggests that differences in high altitude ventilation may have resulted from differences in isocapnic hypoxic ventilatory responses based on subgroups examined after 6 hours of high altitude exposure. In our study, a trend was observed for the entire group between the isocapnic ventilatory response and ventilation on day 1 but this achieved only borderline significance ($p=.08$). In any event, it would seem that the findings of both studies are consistent with

the idea that the isocapnic hypoxic ventilatory response makes an important contribution to high altitude ventilation. But in the early period, there are important contributions by two inhibitory factors (hypocapnia and time dependent hypoxic depression) which weaken the relationship between acute hypoxic response and ventilation. In a study by Sutton et al. (15) no correlation was found between the poikilocapnic hypoxic ventilatory response and ventilations measured at various times following staged ascent to high altitude. Interpretation of these findings is complicated by the uncertainty regarding duration of high altitude exposure introduced by staged ascent. However, their findings resemble ours in that the acute poikilocapnic hypoxic response, by itself, correlated poorly with ventilation both early and late at high altitude.

Thus ventilation following acclimatization to high altitude seems to be largely determined by the ventilatory response to hypoxia as measured at low altitude by the acute isocapnic hypoxic response. In the first few days following altitude ascent, the stimulus of hypoxia on ventilation is inhibited by the combined effects of hypocapnic alkalosis and the tendency of ventilation to decrease when hypoxia is sustained. The inhibitory influences of these two factors on ventilation appears to be overcome during the acclimatization process in ways that remain unclear.

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Table 1. Correlation between hypoxic ventilatory responses at 1600 M and resting ventilation over 5 days at 4300 M.

DAY	1	2	3	4	5
Hypoxic Ventilatory Responses at 1600 M	Resting ventilation at 4300 M				
Isocapnic	P= .08	*	NS	*	*
Poikilocapnic	P= NS	*	NS	NS	NS

* indicates $p<.05$; NS= not significant.

FIGURE LEGENDS

Figure 1 Changes with time at high altitude in measurements relating to ventilation in Denver (D) at 1600 M and for the 5 days on Pikes Peak at 4300 M. Shown for the resting subjects are mean ± SE values for minute ventilation ($\dot{V}_E$), end tidal PCO_2 (P_ACO_2), arterialized hand vein blood pH (pHa), and arterial oxygen saturation by ear oximeter ($Sa0_2$). For each variable, Denver values differ from values on each of the 5 days on Pikes Peak; values on day 3 ($\dot{V}_E$, pHa) and day 4 ($\dot{V}_E$, P_ACO_2, $Sa0_2$) do not differ from day 5 values on Pikes Peak (anova with multiple comparison, $P<0.05$).

Figure 2 Stimulus (arterial oxygen saturation, $Sa0_2$ in %) vs ventilatory response ($\dot{V}_E$) averaged for the group.

TOP: The unbroken line is the acute stimulus-response relationship for the group in Denver (1600 M) during progressive isocapnic hypoxia, as constructed from the normoxic Denver values ($\dot{V}_E$ = 9.2 l/min, $Sa0_2$ = 95.5%) and the average slope ($\Delta\dot{V}_E/\Delta Sa0_2$ = .52 l/min/%) of the acute isocapnic hypoxic ventilatory response curve. The points connected by unbroken arrows represent the sequential changes in $\dot{V}_E$ and $Sa0_2$ from day 1 to day 5 on Pikes Peak. Standard errors are indicated. The broken arrow shows the decrease in ventilation at the same $Sa0_2$ after 10 minutes of isocapnic hypoxia to ventilation after 2 to 6 hours (day 1) on Pikes Peak.

BOTTOM: The unbroken line is the acute stimulus response relationship in Denver (1600 M) during progressive poikilocapnic hypoxia. The slope, $\Delta\dot{V}_E/\Delta Sa0_2$ (.32±.20 l/min/%) was less ($p<.05$) than during isocapnic hypoxia. The broken arrow indicates the decrease in ventilation at the same $Sa0_2$ after 10 minutes of poikilocapnic hypoxia to ventilation after 2 to 6 hours (day 1) on Pikes Peak.

Figure 3 Relationship of resting isocapnic (left) and poikilocapnic (right) hypoxic ventilatory response, each measured as the slope $\Delta \dot{V}_E / \Delta SaO_2$ in Denver (1600 M), to subsequent resting minute ventilation ($\dot{V}_E$) on day 4 on Pikes Peak (4300 M). Each point represents one subject.

Figure 4 Minute ventilation ($\dot{V}_E$) in 9 subjects during 30 minutes of sustained hypoxia and on Pikes Peak day 1. Shown at time 0 is ventilation during room air breathing. Isocapnic hypoxia (Iso, filled circles) was maintained at SaO_2 = 82.6±.8% and P_ACO_2 = 33.4±.8 mmHg. Poikilocapnic hypoxia (Poikilo, open circles) was maintained at SaO_2 81.8±.9%. The P_ACO_2 during poikilocapnic hypoxia rose slightly from 29.9±.9 mmHg at 5 minutes to 31.0±1.0 at 30 minutes ($P<.05$). Ventilation was highest during acute isocapnic hypoxia and lowest on Pikes Peak day 1. Values of ventilation on Pikes Peak day 1 were the same as after 30 minutes of poikilocapnic hypoxia (anova using multiple comparisons, $P<.05$).

