The Humoral Regulation of Breathing

A concept based on the physicochemical composition of mixed venous and arterial blood is presented.

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Few problems in physiology have been more resistant to explanation than the mechanisms which regulate breathing during exercise. In this article the humoral aspects of these mechanisms are presented in terms of a new concept that accounts for the hyperpnea of exercise and also the ventilatory responses to acid-base imbalance (*1*). Here we consider humoral regulation only, with full realization that breathing can be controlled voluntarily; that it is altered by extraneous factors such as posture, emotion, pain, and other stimuli; that there are physiologically significant respiratory reflexes mediated by baroreceptors in the circulatory system; and, that, for a given ventilatory requirement, the regulation of respiratory frequency, in relation to tidal volume, is governed by neural mechanisms in the "biologic oscillator" which comprises the "respiratory center" (*2*).

We have approached the regulation of breathing during exercise in an unconventional fashion. Whereas other investigators have evaluated the ventilatory response of the resting organism to various stimuli, such as inhalation of carbon dioxide and injection of acid, and have applied the results of these observations in attempts to account for the hyperpnea of exercise, we have done the opposite. A quantitative description of the physiological and biochemical responses to exercise has been developed and applied to several situations characterized by hyperpnea. This description of several concomitants of exercise not only predicts the ventilatory response to exercise but also predicts, with acceptable accuracy, ventilatory responses in the other situations characterized by hyperpnea, provided one postulates a peripheral chemoreceptor mechanism which reacts to the composition of mixed venous blood.

In its present state of development the concept is crude, mathematically. It demonstrates, nevertheless, that the ventilatory response to exercise represents a general pattern of physiologic reaction to the composition of mixed venous and arterial blood.

Currently Accepted Theories of Respiratory Regulation

Since there are several recent reviews (*3–8*) of the various theories that have been proposed to explain the regulation of breathing, these will not be re-examined. The principal features of most of these theories are shown diagrammatically in Fig. 1*A*. This depicts a simple, closed-loop servomechanism with negative feedback. Although each investigator would alter the diagram slightly, few would reject its basic premise, that gives central importance to the respiratory center of the brain stem, which is assumed to react to changes in arterial blood. Most would also agree that the medullary center is under the partial influence of afferent impulse traffic from peripheral chemoreceptors in the arterial blood stream—the carotid and aortic bodies. Few would differ strongly with our position that this mechanism cannot explain the most important hyperpnea—that which regulates ventilation and maintains acid-base homeostasis during exercise and recovery.

Description of Unified Concept

The concept presented here is depicted diagrammatically in Fig. 1*B*. On comparing Figs. 1*A* and 1*B*, it is evident that there are two major differences between this concept and previously proposed theories of the respiratory control mechanism.

1) In addition to the known peripheral chemoreceptors which react to the P_{O_2}, P_{CO_2}, and H^+ (*9*) of arterial blood—the carotid and aortic bodies—an additional peripheral chemoreceptor mechanism is postulated whose activity is in some way related to the H^+ and P_{CO_2} of mixed venous blood.

A structure—the glomus pumonale—has recently been found in the wall of the pulmonary artery of several species, including man, by Krahl (*10*). These structures are identical microscopically with the carotid and aortic bodies, and it may be that these are the chemoreceptors of the mechanism postulated above. This is an attractive possibility because of the following embryologic and phylogenetic considerations: The carotid artery is derived from the third branchial arch; the aortic arch and brachiocephalic artery are derived from the fourth branchial arch; and the pulmonary artery is derived from the sixth arch. The carotid arteries and the aortic arch are known to have associated chemoreceptors; hence, it may be that the pulmonary artery also has an associated chemosensitive glomus.

2) The respiratory center in the medulla is no longer considered to be a sense organ which reacts to humoral agents; rather, it is analogous to a "computing mechanism" whose input is the afferent impulse traffic from the peripheral chemoreceptors and whose output is the efferent impulse traffic to the respiratory muscles.

The belief that the respiratory center has physiologically important chemosensitivity is more deeply rooted than almost any other concept in physiology. There is, however, little direct evidence to support this (*6*). While it can hardly be doubted that a respiratory center exists, the fact that hyperpnea is produced by inhalation of CO_2 does not necessarily mean that the respiratory center is being stimulated directly by the increased arterial P_{CO_2} resulting therefrom. Such an assumption is implicit, nevertheless, in most studies of the chemosensitivity of the respiratory center. To cite one of many examples, Hooker (*11*) set out to compare the effects of H^+ and P_{CO_2} on the respiratory

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center. In his experiments he perfused the heads of dogs by way of the innominate artery and assumed that changes in respiratory activity reflected the results of stimulating the respiratory center chemically. Since the carotid arteries are branches of this vessel, it is now apparent that the observed ventilatory responses were mediated, at least partially, by the carotid bodies. But, since peripheral chemoreceptors were unknown in 1917, it did not occur to anyone that such experiments were evaluating anything other than the respiratory center.

A similar situation existed later, after the aortic and carotid bodies had been found and their major characteristics had been determined. To evaluate the respiratory center, Banus *et al.* (*12*) destroyed the known arterial chemoreceptors and related the ventilatory responses to the composition of arterial blood before and after intravenous injection of acidic solutions. They did not consider the possibility that a chemoreceptor mechanism might react to the composition of mixed venous blood, just as in 1917 physiologists did not consider the possibility of arterial chemoreceptors. It is certainly conceivable, therefore, that the observed changes in ventilation were due not to chemical stimulation of the medulla but, rather, to chemical stimulation of a chemoreceptor in the venous circulation.

There are also at least two a priori reasons for believing that the physiologically significant chemoreceptive mechanisms are peripheral: (i) In general, the central nervous system does not act as a sense organ in addition to functioning as a "computing mechanism." (ii) Proper functioning of the central nervous system, especially the brain, requires that the composition of its arterial blood supply be maintained within narrow limits. Since the arterial chemoreceptors are interposed between the lungs and the respiratory center, they are in a position to sense changes in arterial blood before this altered blood reaches the brain. They can thus initiate the ventilatory response necessary to maintain CO_2 and O_2 homeostasis in the brain's arterial blood supply.

Respiratory control mechanism considered as a servosystem. To return to Fig. 1*B*, which depicts the new concept, the medullary respiratory center is considered to receive afferent impulses in proportion to the stimulation provided the mixed venous blood chemoreceptor mechanism by the H^+ and P_{CO_2} of mixed venous blood, plus the stimulation given the carotid and aortic bodies by the H^+, P_{CO_2}, and P_{O_2} of arterial blood. The respiratory center reacts to this afferent impulse traffic from the peripheral receptors and sends efferent impulses to the respiratory muscles in proportion to the total afferent impulse traffic received. The energy expenditure and, concomitantly, the volume of breathing are regulated by this afferent impulse traffic.

The ventilatory response elicited by a given set of conditions in the arterial and mixed venous blood does not differ greatly from one normal individual to another. There are, however, numerous conditions in which the work of breathing is excessive. In these conditions, the response may be normal in terms of energy expended for breathing but impaired in terms of total ventilation (*13*).

