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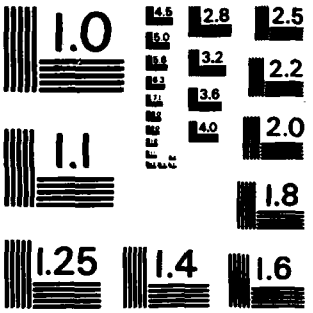

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Acute hypoxia stimulates an increase in ventilation but the resulting hypocapnia limits the magnitude of the increase. Thus, the hypoxic ventilatory response is usually measured during isocapnia, but this may not reflect events at high altitude. Possibly the degree of inhibition by hypocapnia might depend on individual ventilatory response to CO_2 and thus vary between persons. If so, it might be useful to compare between individuals an isocapnic hypoxic ventilatory response (P_ACO_2 maintained by CO_2 addition) with a response in which CO_2 was not

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added and the P_ACO_2 fell to a variable extent (poikilocapnic hypoxia). We found in 14 healthy persons that, although the poikilocapnic hypoxic ventilatory response positively correlated with the isocapnic hypoxic response, the relation was improved by a multiple regression which included the negative association with the normoxic hypercapnic response. Thus the magnitude of the difference between the isocapnic and the poikilocapnic hypoxic responses related to the hypercapnic response ($p < .001$). In those subjects with small hypercapnic responses, a falling CO_2 during hypoxia had little depressant effect on the hypoxic ventilatory response. The results suggested that the CO^2 response in the high CO_2 range related to ventilatory events in the low CO_2 range. Further the magnitude of the ventilatory inhibition by hypocapnia may depend on individual ventilatory responsiveness to CO_2.

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VARIABLE INHIBITION BY FALLING CO_2 OF HYPOXIC VENTILATORY RESPONSE IN MAN

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ABSTRACT

Acute hypoxia stimulates an increase in ventilation but the resulting hypocapnia limits the magnitude of the increase. Thus, the hypoxic ventilatory response is usually measured during isocapnia, but this may not reflect events at high altitude. Possibly the degree of inhibition by hypocapnia might depend on individual ventilatory response to CO_2 and thus vary between persons. If so, it might be useful to compare between individuals an isocapnic hypoxic ventilatory response (P_ACO_2 maintained by CO_2 addition) with a response in which CO_2 was not added and the P_ACO_2 fell to a variable extent (poikilocapnic hypoxia). We found in 14 healthy persons that, although the poikilocapnic hypoxic ventilatory response positively correlated with the isocapnic hypoxic response, the relation was improved by a multiple regression which included the negative association with the normoxic hypercapnic response. Thus the magnitude of the difference between the isocapnic and the poikilocapnic hypoxic responses related to the hypercapnic response ($p<.001$). In those subjects with small hypercapnic responses, a falling CO_2 during hypoxia had little depressant effect on the hypoxic ventilatory response. The results suggested that the CO_2 response in the high CO_2 range related to ventilatory events in the low CO_2 range. Further the magnitude of the ventilatory inhibition by hypocapnia may depend on individual ventilatory responsiveness to CO_2.

INTRODUCTION

Acute hypoxia stimulates ventilation resulting in an hypocapnic alkalosis which, in turn, inhibits the ventilatory response to hypoxia (4,5,11). Thus for the usual measurement of the acute ventilatory response to hypoxia in man, alveolar CO_2 is held constant ("isocapnia") by adding CO_2 to the inspired air (12). Yet isocapnia is not present during acute exposure to high altitude where hypoxia co-exists with a changing alveolar CO_2. In the present study, we measured the ventilatory response to progressive hypoxia in a fashion analogous to high altitude, i.e. the alveolar PCO_2 was allowed to fall (8). Because the alveolar PCO_2 varies during the test, we propose the term "poikilocapnia" (from the greek poikilos, meaning varied). We expected that the falling CO_2 levels would cause the poikilocapnic hypoxic ventilatory response to be less than the isocapnic response. We compared the poikilocapnic with the isocapnic responses and examined the extent to which the differences between them were a function of ventilatory sensitivity to CO_2.

METHODS

Subjects for the study were 14 healthy, non-smoking males. Testing was performed at the Cardiovascular Pulmonary Research Laboratory at the University of Colorado Health Sciences Center in Denver, Colorado, elevation 1600 meters. All subjects gave consent and study procedures were approved by the Human Research Committee. The subjects ranged in age from 21 to 34 with an average of 26.2 years. All were native to and resident at altitudes lower than 1700 meters.

