Low chemoresponsiveness and inadequate hyperventilation contribute to exercise-induced hypoxemia

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Harms, Craig A., and Joel M. Stager. Low chemoresponsiveness and inadequate hyperventilation contribute to exercise-induced hypoxemia. *J. Appl. Physiol.* 79(2): 575–580, 1995.—Is inadequate hyperventilation a cause of the exercise-induced hypoxemia observed in some athletes during intense exercise? If so, is this related to low chemoresponsiveness? To test the hypothesis that exercise-induced hypoxemia, inadequate hyperventilation, and chemoresponsiveness are related, 36 nonsmoking healthy men were divided into hypoxemic (Hyp; n = 13) or normoxemic (Nor; n = 15) groups based on arterial oxygen saturation (Sa_{O_2}; Hyp ≤ 90%, Nor > 92%) observed during maximum O_2 uptake ($\dot{V}O_{2\,max}$). Men with intermediate Sa_{O_2} values (n = 8) were only included in correlation analysis. Ventilatory parameters were collected at rest, during a treadmill maximal oxygen consumption ($\dot{V}O_{2\,max}$) test, and during a 5-min run at 90% $\dot{V}O_{2\,max}$. Chemoresponsiveness at rest was assessed via hypoxic ventilatory response (HVR) and hypercapnic ventilatory response (HCVR). $\dot{V}O_{2\,max}$ was not significantly different between Nor and Hyp. Sa_{O_2} was 93.8 ± 0.9% (Nor) and 87.7 ± 2.0% (Hyp) at $\dot{V}O_{2\,max}$. End-tidal P_{O_2} and the ratio of minute ventilation to oxygen consumption ($\dot{V}E/\dot{V}O_2$) were lower while $P_{ET_{CO_2}}$ was higher for Hyp ($P \leq 0.01$). End-tidal P_{O_2}, end-tidal P_{CO_2}, and $\dot{V}E/\dot{V}O_2$ correlated ($P \leq 0.05$) to Sa_{O_2} (r = 0.84, r = −0.70, r = 0.72, respectively), suggesting that differences in oxygenation were due to differences in ventilation. HVR and HCVR were significantly lower for Hyp. HVR was related to $\dot{V}E/\dot{V}O_2$ (r = 0.43), and HCVR was related to the ratio of $\dot{V}E$ to CO_2 production at $\dot{V}O_{2\,max}$ (r = 0.61). In summary, the results suggest that inadequate hyperventilation, related to low hypoxic and hypercapnic drive is a significant mechanism in the hypoxemia experienced by some athletes during intense exercise.

ventilation; arterial desaturation; hypoxic ventilatory response; hypercapnic ventilatory response

REPORTS SINCE THE 1960s document the existence of exercise-induced hypoxemia (EIH) in healthy humans. This observation suggests that the pulmonary system may be important as a limiting factor to strenuous exercise at sea level in healthy individuals. Although four potential mechanisms have been proposed as contributing to EIH [venoarterial shunt, ventilation-perfusion ratio ($\dot{V}A/\dot{Q}$) inequality, diffusion limitation, and hypoventilation) (16, 21), the role of hypoventilation, or more appropriate, inadequate exercise-induced hyperventilation, remains equivocal.

Hyperventilation during strenuous exercise increases alveolar P_{O_2} ($P_{A_{O_2}}$), which helps provide the necessary gradient required for adequate oxygen diffusion (1). Inadequate hyperventilation can be defined as a reduced ventilatory response, which leads to an insufficient rise in $P_{A_{O_2}}$. A low $P_{A_{O_2}}$ could potentially result in an excessive widening of the alveloar-arterial P_{O_2} difference and consequently hypoxemia during exercise. Whereas several studies have demonstrated that a low hyperventilatory response to strenuous exercise is associated with arterial desaturation and hypoxemia (3, 10, 14, 24), other studies (4, 15) have concluded that ventilation is adequate in hypoxemic subjects. It is likely that more than one single mechanism is responsible for EIH, which undoubtedly contributes to part of this discrepancy in the literature. However, differences in results may also be due to the lack of a clearly defined criteria of hypoxemia as well as methodological differences.