The system depicted in Fig. 1*B* is a pair of closed-loop servomechanisms connected in parallel, each having a negative feedback. Stimulation of either peripheral receptor will tend to produce hyperventilation. But, since hyperventilation lowers the P_{CO_2} and H^+ of both arterial and mixed venous blood, both receptors will soon receive less stimulation, with a resultant tendency toward hypoventilation. Conversely, if the stimulation on either side is reduced, or if the transmission of impulse traffic is impaired, there will be a tendency toward hypoventilation. This results in an increase of H^+ and P_{CO_2} in both mixed venous and arterial blood as well as a reduction of P_{O_2} in arterial blood; thus, the tendency toward hypoventilation is almost neutralized. Because of influences such as these, the system tends to stabilize, since both loops are "closed" and each has negative feedback.

It is believed that the system shown is more stable than the less complex system of Fig. 1*A* for two reasons: (i) A pair of servomechanisms, connected in parallel, is inherently more stable than two servomechanisms connected in series. (ii) "Utilizing" the characteristics of both oxygenated and partially reduced blood results in greater stability than if oxygenated blood alone is "utilized." This is because the amphoteric hemoglobin molecule becomes a stronger base after releasing O_2, and its ability to buffer CO_2 and H^+ is increased thereby.

Postulating a chemoreceptor mechanism which is reactive to agents in mixed venous blood is not new. For many years Pi-Suñer (*14*) persisted in presenting his case for peripheral chemoreceptors in the lungs; Mitchell *et al.* (*15*) have recently suggested a receptor mechanism reacting to the CO_2 system in mixed venous blood; Schmidt (*7*) has considered the problem in detail; and the theoretical groundwork, in terms of the physical chemistry of blood, was laid 35 years ago by Hastings and Murray (*16*).

Development of Present Concept

The concept presented here was developed largely in an effort to explain the hyperpnea of exercise, which cannot be explained by any theory yet proposed. As a first step, the "whole picture" of exercise physiology, as developed by L. J. Henderson and his associates (*17*), was reconsidered. This resulted in appreciation of the fact that, although the composition of arterial blood in an exercising subject differs but slightly from the composition of arterial blood in the same subject at rest, the H^+ and P_{CO_2}, as well as the O_2 and CO_2 content, of mixed venous blood vary in relation to oxygen consumption. In fact, unless the physicochemical characteristics of mixed venous blood are considered in relation to $\dot{V}_{O_2}$, $\dot{Q}$, respiratory quotient, hemoglobin concentration, and so on, there is no "normal" value for any of the physicochemical variables in mixed venous blood.

These relationships are shown in Fig. 2, in which H^+ and P_{CO_2} of arterial and mixed venous blood, together with minute ventilation, are plotted against oxygen consumption. All of the points plotted were obtained by the indirect method (*18*) on normal men, as reported several years ago from the Harvard Fatigue Laboratory (*19–22*).

Cardiac output, $\dot{Q}$, as estimated by the "indirect" Fick method, simultaneously with the other variables, is also plotted. Although there is no direct relationship between the volume of cardiac output and the volume of breathing, an important indirect relationship deserves emphasis. Unless the cardiac output increases appropriately, as the consumption of O_2 and the production of CO_2 are increased, the normal relationship between the composition of arterial and of mixed venous blood will become deranged. Whenever there is

such a derangement, both arterial and mixed venous chemoreceptor mechanisms react accordingly, in the form of a deranged ventilatory response.

It is unnecessary to present values for HCO_3^-, since these can be calculated from H^+ and P_{CO_2}. Values for oxygen in arterial blood have not been plotted, since there is a great deal of evidence that this value changes little with any but extremely severe exercise (*15*, *23*, *24*). Values for O_2 in mixed venous blood have not been presented because the indirect method gives poor estimates of this variable and, also, because we have been unable to detect any generally consistent relationship between ventilation and the P_{O_2} in mixed venous blood.

Figure 2 shows, graphically, that for muscular exercise of any given intensity (definable in terms of increased O_2 consumption) there is an empirically definable change in the physicochemical characteristics of both mixed venous and arterial blood and, also, an increase in both ventilation and cardiac output. Figure 2 also presents equations which define these relationships as functions of $\dot{V}_{O_2}$. From this description of exercise we have inferred that the ventilatory response to exercise may be partially regulated, directly or indirectly, by the physicochemical characteristics of mixed venous blood.

Simulation of concomitants of exercise in experimental animals. In view of the striking relationship between the volume of pulmonary ventilation and the P_{CO_2} and H^+ of mixed venous blood, we attempted to determine whether experimental alterations of P_{CO_2} and H^+ of mixed venous blood would result in ventilatory changes that were independent of the characteristics of arterial blood.

We have not devised a method for perfusing the lesser circulation of a reasonably intact animal without altering the composition of blood in the systemic circulation. In the absence of such a method, the results of a study which allows separate *consideration* of the changes in the two bloods are presented in Fig. 3. This graph relates the hyperpneas resulting from electrically induced muscular exercise, intravenous injections of 1.0*M* lactic acid or sodium bicarbonate solutions, and inhalation of CO_2 to H^+ and P_{CO_2} of arterial and mixed venous blood. Since each procedure is associated with a characteristic $\dot{V} - H^+ - P_{CO_2}$ "profile," the effects of alterations in arterial and mixed venous blood can be considered separately.

The data are subject to the objection that they were obtained from anesthetized dogs lying supine, with varying degrees of acid-base imbalance and hypoxia. However, since the patterns are similar to prior observations [exercise, Henderson *et al.* (*17*, *19*); CO_2 inhalation, Hochrein *et al.* (*21*); metabolic acidosis (shock), Cournand

