Role of Metabolic CO_2 Production in Ventilatory Response to Steady-state Exercise

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ABSTRACT We examined the role of metabolic CO_2 production in the hyperpnea of muscular exercise by comparing the response of alveolar ventilation to moderate levels of exercise with the response to venous infusion of CO_2 at rest. Studies were performed in four awake sheep that were trained to run on a treadmill. The sheep had been cannulated for veno-venous extracorporeal perfusion so that CO_2 could be infused into the peripheral venous blood through membrane lungs in the perfusion circuit. The sheep breathed room air through an endo-tracheal tube inserted through a tracheostomy, and samples of expired gas were collected for measurement of the rates of CO_2 production and O_2 consumption. All measurements were made in the steady state. In each of the four sheep, the relationship between alveolar ventilation and the rate of CO_2 production could be described by a single linear function ($r > 0.99$; $P < 0.001$), regardless of whether CO_2 production was increased by exercise, venous CO_2 infusion, or combinations of both procedures. This relationship applied for values of CO_2 production up to 350% of control. In contrast, no unique relationship was found between the rate of alveolar ventilation and either the rate of O_2 consumption, cardiac output, or mixed venous blood gas pressures. The findings indicate that the hyperpnea of mild to moderate steady-state exercise can be attributed to the associated increase in the rate of CO_2 production. Therefore, there is no need to invoke obligatory nonmetabolic stimuli to account for the ventilatory response to steady-state exercise.

INTRODUCTION

Despite an extensive literature on the subject, considerable uncertainty and controversy surrounds the mechanism(s) responsible for the hyperpnea of muscular exercise. In broad terms it can be stated that ventilation increases during exercise in response to the metabolic demands of the exercising muscles; in particular, the need for increased delivery of O_2 and for increased elimination of CO_2. However it is generally agreed that in the steady-state of moderate exercise, ventilation usually increases without measurable changes in arterial P_{CO_2} (Pa_{CO_2}), P_{O_2} (Pa_{O_2}) or pH (1–4), which are the important physiological variables involved in metabolic respiratory control by virtue of their stimulatory effect on the aortic, carotid, and medullary chemoreceptors. Thus ventilation increases during exercise in a manner that is highly correlated with metabolic rate, but without a measurable change in metabolic variables at their sites of chemoreception. The absence of arterial hypercapnia in particular has been interpreted to mean that the conventional ventilatory response to CO_2 (as defined by inhalation of CO_2) cannot in itself account for the hyperpnea of exercise, since no "error signal" is present to which the increase in ventilation can be attributed.

This paradox has lead to the development of two alternate hypotheses to account for the ventilatory response to exercise. The "neuro-humoral" hypothesis (2) holds that during exercise ventilation is augmented by neural stimuli in addition to metabolic stimuli related to the increased rate of CO_2 production ($\dot{V}_{CO_2}$). Attempts to identify a neural component of exercise hyperpnea have lead to conflicting results, such a component being demonstrated or inferred in some studies (4–11), but not in others (4, 12–15). The second hypothesis maintains that the hyperpnea of exercise is completely attributable to the increased delivery of CO_2 to the lungs (16); but because arterial hypercapnia is absent, the precise CO_2-related stimulus linking ventilation and pulmonary CO_2 excretion, and its site of detection have not been specified. Support for this hypothesis has been derived from a number of studies in which CO_2 was infused into the venous blood of experimental animals (venous CO_2 loading), resulting

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in an increase in ventilation, but no measurable increase in $P_{a}CO_2$ (i.e., isocapnic hyperpnea) (17–20). The demonstration of isocapnic hyperpnea in response to venous CO_2 loading has been extrapolated to imply that the isocapnic hyperpnea of exercise may also be attributable solely to the associated increase in $\dot{V}CO_2$. However, an equally large number of other studies have been unable to demonstrate isocapnic hyperpnea in response to venous CO_2 loading; and have therefore concluded that an increase in $\dot{V}CO_2$ alone cannot account for the isocapnic hyperpnea of exercise (21–26).

A missing element in all of these preceding studies has been the lack of a direct comparison in the same animal of the ventilatory response to exercise and the ventilatory response to venous CO_2 loading. Therefore, the purpose of the present study was to undertake such a comparison to determine if the ventilatory response to exercise is greater than, or merely equal to, the response to a similar increase in $\dot{V}CO_2$ generated by venous CO_2 loading. Studies were performed in awake, intact sheep that were previously trained to run on a treadmill. The sheep were also subjected to venous infusion of CO_2 by means of an extracorporeal perfusion circuit containing two membrane lungs. The results of the study indicate that the steady-state ventilatory response to moderate levels of exercise can be accounted for completely by the increase in $\dot{V}CO_2$ produced by exercise.