Figure 1

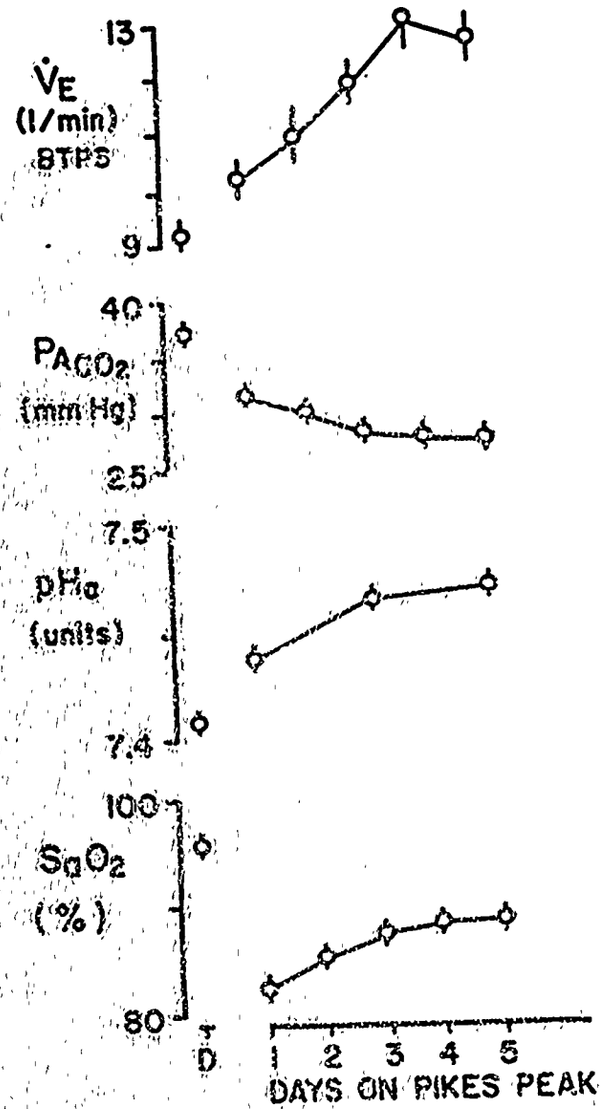
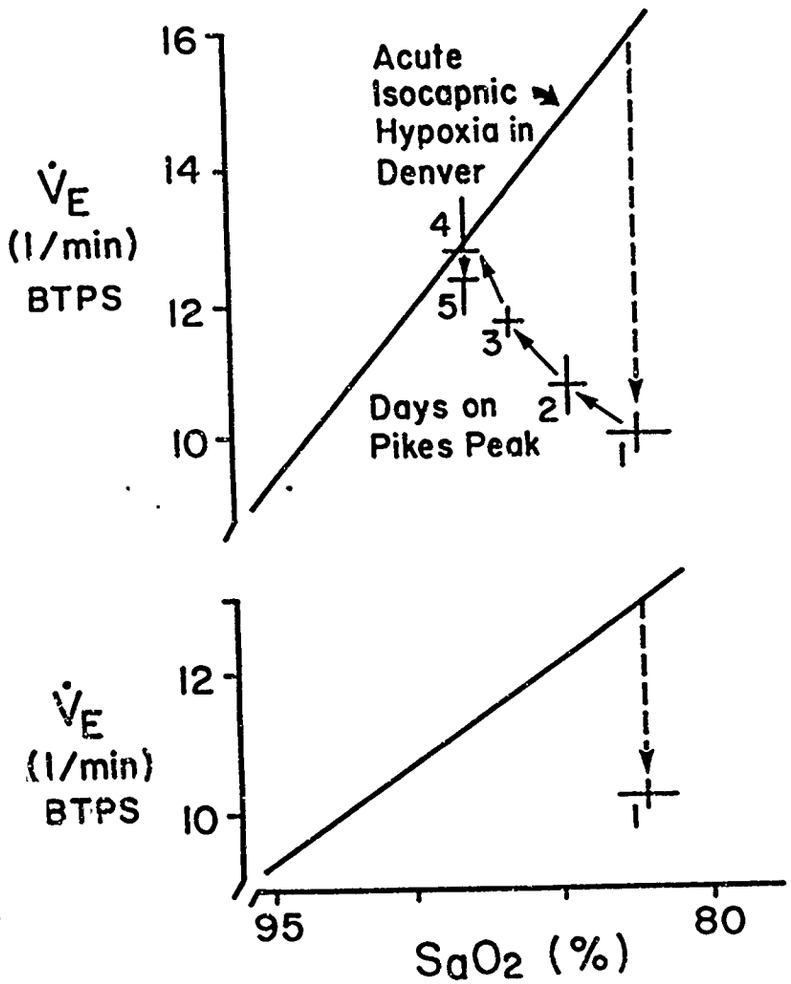