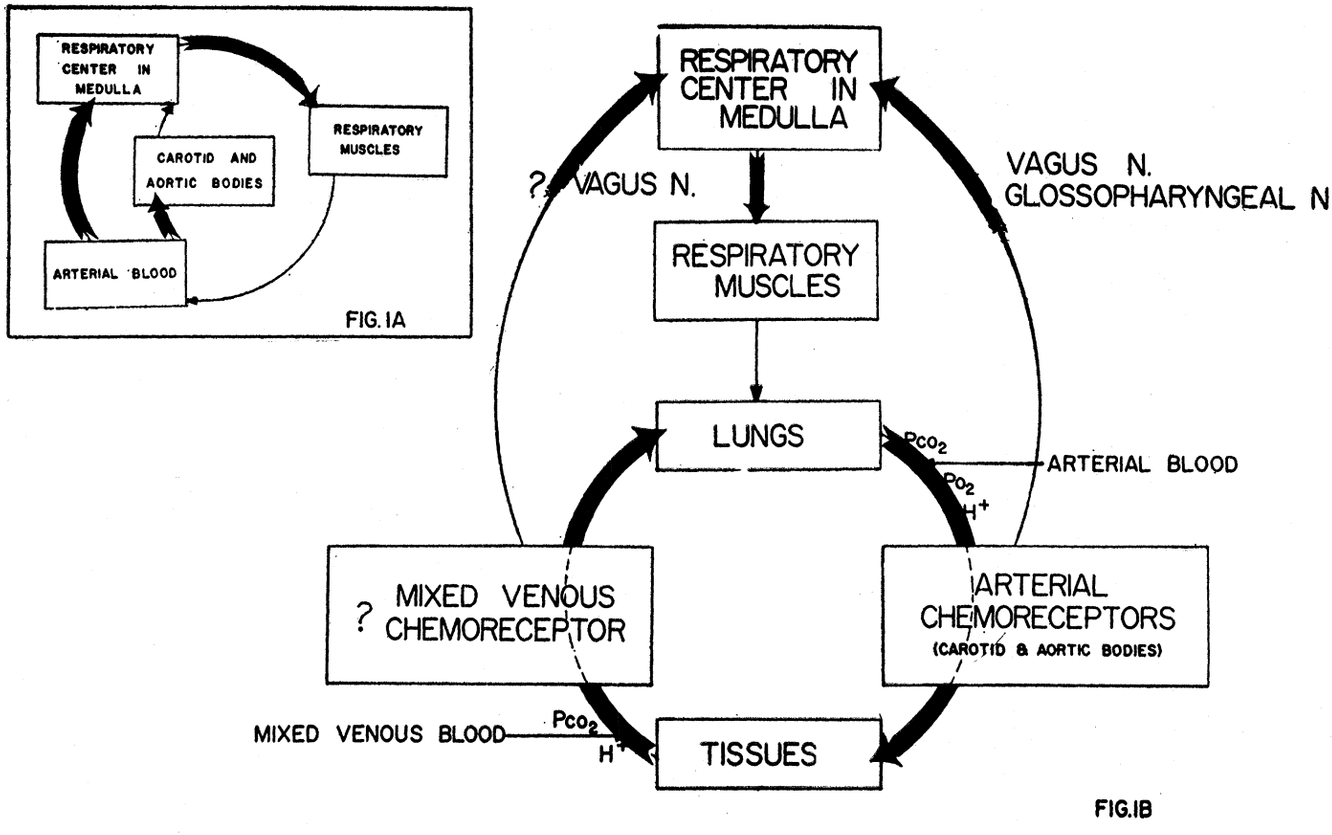

Fig. 1. (*A*) Diagrammatic representation of servomechanism analogous to classic theories of respiratory control mechanism. Arterial blood is thought to stimulate the peripheral arterial chemoreceptors and also the chemosensitive respiratory center; this, in turn, governs the activity of the respiratory muscles which ventilate the lungs and thereby regulate the composition of arterial blood. (*B*) Diagrammatic representation of servomechanism analogous to the present theory proposed to explain the regulation of breathing. In addition to the carotid and aortic bodies, which react to the H^+, P_{CO_2}, and P_{O_2} of arterial blood, it is postulated that there is another chemoreceptor mechanism which reacts to the H^+ and P_{CO_2} of mixed venous blood. The respiratory center receives impulse traffic from both receptors and governs the activity of the respiratory muscles accordingly. The respiratory center is believed to act as a computing mechanism whose functional integrity requires stable, rather than changing, composition of its perfusate.

et al. (*25*)] and since they fit the requirements of the O_2–CO_2 diagram (*26*), they are probably essentially correct.

These experiments are interpreted as follows.

1) Inhalation of CO_2, injection of lactic acid or sodium bicarbonate solution, and muscular exercise all produce hyperventilation, and each is associated with characteristic changes in P_{CO_2} and H^+ of both arterial and mixed venous blood.

2) The ventilatory responses to the four stimuli are not associated with parallel alterations of either agent in arterial blood; neither are they associated with parallel changes of either agent in mixed venous blood.

3) It may be possible to account for all of the responses by postulating that the volume of breathing is related to the *level* of both agents in *both* arterial and mixed venous blood. For instance, when sodium bicarbonate is injected, both arterial and mixed venous blood are made more alkaline and the P_{CO_2} is increased in both. Excluding the possibility that increased alkalinity, per se, produces hyperventilation, one might conclude that the stimulus is either P_{CO_2} of mixed venous blood or P_{CO_2} of arterial blood, or both. Yet, when hyperpnea is produced by giving lactic acid, the P_{CO_2} of mixed venous blood increases but the P_{CO_2} of arterial blood decreases. From consideration of the experiments with both bicarbonate and lactic acid, it might be concluded that

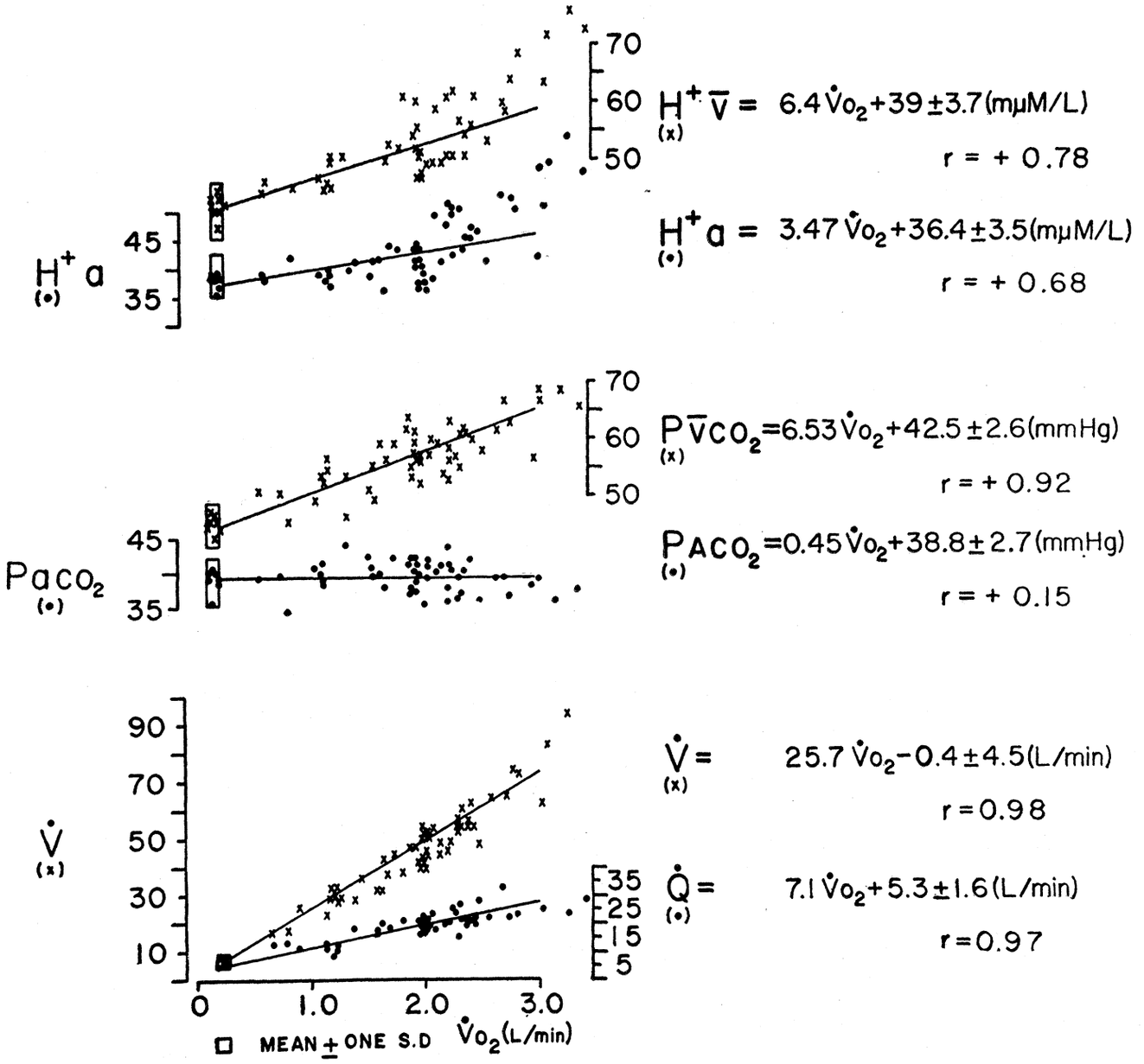

Fig. 2. Graphic representation of $H^+\bar{v}$, H^+a, $P\bar{v}_{CO_2}$, Pa_{CO_2}, $\dot{V}$, and $\dot{Q}$, plotted against $\dot{V}_{O_2}$, for normal males at rest and during steady-state exercise at various levels (*19–22*). All data pertaining to blood were obtained with the indirect method (*18*). The diagonal lines are plots of the equations listed at right. Listed with the equations are the correlation coefficients (r) between the dependent variables and $\dot{V}_{O_2}$, the independent variable. The standard error and the units used to express the dependent variable follow the ± sign.