It has been reported that below 92% arterial oxygen saturation (Sa_{O_2}), aerobic capacity [maximal oxygen consumption ($\dot{V}O_{2\,max}$)] is lowered ~1% per 1% decline in Sa_{O_2} (12, 14). While some investigators (3, 12, 14) have utilized this physiological-based criterion for EIH, others (9, 15) have statistically characterized EIH as a reduction in resting arterial P_{O_2} (Pa_{O_2}) of >4 SDs from the mean maximal exercise-induced change in Pa_{O_2}. However, by using this latter criterion, it can be shown that not all "hypoxemic" subjects actually desaturated to levels below 92%. These two criteria make generalizations and comparisons from previous studies difficult.

As an attempt to clarify the importance of inadequate hyperventilation on EIH, we hypothesized that arterial hypoxemia (Sa_{O_2} <92%) is the result of an inadequate hyperventilatory response to strenuous exercise. We were also interested in the role of chemoresponsiveness as a potential mechanism for inadequate hyperventilation. Because hypoxic and hypercapnic drive have been reported to contribute from 16–30% to total exercise ventilation (8, 22), it was hypothesized that the inadequate hyperventilation demonstrated by hypoxemic individuals was due to lower chemoresponsiveness.

METHODS

Subjects. Thirty-six physically active men were divided into a hypoxemic group (Hyp; n = 13) or a normoxemic group (Nor; n = 15) based on Sa_{O_2} values (Hyp ≤ 90%; Nor >92%) observed during treadmill work eliciting $\dot{V}O_{2\,max}$. Men whose Sa_{O_2} fell between these values (n = 8) were not included as part of these two groups to establish distinct group differences but were included in all correlations for the propose of determining relationships (n = 36). Before any testing, subjects were advised both verbally and in writing as to the nature of the experiments and gave written informed consent in accordance with university regulations governing human research.

All subjects were healthy nonsmoking adults with no history of lung disease and normal pulmonary function, as determined by a questionnaire concerning medical background and activity habits and by pulmonary function tests (vital

TABLE 1. *Descriptive data*

	All Subjects (n = 36)	Normoxemic (n = 15)	Hypoxemic (n = 13)
Age, yr	24.1±3.7	24.0±4.7	24.3±4.7
Wt, kg	72.0±7.8	72.1±7.2	72.0±8.6
Ht, cm	178.6±7.2	179.2±6.7	177.9±7.9
Hct, %	43.0±3.1	43.5±2.6	43.0±3.7
Hb, g/dl	15.6±1.1	15.8±1.1	15.4±1.2
$\dot{V}O_{2\,max}$, ml·kg^{-1}·min^{-1}	64.1±7.8	62.4±7.5	66.0±7.9

Values are means ± SD; n, no. of subjects. Hct, hematocrit; Hb, hemoglobin concentration; $\dot{V}O_{2\,max}$, maximal oxygen consumption.

capacity = 95% predicted; 1-s forced expired volume = 97% predicted; 12-s maximal voluntary ventilation = 108% predicted) performed before initiation of the study (11).

Preexercise. Before exercise, a 8- to 10-ml blood sample was drawn from an antecubital vein into a heparinized syringe. Total hemoglobin (Hb) was measured on a hemoximeter (OSM3, Radiometer, Copenhagen, Denmark). Hematocrit was determined in triplicate by micropipette centrifugation (International micro capillary reader, International Equipment, Needham, MA).

Exercise testing. $\dot{V}O_{2\,max}$ was determined by using a continuous incremental protocol on a motor-driven treadmill. During the test, subjects breathed through a low-resistance two-way valve (Hans Rudolph 2700). Expired air passed through a 90-cm length of 34-mm-diam tubing into a 5-liter mixing chamber, from which continuous samples were drawn for analysis of mixed expired percent oxygen and percent carbon dioxide (S-3A oxygen analyzer and CD-3A carbon dioxide analyzer, Applied Electrochemistry) by using rapid-response electronic gas analyzers. The analyzers were calibrated before and after all tests with gases of known composition in the physiological range. Volume of inspired air was measured by a turbine-based electronic flowmeter (model VMM-2, Sensormedics Anaheim, CA) that had been calibrated by using a Tissot spirometer using pulsatile flow. We have also determined, based on the data from five subjects performing an additional $\dot{V}O_{2\,max}$ test without the flowmeter in place, that the resistance imposed by the flowmeter does not contribute to the desaturation observed. End-tidal partial pressures of oxygen ($P_{ET_{O_2}}$) and carbon dioxide ($P_{ET_{CO_2}}$) were continuously measured with a data acquisition and control software system (Workbench PC 2.0, Strawberry Tree) to estimate $P_{A_{O_2}}$ and alveolar P_{CO_2} ($P_{A_{CO_2}}$).

