were the carotid chemoreceptors also excluded from the circulation of the remainder of the body?

Dr. Levine: In the head perfused animal preparation (ie third preparation), both the carotid chemoreceptors and the brain were excluded from the circulation to the remainder of the body.

Dr. Grodins: In Dr. Levine's first preparation, what was the effect of acute cord transection on blood pressure?

Dr. Levine: My dogs were anesthetized with chloralose (not barbiturate); mean arterial blood pressure following L2 spinal transection was 145 mm Hg. Your question raises the possibility that decreases in arterial blood pressure during exercise may have accounted for the increases in $V_{Be}$ noted in my experiments. In fact, a decrement in mean arterial blood pressure of 13 mm Hg accompanied muscular exercise. However, the literature (as well as my own experience) indicates that this small decrement in blood pressure is not adequate to elicit twofold increments in $V_{Be}$. Moreover, conventional arterial baroreceptors (ie, carotid sinus and aortic baroreceptors) were denervated in the chemodenervated animal experiments; nonetheless, this preparation still responded to exercise of the hindlimbs with twofold increases in $V_{Be}$.

Dr. Grodins: There is a discrepancy between Dr. Levine's findings and those of Kao who observed that venous blood from the exercising hind limbs of a donor dog produced an increase in ventilation in a recipient dog which was less than proportional to the increased $V_{Co2}$ in this dog so that its $PaCO_2$ rose. Since the thoracic receptors postulated by Dr. Levine were intact in this dog and were exposed to "exercise blood," it should have responded with an isocapnic hyperpnea, but it did not. Its response resembled that of $CO_2$ inhalation.

Dr. Levine: Dr. Kao's experiments with his triad preparation failed to demonstrate that venous blood from the exercising hind limbs of one dog will stimulate $V_{Be}$ in a second dog (ie, recipient dog). However, since he failed to demonstrate that the recipient dog in his triad preparation was capable of responding to any ventilatory stimulus, these experiments of Dr. Kao do not permit definitive conclusions regarding humoral exercise stimuli.

**Ventilatory Control Characteristics of the Exercise Hyperpnea as Discerned from Dynamic Forcing Techniques**

Richard Casaburi, Ph.D.; Brian J. Whipp, Ph.D.; Karlman Wasserman, M.D.; and Richard W. Stremel, Ph.D.

*From the Department of Medicine, Division of Respiratory Physiology and Medicine, Harbor General Hospital-UCLA School of Medicine, Torrance, California.
Supported by NIH Grants HL-19410, HL-11907, HL-14967 and HL-25225.
Reprint requests: Dr. Casaburi, Division of Respiratory Physiology, Harbor General Hospital, Torrance, California 90509.

In the steady-state of moderate intensity exercise, mean arterial $Pco_2$, $Po_2$, and $pH$ are precisely regulated, leaving no apparent stimulus for the marked ventilatory increase. We have looked for clues to the underlying mechanisms in the transient state, hoping that the timing of events leading to this "errorless" state would provide information which might help solve this enigma.

The first systematic look into the transient state was taken by Krogh and Lindhard in 1913. They observed that at the onset of cycle ergometer exercise ventilation increased abruptly—too rapidly to be the result of a humorally-borne product of the exercise reaching a known respiratory chemoreceptor. This observation has been confirmed repeatedly. This rapid component has been used to argue that a neurally-mediated signal from the exercising limbs is a major stimulus to the steady-state ventilation. Yet this observation is open to other interpretations—could this initial response to the abrupt onset of work be merely a feature of the transition or even a "startle" response having no relevance to stimuli acting in the steady-state? Another drawback of the use of the stepwise forcing is that we obtain a limited period of observation relevant to the transient state. A sinusoidal forcing function obviates these problems. This forcing produces long periods of data relevant to kinetic interrelations. Further, there exists well founded mathematics suitable for analysis of these responses. The key to the analysis is that, if a linear system is forced with a sinusoid, the response will be a sinusoid of the same frequency. The variation of the amplitude and phase of the response with respect to the input as a function of the stimulus frequency characterizes the system dynamics. Thus, our strategy has been to vary the work rate at which a subject exercises in a sinusoidal fashion between fixed limits. In a series of tests we have studied a range of forcing frequencies and have used the response amplitudes and phases to try to infer the mechanisms underlying the exercise hyperpnea.