P_{CO_2} of mixed venous blood is *the* stimulus, since it is *the* common factor. This would also be consistent with findings for exercise and for breathing CO_2, conditions in which $\dot{V}$ and $P\bar{v}_{CO_2}$ parallel each other. That this conclusion is not strictly valid is evident when the amount of hyperpnea per unit change of P_{CO_2} of mixed venous blood is compared in the different experiments; that is, the $\Delta\dot{V}:\Delta P\bar{v}_{CO_2}$ ratio was much less when $NaHCO_3^-$ was given than in the other experiments. [The conclusion is also inconsistent with the observation that in metabolic acidosis, including the state of recovery from exercise, the hyperventilation associated with a reduced $P\bar{v}_{CO_2}$ (*15, 25, 27*).]

It seems, therefore, that the hyperventilation attendant upon administration of bicarbonate is the result of a transient increase in P_{CO_2} of arterial and mixed venous blood—an increase whose influence temporarily exceeds the influence of simultaneous reduction of H^+.

To extend the interpretation of these results by considering, in turn, the ventilatory responses and blood gas changes in each of the other three experiments seems unnecessary. It was tentatively concluded that any general description of the humoral mechanisms which control breathing must give quantitative consideration to the H^+ and P_{CO_2} of mixed venous as well as arterial blood.

Ventilation and blood gases in subjects at rest and during exercise. Since it may be possible to account for the hyperpnea of exercise by considering the relationship between ventilation and the H^+ and P_{CO_2} of both arterial and mixed venous blood, data were needed to define the relationships that exist between these variables in normal human beings at rest and during exercise. The only known sources of such data are reports from the Harvard Fatigue Laboratory (*17, 19–22*) (Fig. 2). Values obtained with the indirect method in resting individuals are compared in Table 1 with the results of more recent studies in which direct measurements were used. The differences between several of the mean values are known to be statistically significant. This probably reflects differences between the subjects and the experimental situations as much as it reflects differences between the two methods. For example, for most of the variables listed in Table 1, values for recumbent subjects differ significantly from values for subjects who are erect. For this reason—since they are not physiologically significant—the results of statistical analyses have been omitted from the table deliberately.

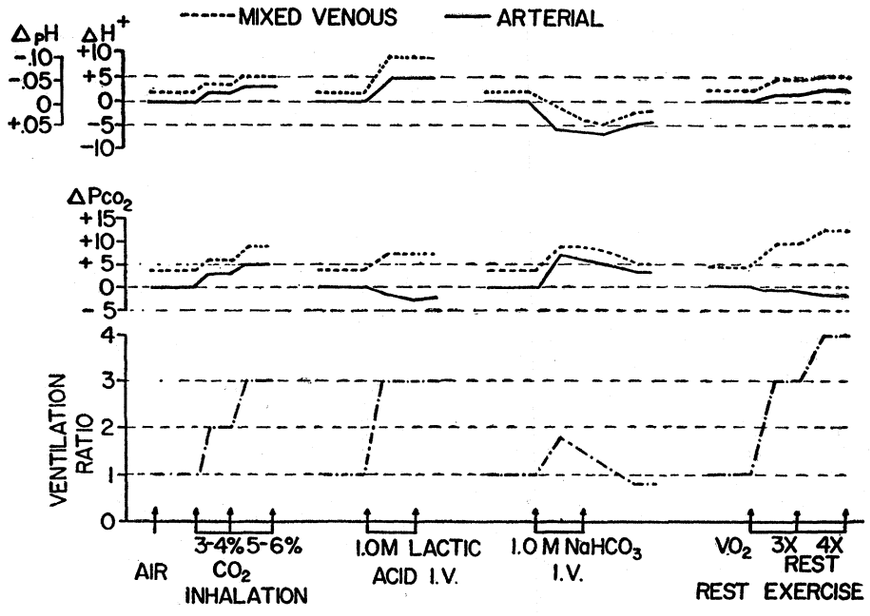

Fig. 3. Semidiagrammatic representation of changes in ventilation, Pa_{CO_2}, $P\bar{v}_{CO_2}$, H^+a, and $H^+\bar{v}$, resulting from muscular exercise, inhalation of CO_2, and intravenous administration of acidic as well as alkaline solutions. All experiments were performed on dogs lightly anesthetized with chloralose.

Results obtained with the two methods in exercising individuals are compared in Table 2. Since there are no reports of direct measurement of the P_{CO_2} or H^+ of mixed venous blood during exercise, it is only possible to compare the relation between O_2 consumption and the variables in arterial blood plus the cardiac-output response to increased consumption of O_2. The results obtained with the indirect method obviously compare very favorably with directly measured values.

Since the indirect method provided valid estimates of H^+ and P_{CO_2} of arterial blood during exercise, and since cardiac-output response to exercise, as calculated from the indirectly estimated P_{CO_2} of mixed venous blood, is very similar to the directly measured cardiac-output response, it follows that the relationships between O_2 consumption and both the P_{CO_2} and the H^+ of mixed venous blood, as shown and quantified in Fig. 2, are essentially correct.

The method used to analyze the data was as follows: O_2 consumption ($\dot{V}_{O_2}$) was assumed to be an independent variable; ventilation ($\dot{V}$), H^+a, $P\bar{v}_{CO_2}$, $H^+\bar{v}$, and Pa_{CO_2} were assumed to be dependent variables. Simultaneous equations, describing $\dot{V}$ in relation to H^+a, $P\bar{v}_{CO_2}$, and so on, were then solved so as to express $\dot{V}$ as a function of H^+a, $P\bar{v}_{CO_2}$ and so on. Standard statistical methods were utilized. Simple and multiple correlation coefficients so derived are shown in Table 3. Six regression equations, developed to define several of the relationships shown in Fig. 2, are listed below:

$$\dot{V} = 25.7\,\dot{V}_{O_2} - 0.4 \pm 4.5 \text{ lit./min} \quad (1)$$

$$\dot{Q} = 7.1\,\dot{V}_{O_2} + 5.3 \pm 1.6 \text{ lit./min} \quad (2)$$

$$Ca_{O_2} - C\bar{v}_{O_2} = \dot{V}_{O_2}/(7.1\,\dot{V}_{O_2} + 5.3)\ (\text{cm}^3/\text{lit.}) \quad (3)$$

$$\dot{V}_{O_2} = 0.19H^+a - 0.12\,Pa_{CO_2} + 0.21\,P\bar{v}_{CO_2} - 0.16\,H^+\bar{v} - 4.61 \quad (4)$$

$$\dot{V} = 1.1\,H^+a + 2.3\,P\bar{v}_{CO_2} - 135 \pm 10.1 \text{ lit./min} \quad (5a)$$

$$VR = 0.17\,H^+a + 0.35\,P\bar{v}_{CO_2} - 21 \quad (5b)$$

$$VR = 5b + \frac{105}{10^{0.038P_{O_2}}} \quad (5c)$$

$$\dot{V} = 4.96\,H^+a - 3.2\,Pa_{CO_2} + 5.3\,P\bar{v}_{CO_2} - 4.2\,H^+\bar{v} - 123 \pm 6.6 \quad (6)$$