After 5 min of rest, each subject warmed up by walking at 3 mph (0% grade). The speed of the treadmill was then increased gradually (over 1 min) to a running pace deemed comfortable by each subject (9.7–12.9 kph), and remained constant thereafter for the remainder of the test. After the subjects ran for 2 min, the grade of the treadmill increased 2% every other minute until the subject reached volitional fatigue (2). During the bout, subjects were verbally encouraged to exercise for as long as possible. The criterion used to assess of $\dot{V}O_{2\,max}$ included *1*) a heart rate in excess of 90% of age-predicted maximum (220 − age), *2*) a respiratory exchange ratio >1.10, and *3*) identification of a plateau (<150 ml increase) in oxygen despite a further increase in power output. If at least two of the three criteria were met, then the highest oxygen recorded was chosen as the subject's $\dot{V}O_{2\,max}$. During exercise, all subjects were found to be at a similar ($P > 0.05$) ventilation relative to their maximal breathing capacity (maximal voluntary ventilation ~65–70%).

A 5-min constant-load exercise bout designed to require 90% of each subject's $\dot{V}O_{2\,max}$ was subsequently performed at least 24 h after the $\dot{V}O_{2\,max}$ test. This test was performed after a 5-min warm-up (60–70% $\dot{V}O_{2\,max}$). Data from the final 2 min of the 5-min constant-load test were averaged and used for statistical analysis.

Percent Sa_{O_2}. Sa_{O_2} was estimated via ear oximetry (model 47201A, Hewlett-Packard) continuously during both exercise tests. Values were collected each second and averaged (1 min) with a data acquisition and control software system (Workbench PC 2.0, Strawberry Tree). The ear oximeter was calibrated before and after each experiment by using an internal calibration protocol as described by the manufacturer. Although pulse oximetry has been questioned as a valid and reliable means of estimating Sa_{O_2} during exercise, the oximeter used in this study measures light absorption from eight, rather than two wavelengths, has a low blood flow warning, and gives readings that are very closely related to arterial blood Sa_{O_2} ($r^2 = 0.85$) at rest, exercise, and during hypoxic conditions (Sa_{O_2} 60%) (13, 18). It has been estimated that blood Sa_{O_2} values >75% are underestimated by <2% by this oximeter (18).

Hypoxic ventilatory response (HVR). HVR was measured within 2 wk of the submaximal exercise bout and at least 8 h postprandial and postcaffeine ingestion. A taped video documentary was shown throughout the test on a television in a darkened room to minimize external distractions. The test to determine HVR was that of Weil et al. (19) and was highly reproducible in this study with a correlation of r = 0.93 in seven subjects who were retested. HVR was calculated as the slope of the line determined by the linear regression relating minute ventilation to oxyhemoglobin saturation, in liters per minute per percent. By convention, the slope estimates are presented as positive numbers. Ten to 15 data points were used in the analysis for each subject, and the relationship between ventilation and Sa_{O_2} was consistently linear ($r > 0.89$) for all subjects.

Hypercapnic ventilatory response (HCVR). HCVR was measured by using a rebreathing technique (17) and was highly reproducible in this study with a correlation of $r = 0.97$ in seven subjects who were retested. HCVR was calculated as the slope of the line determined by the linear regression relating $P_{ET_{CO_2}}$ to minute ventilation ($\dot{V}E$), in liters per minute per millimeter of Hg (17). Fifteen to 20 data points were used in the analysis for each subject, and the relationship between ventilation and $P_{ET_{CO_2}}$ was consistently linear ($r > 0.92$) for all subjects.