In our experiments, subjects exercised on a cycle ergometer modified so that the braking force on the flywheel could be varied sinusoidally. The ventilatory responses of the subjects were determined from expired airflow (pneumotachograph). Gas exchange was assessed by measuring $PcO_2$ and $Po_2$ at the mouth by mass spectrometry. Heart rate was determined from the electrocardiogram. An on-line digital computer processed the sensor signals and computed the breath-by-breath time courses of $V_{Be}$, $V_{Co2}$, $V_{o2}$, $P_{ET}CO_2$, $P_{ET}O_2$ and heart rate.

In a first series of experiments, we studied the response of 10 subjects to 7 forcing frequencies ranging from 0.75 to 13 minutes in period. During each of these half-hour tests, the work rate fluctuated sinusoidally from 25 watts to 80% of that subject's anaerobic threshold. We observed clear fluctuations in $V_{Be}$, $V_{Co2}$, $V_{o2}$, and HR; as the frequency of the work rate fluctuation increased, the amplitude of each of these variables decreased and the phase lag with respect to the forcing increased. Curve fitting techniques revealed that venti-
We observed ventilatory fluctuations of the order of 20% and 50% above the mean when subjects exercised at rates ranging between 25 and 60 watts. Because we could not control CO₂ output, we used a second variable, heart rate, to determine the anaerobic threshold of each subject. Heart rate varied between 155 and 180 beats per minute at an exercise rate of 60 watts. The anaerobic threshold was estimated from the ventilatory response as the point at which ventilatory output increased without a corresponding increase in CO₂ output. The anaerobic threshold was used as a measure of the individual subject's ability to tolerate the exercise, and the anaerobic threshold was used as a measure of the subject's anaerobic threshold. The anaerobic threshold was used as a measure of the subject's anaerobic threshold.

Figure 1A. Comparison of the dynamics of ventilation with carbon dioxide output. Time constants of response of ten subjects as discerned from sinusoidal work rate variation with work rates confined to sub-anaerobic threshold levels.

We calculated the time constant of response for each subject we studied for each of these variables. We then looked for correlation among the kinetics of these variables, reasoning that this might help to suggest a mechanistic linkage. The overwhelming correlation we observed was between the time constants of VE and VCO₂ (r = 0.98) (Fig 1A). The kinetics of ventilation were characteristically slower than CO₂ output, and CO₂ output leads ventilation. This finding suggests that the ventilatory response to sinusoidal work rate forcing is due to a CO₂ linked stimulus.

We have conducted other studies which support this interpretation. Figure 1B compares the amplitude of the ventilatory fluctuation to the amplitude of CO₂ output fluctuation. Each point represents the response to 30 minutes of sinusoidal exercise. In each study, 5 subjects exercised at each of 7 or 8 sinusoidal forcing frequencies. The x's represent the responses to the sinusoidal work rate forcings alluded to above. In a second study (closed circles), we observed the responses of subjects at a higher mean work rate. The work rate fluctuated above and below the anaerobic threshold. Due to the CO₂ produced as a result of the buffering of lactic acid, VCO₂ fluctuation increased by about 20%. As can be seen, the ventilatory response increased in proportion to the additional CO₂ stimulus. In a third study (open circles), we observed the responses to subjects breathing 100% oxygen. We found the kinetics of both ventilation and CO₂ output were slowed, but the relation between the two was virtually unchanged. Finally, we had subjects exercise at a constant work rate, but at a pedalling rate which varied sinusoidally (triangles). We observed fluctuations in CO₂ output due to differences in the work required to move the legs at varying rates and ventilation responded strictly in proportion to the CO₂ stimulus and not in proportion to the changes in rate of moving the limbs. Note that in four appreciably different situations, ventilation fits a single function of CO₂ output. This close coupling is inconsistent with an appreciable role for neurogenic influences from the exercising limbs. Further, we observed no rapid component of ventilatory response analogous to that seen in response to the stepwise forcing.