Equations *5a*, *5b*, and *5c* are of primary interest; their significance is discussed below in detail. Equation 1, which expresses the well-known relation between ventilation and consumption of O_2, is presented for complete-

Table 1. Comparison of data (means, plus or minus standard deviation) obtained by indirect (H F L) and direct methods with subjects at rest.

Author and reference	Subjects (*N*)	$\dot{V}_{O_2}$	$P_{O_2}\bar{v}$	Pa_{CO_2}	H^+a	$P\bar{v}_{CO_2}$	$H^+\bar{v}$	$\dot{Q}$
H F L (*19–21*)	18*	0.246 ± 0.032	41.3 ± 4.2	38.8 ± 2.4	38.7 ± 1.9	43.4 ± 3.8	40.4 ± 2.5	6.5 ± 1.1
Cournand (*28*)	11†	0.240 ± 0.033	39.4 ± 4.2	39.4 ± 3.8	37.9 ± 1.6	45.2 ± 4.4	41.3 ± 1.2	5.6 ± 1.2
Bartels (*38*)	9†	0.304 ± 0.047	39.4 ± 5.8	39.8 ± 2.0	36.1 ± 1.9	42.9 ± 2.1	38.0 ± 1.3	7.5 ± 1.1
M. S. & C. (*15*)	26‡	0.35 ± 0.06	35§	39.0 ± 4.0	40.8 ± 4.0	45§	43§	5.5 ± 0.9

* Eight subjects erect, ten subjects recumbent. † Subjects recumbent. ‡ Subjects erect. § Values calculated from CO_2 or O_2 dissociation curves constructed from $\dot{Q}$, Ca_{O_2}, Ca_{CO_2}, Pa_{CO_2}, R, $\dot{V}_{CO_2}$, Hb (*18*).

ness and need not be discussed. Equation 6 describes the empiric relationships observed between $\dot{V}$ and both P_{CO_2} and H^+ in arterial and mixed venous blood in subjects at rest and during exercise of various intensities. Equation 2 expresses cardiac output as a function of O_2 consumption as depicted in Fig. 2. Equation 3, which expresses arterio-mixed venous O_2 difference as a function of O_2 consumption, was obtained by combining Eq. 2 with the Fick equation [$\dot{V}_{O_2} = \dot{Q}\ (Ca_{O_2} - C\bar{v}_{O_2})$].

Many of the essential points that have been presented can now be highlighted and summarized by two sample calculations with Eq. 5*a* that relate to a hypothetical normal man. The equations on the right side of Fig. 2 state that the H^+ of a resting individual's arterial blood will be about 38 mμmole per liter (pH, 7.42), and the P_{CO_2} of his mixed venous blood will be about 44 mm-Hg. Equation 5*a* now becomes: $\dot{V} = (1.1 \times 38) + (2.3 \times 44) - 135 = 8$ lit./min. This is a reasonable value for a normal person at rest. During mild exercise, which will be assumed to require the consumption of 1.0 liter of O_2 per minute, the equations of Fig. 2 state that the H^+ in arterial blood will be increased from 38 to about 41 mμmole per liter, and the P_{CO_2} of mixed venous blood will be increased from 44 to about 50 mm-Hg. Under these conditions, Eq. 5*a* predicts a minute ventilation of 25 liters per minute, agreeing with the value predicted by Eq. 1. In this example, the hyperpnea of exercise is accounted for by a change in the composition of both arterial and mixed venous blood with the latter seemingly the more important. Much of the remainder of this paper is based on similar, and equally simple, calculations.

Theoretically, Eq. 5*a* will give less valid estimates of ventilation than Eq. 6. Equation 5*a* is much easier to present graphically than Eq. 6, and we use it here to demonstrate the validity of the present concept. Equation 5*b* was derived from 5*a* by dividing all terms by 6.5 liters per minute (an assumed value for minute ventilation for a normal man at rest) so as to express ventilation as a multiple of the value for a subject at rest, or VR [the ventilation ratio of Gray (*8*)], rather than in liters per minute. In Eq. 5*c* Gray's $VR_{P_{O_2}}$ factor has been added to Eq. 5*b*. This factor quantifies the ventilatory response to hypoxia, isolated from the effect of Pa_{CO_2} *and* H^+a. Gray achieved this isolation by using PA_{CO_2} rather than $P\bar{v}_{CO_2}$, and his "$VR = 1$" referred to alveolar ventilation ratios, whereas we have used total ventilation. Hence, Eq. 5*c* is inherently less true than if the coefficient for P_{O_2} had been calculated directly. It is presented only to show the results of using Eq. 5*b* in hypoxic states.

Ventilatory response to exercise as a general mechanism. Next it was necessary to determine whether Eqs. 5 and 6, derived from indirect estimates of H^+ and P_{CO_2} during exercise, could predict ventilation in other normal subjects at rest and during exercise. It also remained to determine whether the equations provided a description of respiratory regulation sufficiently general to predict ventilation under other circumstances.

This problem may be analyzed graphically with the aid of Fig. 4, which is a Cartesian diagram of Eq. 5. In the figure, H^+a is on the horizontal axis, $P\bar{v}_{CO_2}$ is on the vertical axis, and ventilation is plotted with diagonal isopleths. The figure is used to compare the ventilatory response, as predicted and as determined, under various circumstances: rest (*28*), exercise (*15*, *19–22*), inhalation of CO_2 (*29*), administration of sodium bicarbonate (*30*), administration of ammonium chloride (*31*), diabetic acidosis (*27*), shock (*25*), and recovery from exercise (*15*, *32*).

Figure 4 confirms our interpretation of the findings presented in Fig. 3. It shows that if the characteristics of both arterial and mixed venous blood are dealt with quantitatively, the ventilatory responses to several types of acid-base imbalance follow rules similar to those that describe the ventilatory response to exercise.

Figure 4 also provides a new and semiquantitative explanation of several respiratory phenomena that are frequently explained by an assumed alteration of the sensitivity of the respiratory center or the peripheral chemoreceptors. For instance, during breathing of CO_2 the relation between ventilation and Pa_{CO_2} is at least as close as the relation between ventilatory response and the H^+ of the arterial blood. In these circumstances the respiratory control mechanism is considered to be equally

Table 2. Comparison of data obtained by direct (D)* and indirect (I)† methods during exercise. S.E., standard error of estimate; r, correlation coefficient.