Measurements for each subject were performed on 2 separate days. Subjects arrived in the laboratory for the experimental protocol after fasting for at least 4 hours. A scalp vein needle (19g) was inserted in the back of the hand for measuring arterialized CO_2 tensions from a heated hand vein (2,7) and the subject was allowed to rest for 20 minutes. All of the ventilatory response tests were performed with the subject breathing through a respiratory valve (Model 2700, Hans Rudolph, Kansas City, MO) from which end-tidal oxygen tension was measured with a fuel-cell oxygen analyzer (13) (Model 101, Applied Technical Products, Denver, CO); end-tidal carbon dioxide tension with an infrared analyzer (Model LB-2, Beckman Instruments, Fullerton, CA) and expired airflow (V_E) with a hot-film flowmeter (Model 1054B, Thermo-Systems, Inc., St. Paul, MN). The analyzers monitoring end-tidal gases sampled the breathing valve dead space and thus were able to monitor inspired gas composition as well. Inspired airflow was measured with a second hot-film flowmeter (Model MFG-20H, Technology Incorporated, Dayton, OH). Both inspired and expired airflow were digitally integrated to provide inspired and expired minute volume. In addition, blood oxygen saturation ($Sa0_2$) was monitored using an ear-oximeter (Model 47201A, Hewlett-Packard Corp., Waltham, MA). Heart rate and cardiac electrical function were monitored by ECG. The flowmeters were calibrated against a Tissot spirometer and the gas analyzers were calibrated with gases analyzed by the Scholander technique. All electrical signals from the monitoring instruments were processed by a digital computer (Nova 1200, Data General Corp., Southboro, MA) which printed out measurements at 30 second intervals of minute ventilation (V_E),

volume of inspired air, PO_2 in inspired air, endtidal PO_2 ($PETO_2$) and PCO_2 ($PETCO_2$), tidal volume, breathing frequency, heart rate, O_2 consumption, CO_2 production, and SaO_2.

On a given day, measurements were made during quiet breathing and then, in sequence, ventilatory response was measured either during isocapnic hypoxia and hypercapnia or during poikilocapnic hypoxia. The choice as to which sequence was followed first was made at random.

For the isocapnic hypoxic response, progressive hypoxia was induced over 7-10 minutes by the gradual addition of nitrogen to a reservoir bag initially containing 35% O_2 from which the subject breathed. Thus the end-tidal O_2 was reduced from approximately 130 mmHg to a final value of 40 mmHg. Throughout this test, end-tidal PCO_2 was maintained at the resting, room air value by the addition of 100% CO_2 to the inspired gas. Resting, room air end-tidal PCO_2 values were checked for agreement with arterialized CO_2 tensions. The poikilocapnic hypoxic response was measured following the same testing procedure except that no CO_2 was added to the inspired air. Two isocapnic and two poikilocapnic hypoxic responses were measured in all subjects and if the resulting values of hypoxic sensitivity differed by more than 50% of the smaller value, a third test was conducted.

The hypoxic ventilatory responses were analyzed by relating V_E either to SaO_2 or to end-tidal PO_2. The relationship of V_E to SaO_2 is linear and was analyzed by fitting data to a linear equation: $V_E = b(SaO_2)$-Intercept, where b is the slope, V_E/ SaO_2 (10). The SaO_2 values on the abscissa were scaled from high to low, analogous to the scaling employed for end-tidal PO_2, such that the computed slope,

V_E/ SaO_2, was a positive number. Curves relating V_E to end-tidal PO_2 are hyperbolic in shape and were analyzed by fitting data to the hyperbolic equation: $V_E=Vo+A/(PETO_2-32)$ as is discussed in more detail elsewhere (12). The slope V_E/ SaO_2 in the SaO_2 equation and parameter "A" in the hyperbolic equation are useful measures of hypoxic sensitivity in that a large slope and a high "A" value denote a vigorous response to hypoxia and small values, a blunted response.

The hypercapnic ventilatory response was measured using a modified rebreathing technique (9). An approximately 7-liter closed breathing circuit initially containing 35% O_2 with no CO_2 was used. Transducers and the computer used were the same as those described above. A rise in end-tidal PCO_2 of approximately 10 mmHg above the initial value occurred within 5-7 minutes. Curves relating V_E to end-tidal PCO_2 are linear and were analyzed by fitting data to the simple linear equation: $V_E = S(PETCO_2)-B$, where S, the slope, is a measure of the ventilatory sensitivity to hypercapnia and B is the intercept on the abscissa (4).