However, it is important to resolve whether this correlation is due, not to a mechanistic link of the exercise hyperpnea to a CO₂ related variable, but simply due to the fact that a change in ventilation must lead to a transient change in CO₂ output. But it is crucial to recognize that a necessary consequence of a primary change in ventilation is hypocapnia at the time when ventilation is high.

To decide between these alternative explanations, we conducted studies in which six subjects exercised at work rates fluctuating sinusoidally between 25 watts and 80% of the anaerobic threshold with a period of 6 minutes. Arterial blood was sampled via an indwelling brachial artery catheter as they exercised, sampling once every 30 seconds over a 24 minute period (a total of 48 samples over 4 sinusoidal periods). Arterial Pco₂ was found to exhibit a small fluctuation with the work rate, with an average peak-to-peak amplitude of 1.9 mm Hg. Importantly, arterial Pco₂ was high at a time when ventilation was high in all 6 cases. These results strongly suggest that the correlation between VCO₂ and VE is due to a coupling of the exercise hyperpnea to CO₂. Further, we believe that these results tell us much about the kinetics of the process which leads to isocapnia in the steady-state. In response to a fluctuation in work rate with a 6 minute period, ventilation does not change.
rapidly enough to regulate PaCO₂ precisely, but lags behind by a tiny amount, allowing PaCO₂ to fluctuate slightly. However, this apparent sensitivity to PaCO₂ change is considerably greater than that seen during response to CO₂ inhalation. In this study, we saw “CO₂ response slopes” (i.e., amplitude Vₜ/amplitude PaCO₂) averaging 6 liters/min/mm Hg, in contrast to CO₂ inhalation slopes which typically average 3 liters/min/mm Hg.

We have thus identified the nature of the kinetic relation of ventilation to a CO₂-linked stimulus. But what of the response to exercise onset? To gain insight into the nature of the abrupt ventilatory response, we averaged 40 responses of 5 subjects in the transition from rest to a work rate of about 70 watts (Fig 2, left panel). The ventilatory and heart rate responses are normalized among subjects by expressing them as a percentage of each subject’s steady-state response. End-tidal Pco₂ is plotted as the difference from the control value. The mean and standard error of the responses from 6 breaths before onset to 15 breaths after onset are shown. Note that ventilation achieves 32% of its steady-state response upon the first breath. However, despite this abrupt ventilatory increase, end-tidal Pco₂ is not driven down. Though products of the exercise metabolism cannot reach the lung for several seconds (as seen in the slow rise of PetCO₂ commencing as the alveolar phase steepens), apparently an abrupt increase in cardiac output (as indicated by the abrupt heart rate response) delivers more CO₂ to the lung. The ventilatory response is just sufficient to maintain Pco₂ at its control level.

This interpretation is reinforced if, instead of commencing the exercise from rest, we consider the average of 40 transitions from loadless pedalling to an identical work rate (Fig 2, right panel). Note that we do not observe the abrupt increase in ventilation in the first few breaths. Yet, apparently because the abrupt increase in blood flow to the lung does not take place in this case (as suggested by the delayed onset of heart rate changes), an abrupt ventilatory increase is not required to maintain Pco₂ at a constant value.

Two reservations must be stated above CO₂ from the responses at exercise onset. We actually available gas investigators have reported a nation. We have hopes exercise onset. But the major utilizing polypropylene concerned treadmill exercise.
ences would be expected to be more pronounced. Secondly, these abrupt increases in heart rate and ventilation at exercise onset could conceivably be manifestations of simultaneous drives on both the cardiovascular and respiratory systems. However, this hypothesis could not explain how the 2 independent drives would interact to produce an apparent regulation of $\text{PCO}_2$ in this transient state.