Method	Observations (*N*)	Regression Eq.‡	S.E.	r	References
D	83	$H^+a = 36.7 + 2.9\ \dot{V}_{O_2}$ (1.5 to 4.3)	± 5.4 + 0.42		(*23*, *39*)
I	56	$H^+a = 36.4 + 3.5\ \dot{V}_{O_2}$ (2.5 to 4.5)	± 3.5 + 0.68		(*19–21*)
D	83	$Pa_{CO_2} = 39.9 - 0.60\ \dot{V}_{O_2}$ (−0.16 to + 0.43)	± 3.9 − 0.13		(*23*, *39*)
I	56	$P_{ACO_2} = 38.8 + 0.45\ \dot{V}_{O_2}$ (−0.34 to + 1.24)	± 2.7 + 0.15		(*19–21*)
D	271	$\dot{Q} = 5.6 + 6.5\ \dot{V}_{O_2}$ (6.2 to 6.8)	± 1.2 + 0.94		(*40*)
I	56	$\dot{Q} = 5.3 + 7.1\ \dot{V}_{O_2}$ (6.5 to 7.7)	± 1.6 + 0.97		(*19–21*)

* Range of work, $\dot{V}_{O_2}$ 0.11 to 3.0 lit./min. † Range of work, $\dot{V}_{O_2}$ 0.21 to 3.45 lit./min. ‡ Values in parentheses, fiducial limits ($P = .05$) of regression coefficient.

sensitive to P_{CO_2} and to H^+. However, in the situation of metabolic acidosis [in the lactic acid injection experiments of Fig. 3, in shock (*25*), in diabetic acidosis (*27*), and during recovery from exercise (*15*)], there is hyperpnea even though the P_{CO_2} of the arterial blood drops below normal. Thus, it might be concluded that the mechanism has become less sensitive to P_{CO_2} than to H^+. Likewise, the hyperpnea of exercise is frequently explained by an alleged increase of the mechanism's sensitivity to both agents. This argument requires that there be a change in "sensitivity" at the beginning and end of exercise.

It is preferable to account for the change in sensitivity with a different argument—that ventilatory response is determined by the *resultant* of chemoreceptor influences in arterial and mixed venous blood, these influences being dependent on the physicochemical characteristics of their respective blood supplies. Specifically, then, during breathing of CO_2 the H^+ and P_{CO_2}, of both arterial and mixed venous blood are increased; the same is true during exercise except that the Pa_{CO_2} does not rise. In either case, both chemoreceptors are stimulated. The resultant curve, as plotted in Fig. 5, is nearly perpendicular to the isoventilation lines, and a large ventilatory response is to be expected. In situations of metabolic acidosis the HCO_3^- is decreased—by the reaction:

$$HA + NaHCO_3^- \rightarrow NaA + H_2O + CO_2 \uparrow$$

—the CO_2 being exhaled. The differences between the H^+ and the P_{CO_2} of arterial and of mixed venous blood must now increase, and the mixed venous blood will be considerably more acidotic and hypercarbic than the arterial blood. The resultant of these influences nearly parallels the isoventilation lines, and mild hyperpnea is to be expected.

It seems evident that Eqs. *5a*, *5b*, and *5c* are more than a description of the relationship between ventilation and alterations in the H^+ and P_{CO_2} of arterial and mixed venous blood in a subject at rest and during exercise. They also predict the ventilatory response to several types of acid-base imbalance with acceptable accuracy.

It was obviously necessary to determine whether Eq. 5 could be improved upon by considering the H^+ and the P_{CO_2} of arterial and of mixed venous blood together. This resulted in Eq. 6. Values for ventilation, as predicted with the four independent variables of Eq. 6, were not appreciably different from the values predicted with the two independent variables of Eq. 5. This is not surprising in view of the variability inherent in the data, plus the known deficiencies of our procedure. It was assumed, for instance, that there were linear relationships between the variables. Inspection of Fig. 2 shows that this is not the case, especially for the $\dot{V}_{O_2}$—H^+a relationship. In the development of Eq. 5, only three such assumptions are made; in Eq. 6 it is assumed that nine relationships are linear. It seems probable, therefore, that adding two more variables, $H^+\bar{v}$ and Pa_{CO_2}, introduced at least as much error as was removed.

Table 3. Statistical analysis of data from the Harvard Fatigue Laboratory reports, obtained by the indirect method (*18–22*).

	Simple and multiple correlation coefficients					
	$\dot{V}$	$\dot{V}_{O_2}$	Pa_{CO_2}	H^+a	$P\bar{v}_{CO_2}$	$H^+\bar{v}$
$\dot{V}$	1					
$\dot{V}_{O_2}$	+0.98	1				
Pa_{CO_2}	+0.17	+0.15	1			
H^+a	+0.70	+0.68	+0.10	1		
$P\bar{v}_{CO_2}$	+0.88	+0.83	+0.43	+0.62	1	
$H^+\bar{v}$	+0.82	+0.78	+0.31	+0.92	+0.85	1
$\dot{Q}$		+0.97				
$H^+a \cdot P\bar{v}_{CO_2}$	0.92					
$H^+a \cdot Pa_{CO_2} \cdot H^+\bar{v} \cdot P\bar{v}_{CO_2}$	0.98					
$Pa_{CO_2} \cdot H^+\bar{v}$	0.82					

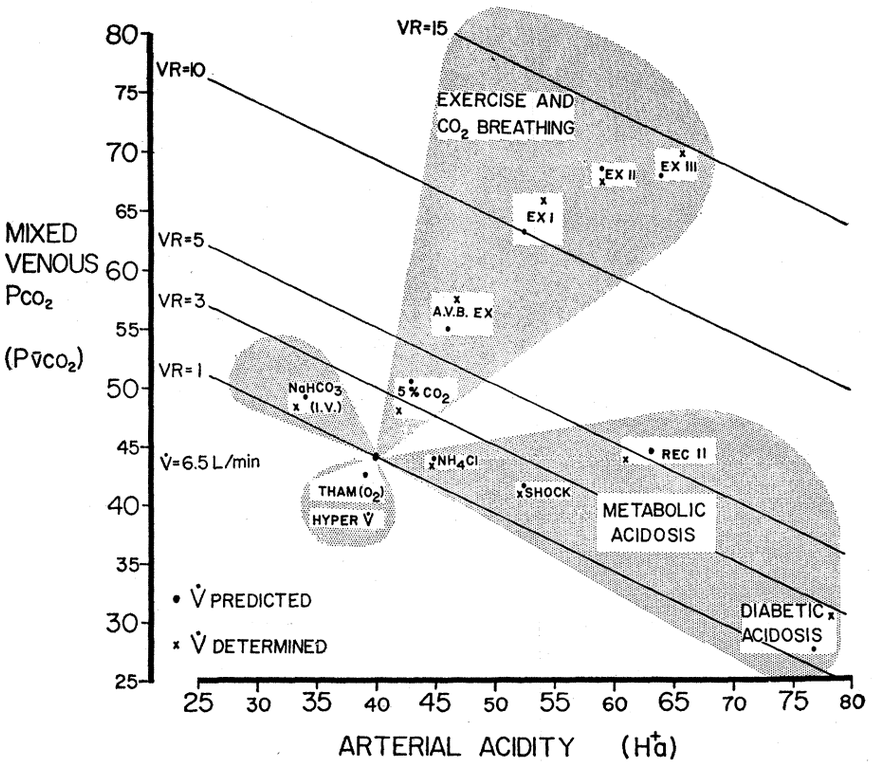

Fig. 4. Application of Eq. *5a* or *5b* in normal persons during exercise, during recovery from exercise, and in several situations characterized by acid-base imbalance. Diagonal lines represent isoventilation isopleths. Values for ventilation, as determined (×) and as predicted by Eq. 5 (•) in several conditions, are shown. The points were obtained from sources referred to in the text.