METHODS

Studies were performed in four adult sheep, weighing 35–40 kg, that were selected for study on the basis of being in good health (by veterinarian examination) and of calm temperament, and of a demonstrated ability to run on a treadmill. The sheep were trained to stand quietly in place and to run on the treadmill at speeds of 0.7–2.0 mph for 20–30 min at each speed. Training was maintained for 2–3 wk before the study.

Surgical preparation. The sheep underwent surgical preparation for study at least 24 h before the experiment. The preparation, which was performed under ketamine hydrochloride sedation and local anesthesia, included creation of a side-hole tracheostomy and insertion of the vascular cannulas required for extracorporeal perfusion. These procedures have been described in detail elsewhere (27). All vascular cannulations were performed through the jugular veins or carotid arteries. One cannula was inserted into the left jugular vein and advanced to the superior vena cava to be used eventually as the venous return line. Another cannula was inserted through the right jugular vein and advanced to the inferior vena cava at the level of the diaphragm, to be used eventually as a venous drainage line. A second cannula was inserted into each jugular vein in a cephalad direction, to allow drainage of the head. The two cannulas in each jugular vein (one directed cephalad, the other caudad) were connected to each other to function as a temporary venous shunt until needed for extracorporeal perfusion on the subsequent day. A small catheter was inserted into the left carotid artery and advanced in a retrograde direction to the aortic arch. This catheter was used eventually to monitor systemic blood pressure and to permit sampling of arterial blood. Finally, a Swan-Ganz thermodilution catheter (with a proximal injection site 12.5 cm from the tip) was inserted into the left jugular vein and advanced to the pulmonary artery, to permit measurement of pulmonary arterial pressure and cardiac output, and sampling of mixed venous blood.

Before the vascular cannulations, the sheep received heparin, 125 U/kg, i.v. Heparin was then infused continuously with hemostatic monitoring, to maintain anticoagulation until completion of the experiment.

The sheep were generally alert and standing up within 30 min of completion of the surgical procedures.

Extracorporeal gas exchange. The veno-venous perfusion circuit used for these studies has been described in detail previously (27). In essence, venous blood was drained from the inferior vena cava and from both jugular veins through silicone-rubber tubing into a distensible reservoir that activated a servo-controlled roller pump. The blood was then directed through two membrane lungs in parallel, and after passage through a heat exchanger, was returned to the superior vena cava of the sheep. Venous temperature was measured by means of a temperature probe positioned in one of the jugular venous cannulas draining the head, and was maintained within ±0.2°C of control by adjusting the heat exchanger.

The membrane lungs used in these studies (CDML-3, Sci Med Life Systems, Inc., Minneapolis, Minn.) each had a surface area of 3 m^2. The lungs, developed by Kolobow and colleagues (28), were designed to facilitate the transfer of CO_2, and their gas exchange properties have been reported previously (27). The membrane lungs were ventilated with gases from cylinders through calibrated rotameters. When ventilated with a CO_2-free gas (generally O_2–N_2 mixtures), the lungs were capable of removing CO_2 from the venous blood at rates equal to or even in excess of the resting $\dot{V}CO_2$ of a large sheep (i.e., over 200 ml/min). Alternatively, by ventilating the lungs with a CO_2-enriched gas, large volumes of CO_2 (up to 2 liter/min) could be loaded into the venous blood. The perfusion rate of the membrane lungs was kept constant throughout the entire experiment at 2–3 liter/min, representing 50–75% of the total resting venous return. Therefore variations in gas transfer through the membrane lungs were achieved by altering the gas composition and flow rate with which the lungs were ventilated.

Ventilatory and circulatory measurements. During the studies the sheep breathed room air through a cuffed endotracheal tube (i.d., 10 mm) that was inserted through the tracheostomy and attached to a pneumotachograph (Fleisch no. 2) and non-rebreathing (Lloyd) valve (Warren E. Collins, Inc., Braintree, Mass.). The pneumotachograph was connected to a differential pressure transducer (Statham PM5, Statham Instruments, Inc., Oxnard, Calif.) for monitoring of airflow rates. Systemic and pulmonary arterial pressures were measured through the aortic and pulmonary arterial catheters by means of appropriate pressure transducers (Statham P23Db). Cardiac output was measured intermittently in two of the sheep through the pulmonary arterial catheter using a thermodilution technique (Cardiac Output Computer, model 9510, Edwards Laboratories, Santa Ana, Calif.). All signals were conditioned and displayed continuously on an ink writing recorder (Beckman R-612, Beckman Instruments, Inc., Schiller Park, Ill.).