In any case, one remains with the finding that there appears to be no component of the ventilatory response to exercise which is clearly unrelated to $\text{CO}_2$. It hardly needs to be added that nowhere is there an indication of the mechanism linking ventilation to $\text{CO}_2$, but at least these findings suggest where to look!

References

Chemical Drives to Breathe as Determinants of Exercise Ventilation*

Bruce Martin, Ph.D.; John V. Weil, M.D.; Kenneth Sparks, Ph.D.; Robert E. McCullough; and Robert F. Grover, M.D.

Causes of hyperpnea during muscular exercise remain unknown. Because blood gases remain near resting levels during work, ventilatory responsiveness to changes in $\text{PO}_2$ and $\text{PCO}_2$ in blood have been thought unimportant. However, chemoreceptor gain may be increased during exercise, possibly contributing to augmented breathing during work. To assess the role of the $\text{O}_2$ and $\text{CO}_2$ chemoreceptors in exercise ventilation ($V_{E}$), we studied the relationship between chemoresponsiveness and $V_{E}$ during exercise in 8 subjects. $V_{E}$, $\text{O}_2$ uptake ($\text{VO}_2$), and ventilatory responses to $\text{PO}_2$ and $\text{PCO}_2$ changes were measured at rest and during mild and heavy treadmill exercise (% and % of the maximum $\text{VO}_2$). The subjects were college varsity athletes engaged in a variety of sports, and encompassed a wide spectrum of fitness as measured by $\text{VO}_{2\text{max}}$ (range 41 to 81 mLkg$^{-1}$ min$^{-1}$). Resting $\text{CO}_2$ chemoresponsiveness as measured by slope $S$ of $V_{E}$ vs $\text{PAPO}_2$ was unchanged by exercise at either intensity. In contrast, $\text{O}_2$ chemoresponsiveness as measured by shape parameter $A$ was greatly increased from rest ($A = 136 \pm 39$ [SEM]) by mild ($A = 551 \pm 152$; $P < 0.01$) and heavy ($A = 1264 \pm 382$; $P < 0.01$) exercise. $V_{E}$ during exercise expressed per unit metabolic rate ($V_{E}/\text{O}_2$) was highly variable among subjects and correlated with both $\text{O}_2$ and $\text{CO}_2$ chemoresponsiveness.

To assess the role of $\text{O}_2$ chemoresponsiveness in determining both the magnitude and interindividual variability of exercise $V_{E}$, we studied the difference between normoxic and hyperoxic $V_{E}$ to determine the "hypoxic" contribution to $V_{E}$ in normoxia. The "hypoxic" contribution averaged 25 to 30% of $V_{E}$ both at rest and exercise. However, the "hypoxic" component of exercise $V_{E}$ varied among individuals (range 13-54%) and was correlated with $\text{O}_2$ chemoresponsiveness ($r = 0.92$, $P < 0.01$). This variability in "hypoxic" component explained much of the interindividual variation in $V_{E}$: the coefficient of variation (SD/X) of the "hypoxic" component was 57% and of the "non-hypoxic" component 12%

In summary, $V_{E}$, during both mild and heavy exercise, could be divided into 2 components; a large (mean 70-75% of the total) fraction independent of hypoxic sensitivity and relatively constant among individuals, and a smaller (mean 25-30% of the total) and much more variable component closely related to $\text{O}_2$ chemosensitivity. Individuals with lower $\text{O}_2$ chemosensitivity thus showed lower exercise $V_{E}$. Decreased hypoxic ventilatory responses have been described in endurance athletes. The present study may indicate a mechanism linking chemoresponsiveness and athletic performance.

Ventilatory Responses to Transient and Steady State Hypoxia during Exercise*


*From the Cardiovascular Pulmonary Research Laboratory, University of Colorado Medical Center, Denver, and Department of Physical Education and Recreation, University of Colorado, Boulder.

*From the Department of Medicine, University of Edinburgh, Royal Infirmary, Edinburgh, Scotland.

CHEST, 73: 2, FEBRUARY, 1978 SUPPLEMENT