Present Concept and Multiple-Factor Theory

Equation 5*b* [$VR = 0.17\ H^+a + 0.35\ P\bar{v}_{CO_2} - 21$], which was derived from Eq. 5*a* by dividing each term by an assumed value of 6.5 liters per minute for the ventilation of a normal man at rest, is strikingly similar to the equation presented by Gray (*8*) to quantify his multiple-factor theory:

$$VR_{H^+P_{CO_2}} = 0.22\ H^+ + 0.26\ P_{CO_2} - 18 \quad (7)$$

This equation is the best available quantitative description of the ventilatory response of normal resting individuals to alterations in acidity and CO_2 tension in *arterial* blood. If it is to be used in conditions where arterial hypoxia exists, a third term, $105/10^{0.038P_{O_2}}$, is added.

Our equations are compared with Gray's in Fig. 5, which shows the ventilatory responses to acute and chronic hypoxia (*33*) in addition to responses in several of the situations presented in Fig. 4.

Although neither Gray nor his colleagues (*4*) have claimed that the multiple-factor theory explained the hyperpnea of exercise, it probably gives a valid estimate of the amount of hyperpnea due to activity of *arterial* chemoreceptors. Thus, the exercise point in Fig. 5 shows that the arterial stimulus accounted for about two-sevenths of the exercise hyperpnea of the subject (A.V.B.) (*17*).

It is surprising that Eq. 5*b* and Gray's equation are so similar, especially since our equations were developed from data obtained by studying normal men at rest and during exercise, whereas Gray's equation was developed from data collected from a completely different group—resting persons breathing CO_2 or with metabolic alterations of acid-base balance.

A partial explanation for this similarity is that identical assumptions were made in both derivations. Gray's procedure was essentially as follows. If ventilation is assumed to be regulated by the algebraic summation of the H^+ and the P_{CO_2} of arterial blood, the following equation holds in the absence of hypoxia:

$$VR = a\,H^+ + b\,P_{CO_2} - c$$

The coefficients and the intercept were derived by solving simultaneous equations which described the buffer systems of blood, alveolar ventilation as a function of both Pa_{CO_2} and H^+a, and the empirical relationship between Pa_{CO_2} and H^+a. An identical assumption that there is algebraic summation is also made when a multiple regression equation is derived by the least squares method; hence, it is not surprising that Gray's equation resembles Eq. 5*b* in *form*.

If the Pa_{CO_2} *in* Gray's equation is changed to $P\bar{v}_{CO_2}$, it will be found that the intercept becomes 20 rather than 18. This modification of Gray's equation

$$VR_{H^+a\,P\bar{v}CO_2} = 0.22\ H^+a + 0.26\ P\bar{v}_{CO_2} - 20$$

predicts the ventilatory response to exercise and to acid-base imbalance in resting persons nearly as well as Eqs. 5*b* or 7. The similarity between these equations is interpreted to mean that both describe a general physiologic reaction pattern.

Unified Concept Applied to Cross-Perfusion Experiments

If this concept is valid, it should provide an explanation for the results observed by Kao (*34*) in his studies of respiratory regulation in cross-perfused dogs.

These were of two types.

1) In one, the two dogs were connected, jugular veins to jugular veins and common carotid arteries to common carotid arteries. Arterial blood from the central ends of the carotid arteries of the donor (Kao's "neural" dog) passed through *T* tubes into the distal ends of the carotid arteries of both dogs. The proximal ends of the recipient's carotid arteries were ligated. By a similar arrangement, blood from the head of the recipient (Kao's "humoral" dog) was returned by way of the jugular veins. The vertebral arteries and neck muscles of the recipient were ligated so as to separate the blood supply of the head and body. It is important to note that in both dogs the anastomosis was interposed between the carotid and the aortic bodies. Thus, the recipient had a humoral connection between his body and his aortic chemoreceptors, but no humoral connection to his respiratory center or carotid bodies. The neural pathways were not interrupted in either dog.

When the donor was made to exercise by means of electrical stimulation, the donor manifested hyperventilation but the recipient did not. We interpret these findings as follows. (i) The donor dog was normal except for the aforementioned vascular anastomosis, and hyperventilation should occur with exercise if $\dot{V}$ is mediated by chemoreceptors responding to the composition of mixed venous blood. (ii) However, if the arterial blood had carried the stimulus, the recipient would also be expected to manifest hyperventilation. The absence of hyperventilation in the recipient indicates that the arterial blood was not providing an important stimulus—to either the medullary respiratory center or the carotid bodies.

When the recipient was made to exercise, hyperventilation occurred in the recipient only. We interpret these findings as follows. (i) Since the arterial blood did not contain the necessary stimulus, hyperpnea in the recipient cannot be accounted for on the basis of aortic-body stimulation. (ii) However, during exercise, the mixed venous blood of the recipient was undoubtedly hypercarbic and hyperacidic and, by acting on a chemoreceptor, could produce the observed hyperpnea.

2) In another series of experiments, the anastomosis was established by connecting common iliac artery with common iliac artery and common iliac vein with common iliac vein. In the donor dog, these vessels were ligated above the anastomosis; in the recipient, below the anastomosis. Thus, except for a small amount of collateral circulation, all blood draining the legs of the donor passed into the body of the recipient.

When the donor was exercised, the recipient manifested hyperventilation; the donor did not. It can be assumed that the venous blood draining the exercising legs of the donor was more acidic and hypercapneic than the recipient's resting blood; this is thought to have stimulated the mixed venous chemoreceptor mechanisms of the recipient and to have produced hyperventilation (*35*).

Indices of Chemoreceptor Activity and Respiratory Drive

Throughout previous sections of this article reference has been made to P_{CO_2} and H^+ as if they were the agents which stimulate the chemoreceptors and thereby regulate breathing. They should probably be considered *indices* of stimulation rather than agents which stimulate. Although the nature of the

stimulus actually responsible for action potential activity in the carotid and aortic bodies is not known, it is reasonably certain that acetylcholine and choline esterase are involved (*5, 36*). Whatever the substances responsible for this activity may be, there is fairly good evidence that the reactions are governed, indirectly, by the composition of the fluid perfusing the glomera.

For instance, Witzleb *et al.* (*37*) have observed a direct relation between the frequency of action potential discharge in the sinus nerve and the H^+ or P_{CO_2}, but an inverse relationship with the P_{O_2}, of fluid perfusing the carotid body. The approximately linear relation between action potential discharge and either H^+ or P_{CO_2} in these studies is paralleled by a similar relation between either the P_{CO_2} or the H^+ of arterial blood and ventilatory response, reported by Gray (*8*). The exponential increase in action potential frequency as the P_{O_2} of the perfusate is decreased (*37*) is also paralleled by an exponential increase in ventilation in relation to P_{O_2} of arterial blood when the influence of P_{CO_2} and H^+a is eliminated mathematically (*8*). It seems, therefore, that either ventilatory response or chemoreceptor activity can be estimated by measuring the H^+, P_{CO_2}, or P_{O_2} of the perfusate and using them as *indices* with which chemoreceptor activity or ventilatory drive can be monitored.