Data analysis. SPSS-X statistical package was used to perform two-by-three (group-by-treatment) split-plot factorial analysis of variance to determined group differences during exercise eliciting $\dot{V}O_{2\,max}$ and during constant-load submaxi-

TABLE 2. $\dot{V}O_{2\,max}$ *test results*

	All Subjects (n = 36)	Normoxemic (n = 15)	Hypoxemic (n = 13)
$\dot{V}O_2$, l/min	4.62±7.13	4.50±7.11	4.75±7.32
Sa_{O_2}, %	91.0±3.4	93.8±0.9	87.7±2.0*
$P_{ET_{O_2}}$, Torr	117.3±5.1	121.1±1.9	112.4±3.0*
$P_{ET_{CO_2}}$, Torr	33.2±3.6	31.2±2.9	35.6±2.9*
$\dot{V}E$ l/min	124.2±17.5	128.9±15.0	118.7±19.1
$\dot{V}E/\dot{V}O_2$	27.0±2.8	28.6±2.2	25.1±2.2*
$\dot{V}E/\dot{V}CO_2$	25.3±2.8	26.9±2.3	23.3±2.0*
f, breaths/min	56±8	58±8	53±8
V_T, liters	2.26±0.40	2.24±0.35	2.31±0.48

Values are means ± SD; n, no. of subjects. $\dot{V}O_2$, oxygen consumption; Sa_{O_2}, arterial oxygen saturation; $P_{ET_{O_2}}$, end-tidal P_{O_2}; $P_{ET_{CO_2}}$, end-tidal P_{CO_2}; $\dot{V}E$, minute ventilation; $\dot{V}CO_2$, carbon dioxide production; f, breathing rate; V_T, tidal volume. * Significantly different from normoxemic ($P \leq 0.01$).

TABLE 3. *Regression estimates at $\dot{V}O_{2\,max}$*

	Sa_{O_2}	$P_{ET_{O_2}}$	$P_{ET_{CO_2}}$	$\dot{V}E/\dot{V}O_2$	$\dot{V}E/\dot{V}CO_2$	f	VT
$\dot{V}O_{2\,max}$	−0.27	−0.23	0.09	−0.26	−0.25	0.11	0.30
Sa_{O_2}		0.84*	−0.70*	0.72*	0.73*	0.30	−0.09
$P_{ET_{O_2}}$			−0.74*	0.75*	0.74*	0.31	−0.09
$P_{ET_{CO_2}}$				−0.89*	−0.84*	−0.53*	0.12
$\dot{V}E/\dot{V}O_2$					0.88*	0.46*	−0.13
$\dot{V}E/\dot{V}CO_2$						0.59*	−0.20
f							−0.72*

Values are for 36 subjects. * $P \leq 0.05$.

mal exercise. A Bonferroni adjustment was used due to the multiple planned comparisons being made (6). As a result, the alpha was corrected to $P \leq 0.01$ required to identify statistical significance. Pearson product moment correlations was implemented to determine relationships between all dependent variables. The alpha was set at $P \leq 0.05$ for all correlations.

RESULTS

Descriptive data. Descriptive data for all subjects, normoxemic (Nor) and hypoxemic (Hyp) are presented in Table 1. Nor and Hyp were well matched with respect to age, weight, height, and maximal oxygen consumption ($\dot{V}O_{2\,max}$) as no significant differences between groups were noted.

$\dot{V}O_{2\,max}$. As designed, arterial oxygen desaturation at $\dot{V}O_{2\,max}$ was significantly greater from resting values for Hyp (9.4%) than for Nor (3.1%). $P_{ET_{O_2}}$, the ratio of $\dot{V}E$ to oxygen consumption ($\dot{V}O_2$), and the ratio of $\dot{V}E$ to carbon dioxide production ($\dot{V}CO_2$) were lower in Hyp (7.5, 12.2, and 14.5%, respectively). $P_{ET_{CO_2}}$ was higher in Hyp (12.3%). These data are summarized in Table 2.