Statistics

Data are reported for each subject as the average of the two measurements of resting isocapnic hypoxic ventilatory responses and the two resting poikilocapnic hypoxic responses. Pearson product-moment correlation coefficients were computed to examine bivariate relationships. Multiple regression techniques were used to analyze relationships between an independent variable and two dependent variables. Probability level chosen for rejecting the null hypothesis of no relationship between variables was $P<.05$.

RESULTS

Ventilatory responses to isocapnic and poikilocapnic hypoxia and to hypercapnia all showed a several fold range of variation between subjects. Differences in age, height, weight, and resting end-tidal CO_2 tensions were not related to the observed variations (Table 1).

Resting ventilatory responses to poikilocapnic hypoxia were, on the average less than those to isocapnic hypoxia ($V_E/ Sa0_2$=32±.05 vs .56±.09, P<.01, Table 1). The two responses were closely correlated (Figure 1). This was true when the hypoxic ventilatory response was expressed either as the slope $V_E/ Sa0_2$ (Figure 1) or parameter A (r=.68, P<.001).

The difference between the isocapnic and poikilocapnic hypoxic ventilatory response, i.e. the depressant effect of falling CO_2, was correlated with the hypercapnic ventilatory response (Figure 2). That is, subjects with low hypercapnic ventilatory responsiveness (HCVR "S" <1.4) had little diminution of their hypoxic ventilatory response with poikilocapnia. In contrast, subjects with high hypercapnic ventilatory drives (HCVR "S" >1.4) had greater response to isocapnic than to poikilocapnic hypoxia. The hypoxic ventilatory response curves illustrated in Figure 3 for two subjects having, respectively, large and small hypercapnic responses show that poikilocapnia depressed the hypoxic response in the former but not in the latter.

Analysis by multiple regression indicated that 59% (R^2 = .59, p<.001) of the variation in poikilocapnic hypoxic ventilatory response (poik HVR) could be accounted for by its positive association with the isocapnic hypoxic response (iso HVR). An additional 13% could be accounted for by its negative association with the hypercapnic response (HCVR) in the multiple regression equation (poik HVR = .63 [iso HVR] - .16 [HCVR] + .22). Taken together, the isocapnic hypoxic

and hypercapnic ventilatory responses accounted for 72% of the variation in the poikilocapnic hypoxic ventilatory response (multiple R^2=.72, P<.001). In our study, as has been previously reported, the ventilatory response to hypercapnia was correlated with the ventilatory response to isocapnic hypoxia (r=.65, P<.01). However, this positive association is in the opposite direction and thus cannot account for the negative relationship observed between the hypercapnic and poikilocapnic hypoxic ventilatory responses.

DISCUSSION

The present report evaluated an acute ventilatory response at low altitude under conditions resembling high altitude exposure in that the alveolar CO_2 level was allowed to fall. While such a ventilatory response has been utilized by others (1,5,8), we are not aware of systematic comparisons between it and the more often measured responses to isocapnic hypoxia and to hypercapnia. Results from the present study indicated that when ventilatory response is measured under conditions which simulate acute high altitude exposure, i.e. falling CO_2 or poikilocapnia, the response is dominated by two factors - sensitivity to isocapnic hypoxia and sensitivity to CO_2. The first acts positively; the second acts negatively.

Isocapnic hypoxia is considered a "pure" stimulus to increase ventilation because the inhibition by hypocapnic alkalosis is prevented by adding CO_2 to the inspired air to maintain CO_2 and pH at their normoxic levels. The close relationship between the isocapnic and poikilocapnic ventilatory responses suggested that sensitivity to hypoxia was the primary determinant of the poikilocapnic hypoxic ventilatory response.

The secondary determinant of the poikilocapnic hypoxic ventilatory response was the CO_2 response which correlated with the extent to which the poikilocapnic response was depressed compared to the isocapnic response. It should be noted that in these studies we measured the V_E-PCO_2 relationship during hypercapnia and related this information to events in the hypocapnic range during poikilocapnic hypoxia. We did not perform experiments measuring the ventilatory inhibition by hypocapnia during normoxia (1). We recognize that the absolute magnitude of the hypercapnic and the hypocapnic responses probably differ, attested to by the familiar "dog leg" of the V_E-PCO_2 relationship; yet the ventilatory response to high CO_2 seems informative about the sensitivity of the individual to the inhibitory effects of low CO_2. Specifically, persons whose ventilation was relatively insensitive to high CO_2 appeared to have little or no inhibition of their hypoxic ventilatory responses when their end-tidal CO_2 tensions were allowed to fall. Conversely falling end-tidal CO_2 tensions blunted the hypoxic ventilatory responses most in those persons having the greatest ventilatory responsiveness to high CO_2. The implication was that the degree to which ventilation was stimulated by hypercapnia related to the degree of inhibition of hypoxic ventilation by a falling CO_2.