The rates of pulmonary CO_2 excretion and of O_2 consumption ($\dot{V}O_2$) were measured by collecting expired gas in a 120-liter gasometer (Warren E. Collins, Inc.) over a steady-state period of 2–10 min. The O_2 and CO_2 content of this gas was analyzed in a mass spectrometer (Medspect, G. D. Searle & Co., Baltimore, Md.) that was calibrated with gases whose O_2

and CO_2 content had been determined by the Scholander technique. During the period of gas collection, samples of systemic and pulmonary arterial blood were drawn anaerobically over a period of 30–60 s. The pressures of CO_2 and O_2 and the pH of these samples were analyzed within 2–5 min with standard electrodes (Radiometer Co., Copenhagen, Denmark) that were calibrated frequently with gases of known composition and with precision buffers. The measured values were corrected to the temperature of the sheep using the Severinghaus blood gas calculator (29). From these various measurements we calculated pulmonary $\dot{V}CO_2$, $\dot{V}O_2$, and the rate of alveolar ventilation ($\dot{V}A$) using the measured respiratory quotient, calculated wasted ventilation and standard formulas (30). $\dot{V}CO_2$ and $\dot{V}O_2$ were corrected to standard temperature, pressure, dry (STPD) conditions and $\dot{V}A$ to body temperature, pressure, saturated (BTPS) conditions.

Procedures. The procedures followed to establish extracorporeal perfusion have been described in detail previously (27). Once the sheep was connected to the extracorporeal circuit, a constant rate of blood flow through the membrane lungs of 2–3 liter/min was established and fixed for the duration of the study. Thus control measurements were made with blood perfusing the membrane lungs, but with no ventilation of the membrane lungs and therefore no gas exchange. After control measurements, the sheep underwent a series of measurements at several levels of exercise (treadmill running at zero grade); and a series of measurements at rest during which CO_2 was either removed from or added to the peripheral venous blood (by ventilating the membrane lungs with CO_2-free or CO_2-enriched gas). The different levels of exercise and of venous CO_2 loading and unloading were administered in a pseudo-random manner, and were frequently interspersed with measurements made during combinations of exercise and venous CO_2 loading or unloading. In each condition (exercise; venous CO_2 loading or unloading; or combinations of both) at least 10 min was allowed for all variables to reach a steady-state before samples of expired gas and of blood were collected over the subsequent 2–10 min.

RESULTS

In the first sheep used in the studies, seven steady-state measurements were made relating $\dot{V}A$ to $\dot{V}CO_2$ during exercise, venous CO_2 loading or unloading, or combinations of both (this sheep also being used for another research protocol). In each of the other three sheep, 14 or 15 such measurements were made. Thus a total of 51 steady-state measurements was made in the four sheep. In all instances $\dot{V}A$ varied directly with $\dot{V}CO_2$ and the relationship between the two variables could be described by a single linear regression (correlation coefficient in each of four sheep was >0.99; $P < 0.001$) regardless of whether $\dot{V}CO_2$ was altered by exercise alone, venous CO_2 loading or unloading alone, or both (Fig. 1). This relationship applied over a range of $\dot{V}CO_2$ values from 0 to 350% of control. Since the relationship of $\dot{V}A$ to $\dot{V}CO_2$ is proportional to the reciprocal of $PaCO_2$, the unique function describing this relationship in each sheep implied that $PaCO_2$ was the same for a given $\dot{V}CO_2$, whether the latter was achieved by exercise, venous CO_2 loading or unloading, or combinations of both procedures. This implication was verified by direct measurement of $PaCO_2$ (Fig. 2). In three of the sheep, changes in $\dot{V}A$ secondary to changes in $\dot{V}CO_2$ were achieved with little or no change in $PaCO_2$; whereas in the fourth sheep increases in $\dot{V}A$ above the control value were progressively hypercapnic.[1] However in each of the sheep the relationship between $\dot{V}A$ and $PaCO_2$ could be described by a single function. Simultaneous measurements of arterial pH reflected the changes in $PaCO_2$ (when present), and indicated that the levels of exercise used in the study

[1] Although the relationship between $\dot{V}A$ and $\dot{V}CO_2$ in sheep 4 could be described by a linear function (Fig. 1), the relationship was in fact slightly alinear at the higher values of $\dot{V}CO_2$, with $\dot{V}A$ increasing proportionately less than $\dot{V}CO_2$. Because $PaCO_2$ varies inversely with $\dot{V}A$ ($PaCO_2 = k \cdot \dot{V}CO_2/\dot{V}A$), the slight alinearity in the $\dot{V}A/\dot{V}CO_2$ relationship resulted in the progressive hypercapnia that developed in sheep 4 at the higher levels of $\dot{V}A$.