The correlation matrix for the dependent variables at $\dot{V}O_{2\,max}$ is located in Table 3. Sa_{O_2} at $\dot{V}O_{2\,max}$ was related to $P_{ET_{O_2}}$, $P_{ET_{CO_2}}$, and $\dot{V}E/\dot{V}O_2$ ($r = 0.84$, $r = -0.70$, $r = 0.72$, respectively; Fig 1). Despite a wide range in values, Sa_{O_2} was not significantly correlated with $\dot{V}O_{2\,max}$ at $\dot{V}O_{2\,max}$.

Submaximal exercise. Averaged data from the last 2 min of this exercise bout are summarized in Table 4. The data confirmed that all subjects ran at an intensity that elicited at least 90% of their $\dot{V}O_{2\,max}$. There was no difference between Nor and Hyp in submaximal $\dot{V}O_2$ in absolute or relative units during steady-state conditions (Nor 93.4 ± 2.0%, Hyp 92.9 ± 2.3%). The dependent variables that were different at $\dot{V}O_{2\,max}$ (Sa_{O_2}, $P_{ET_{O_2}}$, $P_{ET_{CO_2}}$, $\dot{V}E/\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$) were also different during submaximal exercise, indicating that desaturation due to lower ventilation also occurs during intense steady-state exercise. There was no interaction effect between groups (Nor, Hyp) and the exercise bouts. Breathing frequency was significantly less in Hyp than in Nor (14.6%) during submaximal exercise.

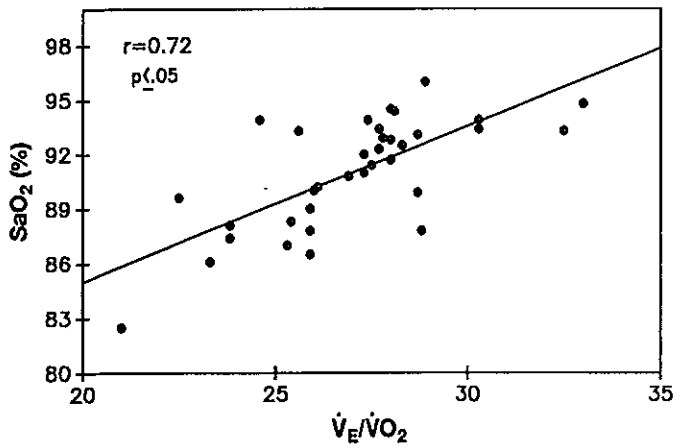

FIG. 1. Relationship between arterial oxygen saturation (Sa_{O_2}) and ratio of minute ventilation to oxygen consumption ($\dot{V}E/\dot{V}O_2$) at maximal oxygen consumption ($\dot{V}O_{2\,max}$; $n = 36$).

TABLE 4. *Submaximal exercise test results*

	All Subjects ($n = 36$)	Normoxemic ($n = 15$)	Hypoxemic ($n = 13$)
$\dot{V}O_2$ l/min	4.31±0.56	4.23±0.58	4.40±0.56
Sa_{O_2}, %	93.3±2.7	94.5±1.6	90.8±3.0*
$P_{ET_{O_2}}$, Torr	113.9±4.6	116.0±4.4	108.0±3.7*
$P_{ET_{CO_2}}$, Torr	36.1±3.3	34.4±2.4	37.9±3.2*
$\dot{V}E$, l/min	105.5±17.1	110.6±17.1	99.6±15.6
$\dot{V}E/\dot{V}O_2$	24.6±3.3	26.3±3.2	22.6±2.0*
$\dot{V}E/\dot{V}CO_2$	24.5±3.0	25.8±2.8	22.6±2.1*
f, breaths/min	45±9	48±8	41±7*
VT, liters	2.39±0.43	2.34±0.42	2.46±0.44

Values are means ± SD; n, no. of subjects. * Significantly different from normoxemic ($P \leq 0.01$).