The classical concept (3,5) is that hypoxia stimulates ventilation and that hypocapnia inhibits the ventilatory response to hypoxia. If correct, our interpretation of the present study suggests that the concept is more valid for the persons with higher CO_2 responses. In them, falling CO_2 depresses the ventilatory response to hypoxia. However, persons whose ventilatons are relatively insensitive to CO_2 may have little or no inhibition by hypocapnia of

the hypoxic ventilatory response. Although persons who have high sensitivity to hypoxia tend also to have large responses to CO_2, there are clear individual exceptions. The present study suggests that the interaction between O_2 and CO_2 in the control of ventilation depends on the individual's sensitivity to both moities.

FIGURE LEGENDS

Figure 1. Varation among subjects in ventilatory response to poikilocapnic hypoxia (Poikilocapnic HVR) is correlated with their ventilatory response to isocapnic hypoxia (Iso HVR). Ventilatory response was measured as the slope of ventilation vs arterial O_2 saturation (Ve/ SaO_2) in each subject.

Figure 2. The depression of hypoxic ventilatory sensitivity by poikilocapnia (iso-poik HVR) in each subject is related to his hypercapnic ventilatory response. Depression is greatest in persons with high CO_2 responses and least among persons with low CO_2 responses. Ventilatory response was measured as the slope of ventilation vs SaO_2 or end-tidal CO_2 tension in each subject.

Figure 3. A subject with a high CO_2 response decreased his ventilatory response to poikilocapnic hypoxia (Poik) compared to isocapnic hypoxia (Iso). A subject with a low CO_2 response had equivalent isocapnic and poikilocapnic ventilatory responses.

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Table 1. Anthropomorphic and ventilatory characteristics of each subject.

SUBJECT	AGE YRS	HEIGHT CM	WEIGHT KG	P_ACO_2 mmHg	ISOCAPNIC HVR "A"	V_E/SaO_2	POIKILOCAPNIC HVR $P_{A_{CO_2}}$ mmHg	"A"	V_E/SaO_2	HCVR "S"
1	33	187	68.1	36.4	61	.23	35.4	22	.14	1.24
2	30	163	53.6	35.2	33	.14	32.2	63	.40	0.98
3	24	180	78.8	37.7	321	1.33	24.1	186	.84	2.47
4	22	182	81.3	38.8	283	.96	33.3	75	.51	1.49
5	32	178	78.5	39.6	139	.65	33.0	100	.42	1.65
6	23	178	64.5	38.9	78	.30	35.7	29	.14	1.51
7	34	184	81.3	36.8	120	.57	31.4	24	.13	2.72
8	30	175	78.5	37.2	74	.30	31.9	75	.23	0.57
9	24	185	81.7	38.6	136	.72	29.6	95	.45	1.35
10	23	184	74.9	36.8	127	.62	32.9	34	.22	1.47
11	23	180	73.1	39.4	38	.20	33.7	51	.24	1.20
12	26	189	74.0	40.1	66	.20	37.0	20	.11	1.23
13	22	174	65.4	31.2	174	.82	29.9	80	.44	1.71
14	33	168	66.3	38.0	182	.86	31.9	49	.26	2.73
MEAN	27	179	72.8	37.5	131	.56	32.3	65	.32	1.59
±SEM	±1.2	± 2	±2.2	± .6	±23	±.09	± .8	±12	±.05	±.17

Shown above for each resting subject breathing air are the values of alveolar PCO_2, P_ACO_2. The hypoxic ventilatory response, HVR, is shown during isocapnic hypoxia (P_ACO_2 = 37.7±.4 mmHg) as the parameter "A" and the slope of the line relating ventilation, V_E, to arterial oxygen saturation, SaO_2, as described in the text. In addition, for poikilocapnic hypoxia, P_ACO_2 is given as measured at the end of the hypoxic exposure. For the hypercapnic ventilatory response, HCVR, the slope "S" of the line relating V_E to P_ACO_2 is shown. The intercept "B" extrapolated to zero ventilation averaged 33±1 mmHg.

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.


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