It is not supposed that the chemoreceptors are sensitive to each of these agents; rather, it is generally believed that their effect is produced by a common factor—possibly by alteration of the intracellular acidity of the glomeral cells.

This again brings up the important point of changes in the sensitivity of the respiratory control mechanism. It is known, for example, that after acclimatization to high altitudes the mechanism becomes more sensitive, in that the ventilatory response to a given amount of exercise is greater at altitudes than at sea level. A similar situation exists in anemia. What feature is common to both conditions? It is believed that the explanation lies in the reduced buffering power of blood. After acclimatization, the HCO_3^- is reduced; in anemia, the hemoglobin concentration is reduced. In either case the buffering power of the blood is reduced. Consequently, addition of a given volume of CO_2 or acid produces greater alteration of H^+ and P_{CO_2} in the mixed venous blood than if the hemoglobin or HCO_3^- concentrations are normal. This increased "sensitivity" of the blood buffer system is probably reflected in a simultaneously increased lability of the H^+ within chemoreceptor cells.

When using Eq. 5 we have taken H^+ concentration as an index for monitoring the entire physicochemical system of arterial blood, which partially governs the intracellular acidity of the arterial chemoreceptors. The P_{CO_2} has been taken similarly as an index in the case of mixed venous blood. Because of this, it may appear that we attach undue importance to the P_{CO_2} of mixed venous blood. To refute this, another equation is presented which accounts for the various ventilatory responses nearly as well as Eq. 5. This other equation was derived from the same data but uses the H^+ of mixed venous blood and the P_{CO_2} of arterial blood:

$$\dot{V} = 0.85\ H^+\bar{v} + 0.10\ Pa_{CO_2} - 5.2 \quad (8)$$

$$r\dot{V} \ldots .H^+\bar{v} \cdot P_{ACO_2} = 0.82$$

(S.E., ± 11.5 lit./min)

When applied to the group-1 exercising subjects of Mitchell *et al.* (*15*), this equation predicts a $\dot{V}$ of 55; the measured $\dot{V}$ was 73 liters per minute.

Thus, Eq. 8 uses the H^+ of mixed venous blood as an index of the activity of the mixed venous chemoreceptor mechanism and the P_{CO_2} of arterial blood as an index of carotid- and aortic-body activity.

Rather than use H^+a and $P\bar{v}_{CO_2}$ as indices, it would be preferable, of course, to estimate intracellular acidity from P_{CO_2}, H^+, HCO_3^-, and other blood buffers. We have not yet used this approach, principally because the data obtained with the indirect method do not justify the massive computation that would be required.

Summary

The clasic concept that breathing is regulated only by chemoreceptor mechanisms in the arterial blood stream—the respiratory center, the carotid and aortic bodies—has been modified in two ways. It has been expanded by postulating another chemoreceptor which reacts to the composition of mixed venous blood. It has been qualified by questioning the assumption that the respiratory center has physiologically significant chemosensitivity. (The respiratory center is considered to be, on the contrary, primarily a computing mechanism that integrates information received from chemoreceptors responding to both arterial and mixed venous blood.)

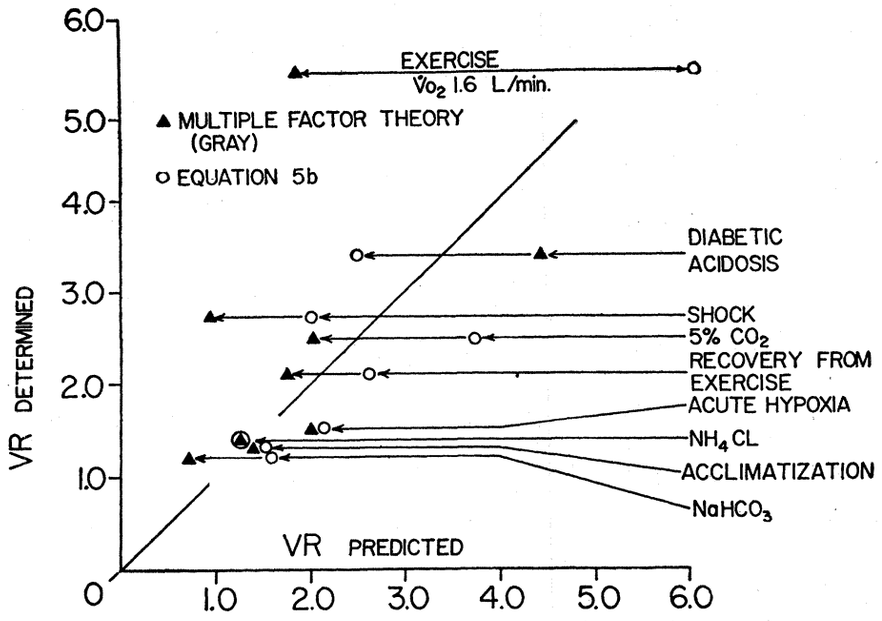

Fig. 5. Correlation of *VR* (determined) and *VR* (predicted) in several conditions—a comparison of Eq. 5 and the multiple-factor theory equation of Gray. *VR* (determined) is on the vertical axis, and *VR* (predicted) is on the horizontal axis. Since the scales are identical, perfect agreement is represented by the 45° diagonal. The graph shows that Eq. 5 and the multiple-factor theory equation have about equal ability to predict the various ventilatory responses of resting individuals. It also shows the approximate magnitude of the arterial stimulus, as estimated from Pa_{CO_2} and H^+a during exercise.

By postulating a chemoreceptor mechanism which reacts to the composition of mixed venous blood, a variety of ventilatory responses can be accounted for with a unified and semiquantitative concept based on the ventilatory response to exercise.

For the quantitative description of exercise, data obtained from normal men at rest and during exercise have been used to develop several equations which describe the ventilatory response to exercise in terms of P_{CO_2} and H^+ of arterial and mixed venous blood. The simplest of these equations, yet a useful one, is the following:

$$\dot{V} = 1.1\ H^+a + 2.3\ P\bar{v}_{CO_2} - 135 \quad (5a)$$

which states that the volume of breathing is determined by the algebraic summation of influences in arterial and mixed venous blood.

Ventilatory responses, as measured in several experimental and clinical situations characterized by acid-base imbalance and associated hyperpnea, have been compared with the ventilation predicted by this equation and by the equation which quantifies Gray's multiple-factor theory. Equation 5*a* estimated the various ventilatory responses as closely as the multiple-factor theory equation did. Equation 5*a* was also able to predict ventilation during exercise. It is concluded, therefore, that the hyperpnea of muscular exercise may be a generally applicable expression of the ventilatory response to alterations of the composition of both arterial and mixed venous blood.

When applied to the ventilatory responses of cross-perfused animals during exercise, the concept gives a satisfactory qualitative explanation of the various observations.

Although there is strong indirect evidence that a chemoreceptor mechanism exists which reacts to the composition of mixed venous blood and whose activity can be quantified, the equations that have been developed are not definitive expressions of the stimuli which regulate breathing. That the equations apply as well as they do, in view of the known errors of fact in their development, is probably the best evidence yet adduced for the essential validity of the present concept.

References and Notes

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