Chemoresponsiveness. A significant positive relationship between HVR and Sa_{O_2} at $\dot{V}O_{2\,max}$ and between HCVR and Sa_{O_2} at $\dot{V}O_{2\,max}$ was demonstrated (Fig. 2). Also, Hyp exhibited a lower HVR (0.15 ± 0.07 vs. 0.61 ± 0.36) and HCVR (1.78 ± 0.35 vs. 2.73 ± 0.66) compared with Nor, as indicated by the slope of the ventilatory responses (Fig. 3). Ventilation at the initiation of the respective tests was similar between Nor and Hyp (HVR 4.9 ± 1.7 vs. 5.0 ± 2.0 l/min, not significant (NS); HCVR 5.0 ± 1.9 vs. 5.0 ± 1.8 l/min, NS). Isocapnic conditions were well maintained during the HVR test as $P_{ET_{CO_2}}$ did not significantly change during any of the tests from normoxic (38.8 ± 3.6 Torr) to hypoxic conditions (38.1 ± 2.7 Torr). $P_{ET_{O_2}}$ values during the HCVR test were maintained between 275 and 350 Torr for the duration of the tests.

DISCUSSION

The principle findings of the present study are that *1)* subjects who demonstrated a reduced hyperventilatory response to strenuous exercise tended to be those who were the most hypoxemic and *2)* ventilatory response to exercise is partly dependent on resting responses to hypoxia and hypercapnia. The existent literature is conflicting in regard to the first finding. Several reports have concluded that "relative hypoventilation" during intense exercise is responsible for the arterial desaturation observed (3, 10, 14, 24), whereas several others have concluded otherwise (4, 15). While other factors, such as $\dot{V}A/\dot{Q}$ inequality and diffusion limitations (16, 21), are known to contribute to EIH, this discrepancy in the literature appears to be largely a result of differ-

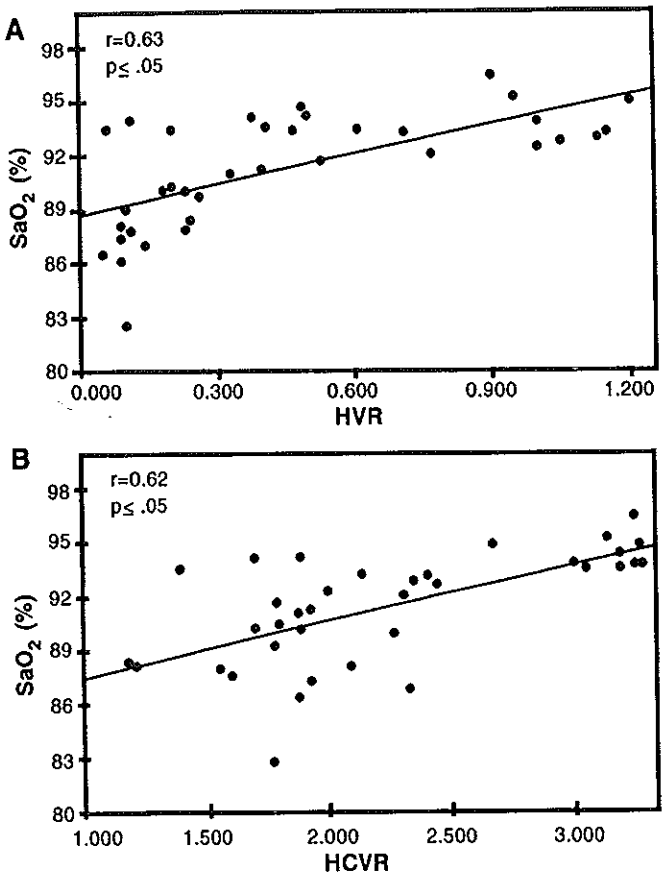

FIG. 2. Relationship between chemoresponsiveness and Sa_{O_2} at $\dot{V}O_{2\,max}$ (n = 36). *A*: hypoxic ventilatory response (HVR). *B*: hypercapnic ventilatory response (HCVR).