Figure 2



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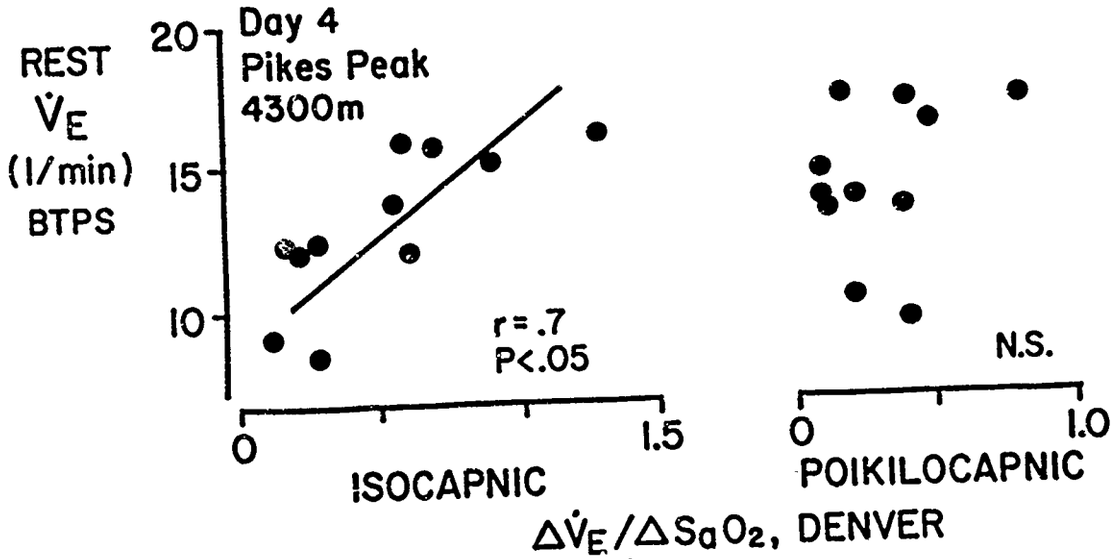

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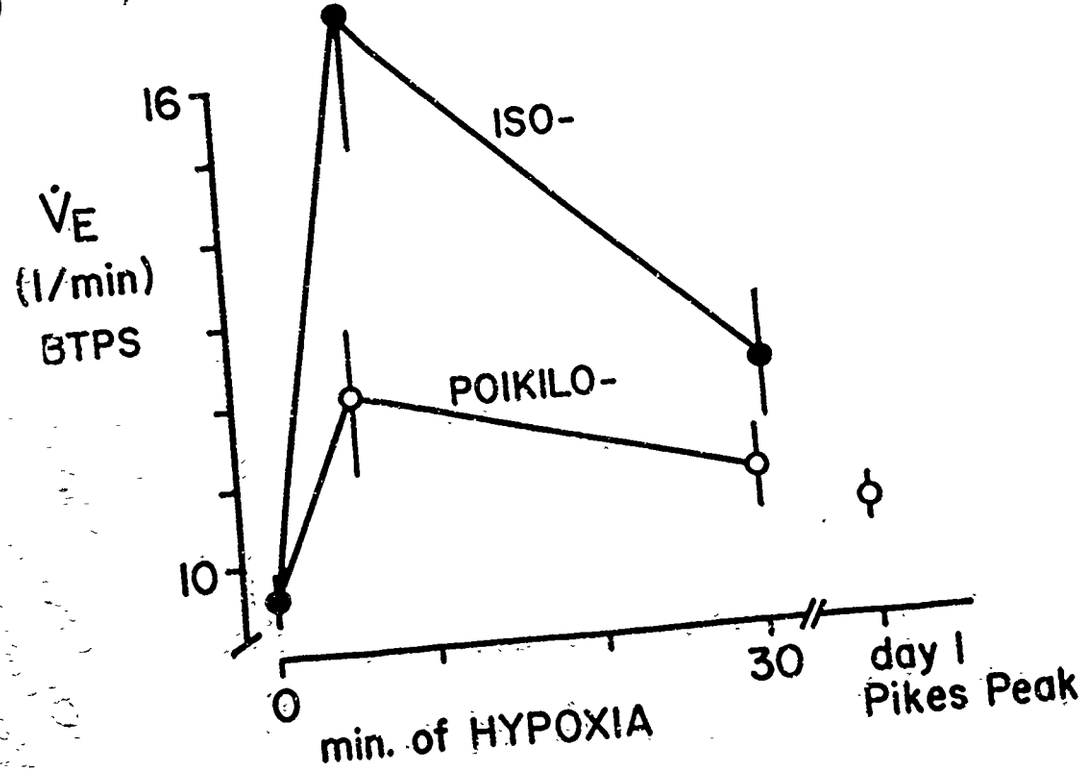

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Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of Volunteers in Research.