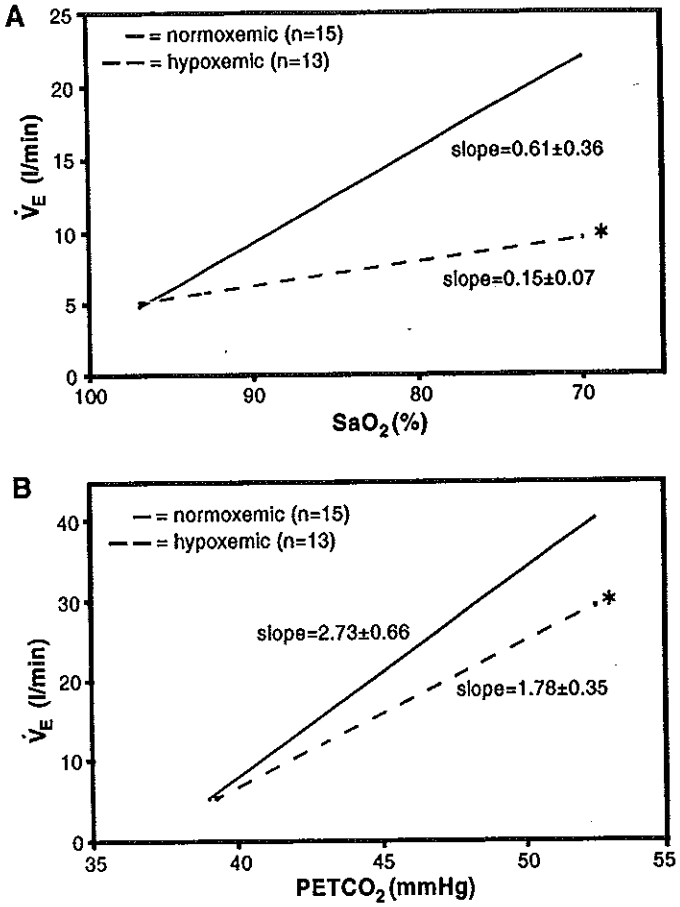

FIG. 3. Group (normoxemic and hypoxemic) differences in chemoresponsiveness. *Top*: HVR. *Bottom*: HCVR. $\dot{V}E$, minute ventilation; $P_{ET_{CO_2}}$, end-tidal P_{CO_2}. Slope is expressed as means ± SD. * Significantly lower than normoxemic ($P \leq 0.01$).

ences in methodology and the criteria employed to define hypoxemia.

It has been observed that below an Sa_{O_2} of 92%, a decline in $\dot{V}O_{2\,max}$ is observed proportional to the further drop in Sa_{O_2} (12, 14). Thus Sa_{O_2} values during exercise below 92% have been used by several authors as the prime criteria for hypoxemia. This level of arterial desaturation is observed at a Pa_{O_2} of ~75 Torr, close to the upper shoulder of the Hb-oxygen affinity curve and was the definition employed in the present study. A second approach that has been used to define hypoxemia identifies values for Pa_{O_2} that are more than 4 SDs lower than Pa_{O_2} values obtained at rest (9, 11). With this statistical definition, subjects have been judged to be hypoxemic with end-exercise Pa_{O_2} values in excess of 75 Torr and Sa_{O_2} above 92%. On this basis alone, comparisons between studies and interpretation of their respective results are questionable.

For example, Powers et al. (15), using the statistical definition for hypoxemia, categorized 12 men by the degree of hypoxemia experienced at $\dot{V}O_{2\,max}$ (i.e., normal, hypoxemic, highly hypoxemic) and concluded that an inadequate hyperventilatory response was not responsible for EIH. However, by using the physiologically relevant definition for hypoxemia (Pa_{O_2} <75 Torr) to recategorize the subjects of Powers et al., it can be shown that none of the 12 subjects studied can be classified as hypoxemic after the exercise bout employed. In another report, Martin and O'Kroy (9) compared trained and untrained men in terms of the observed desaturation during intense exercise. These authors stated that the trained but not the untrained men desaturated at $\dot{V}O_{2\,max}$. The dilemma in this approach is that one-quarter of the trained men failed to desaturate while nearly 40% of the untrained displayed significant desaturation. A similar research design was employed by Williams et al. (23) with analogous problems. Conclusions based on comparisons of normal and hypoxemic or of trained and untrained appear unwarranted. Once again, to determine whether the current literature supports the contention that relative hypoventilation is a significant factor in EIH is complicated by these conflicting definitions.

The proposed mechanism therefore, originally put forth by Dempsey et al. (3), is that a lower PA_{O_2} results from the inadequate hyperventilation in those subjects who desaturate during strenuous exercise. This in turn reduces the driving force for oxygen across the lung-capillary interface. This hypothesis is supported by the significant correlation coefficients between the ventilatory equivalents for O_2 ($\dot{V}E/\dot{V}O_2$), and $P_{ET_{O_2}}$ (r = 0.75) and between $P_{ET_{O_2}}$ and Sa_{O_2} (r = 0.84) derived from our data. These findings corroborate the work of Miyachi and Tabata (10).

In the only known study available in the literature

to examine the relationship between HVR and EIH, Hopkins and McKenzie (4) concluded that hypoxic drive was not related to the development of arterial desaturation during maximal exercise. Their conclusions were based principally on nonsignificant correlation coefficients between their measures. This appears to be in direct opposition to the conclusion of the present study. Once again, however, their results are contestable. If the subjects observed are separated into groups based on the physiological criteria for hypoxemia (Pa_{O_2} <75 Torr, Sa_{O_2} <92%) at the end of exercise a significant difference in HVR is observed. The group that maintained arterial saturation had greater ventilatory responses similar to the findings of the present study.

Taking this a step further, our results corroborate with data from Martin et al. (8) in demonstrating a significant positive relationship between $\dot{V}E/\dot{V}O_{2\,max}$ and HVR ($r = 0.43$) and between $\dot{V}E$/maximal $\dot{V}CO_2$ and HCVR ($r = 0.61$), suggesting that ventilation during maximal exercise is proportional to chemoresponsiveness (HVR, HCVR). Although the central nervous system undoubtedly plays a large role in accounting for the differences in ventilation, the modest relationships obtained in the present study suggest that peripheral chemosensitivity also contributes significantly to differences in ventilation between Hyp and Nor during intense exercise. It is likely, however, that end-products of skeletal muscle metabolism and sympathetic nerve stimulation (lactic acid, H^+, potassium, norepinephrine), which are closely associated with carotid chemo- and/or ventilatory stimulation, are of greater importance during strenuous exercise.

One possible limitation of our study was that HVR and HCVR were measured at rest rather than during exercise, which is more difficult to determine accurately. Weil et al. (20) have suggested that chemosensitivity is enhanced during exercise. Consequently, our results may in fact underestimate the importance of chemoresponsiveness in ventilatory differences detected between Nor and Hyp. This speculation obviously requires further testing.

Mechanical limitations may act to constrain ventilation during strenuous exercise. Significant mechanical limitations to $\dot{V}E$ during strenuous exercise, as determined by expiratory airflow and inspiratory pleural pressure, have been reported by Johnson et al. (5). These authors have demonstrated that mechanical limits to $\dot{V}E$ were reached in endurance athletes coincident with the achievement of $\dot{V}O_{2\,max}$; the greater the ventilatory response, the greater was the degree of mechanical limitation. Also, Dempsey et al. (3) observed an immediate and sustained increase in $\dot{V}E$ with helium-oxygen gas mixture in highly fit male endurance runners. They have proposed that helium-oxygen increased the maximum envelope of the flow-volume loop, which allowed for a greater mechanical reserve and consequently increased ventilation. Therefore, the findings from these reports, together with the results from our study suggest that the sluggish hyperventilatory response of our hypoxemic subjects during strenuous exercise may be due to a combination of both a low chemoresponsiveness as well as increased mechanical limitations.

In principle, arterial hypoxemia can be mediated by one or some combination of the additional factors: *1*) venoarterial shunt; *2*) ($\dot{V}A/\dot{Q}$) inequality; and *3*) diffusion limitations. The contribution of these other mechanisms to EIH have been reported elsewhere (16, 21).

In summary, the results from this study suggest that an inadequate hyperventilatory response is a significant mechanism in the development of EIH experienced by some athletes during intense exercise. Our data indicate that inadequate hyperventilation accounts for ~50% of the variability in Sa_{O_2}. Also, we propose that a low hypoxic and hypercapnic drive may be responsible for a significant portion of the sluggish exercise ventilatory response by hypoxemic individuals.

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