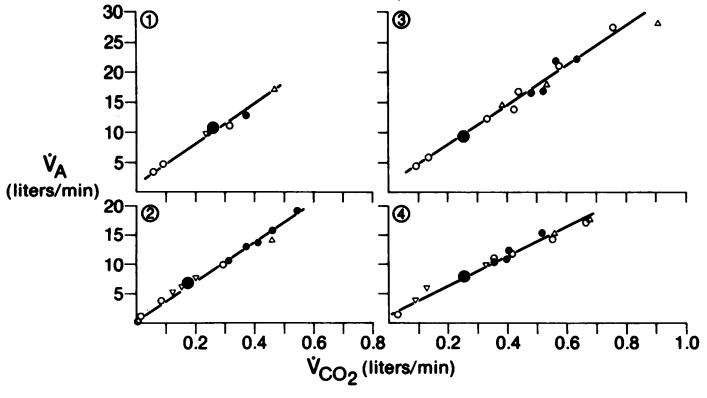

FIGURE 1 Response of alveolar ventilation ($\dot{V}A$) to changes in the rate of CO_2 production ($\dot{V}CO_2$), induced by exercise alone (●); venous CO_2 loading or unloading alone (○); venous CO_2 unloading plus exercise (▽); venous CO_2 loading plus exercise (△). Large solid circle represents control value. Each panel represents a different sheep.

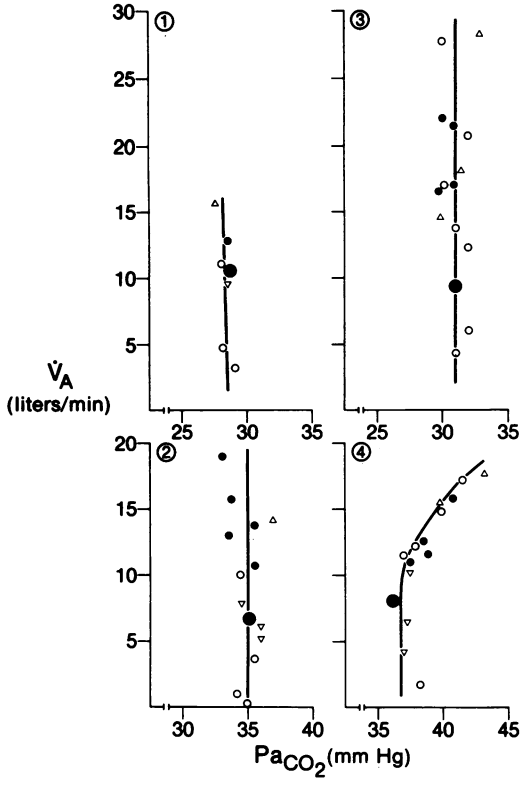

FIGURE 2 Relationship of alveolar ventilation ($\dot{V}A$) and arterial CO_2 pressure ($PaCO_2$), as the rate of CO_2 production was changed by exercise alone (●); venous CO_2 loading or unloading alone (○); venous CO_2 unloading plus exercise (▽); venous CO_2 loading plus exercise (△). Large solid circle represents control value. Data derived simultaneously with data of Fig. 1, and panel numbers correspond to those in Fig. 1.

were below those associated with increased anaerobic metabolism and development of metabolic acidosis (3). PaO_2 remained in the normoxic range (85 to 105 mm Hg) throughout all procedures in the four sheep, and

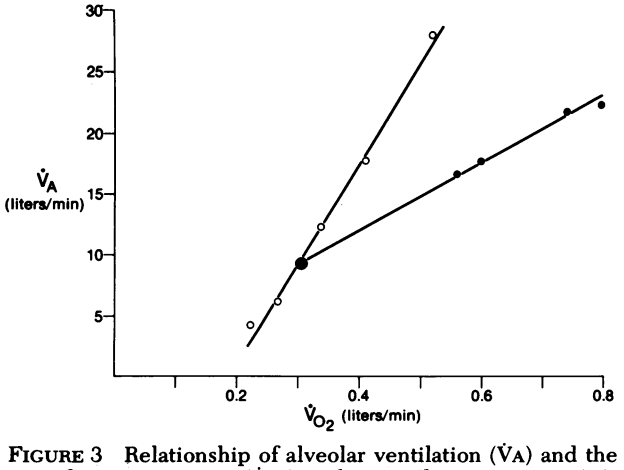

FIGURE 3 Relationship of alveolar ventilation ($\dot{V}A$) and the rate of O_2 consumption ($\dot{V}O_2$) in sheep 3, during exercise (●); and during venous CO_2 loading or unloading (○). Large solid circle represents control value.

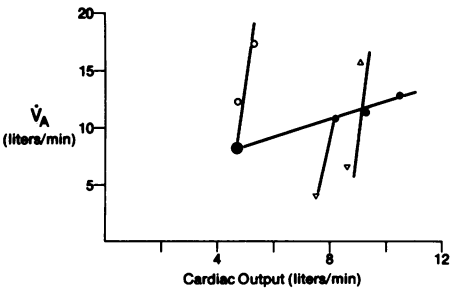

FIGURE 4 Relationship of alveolar ventilation ($\dot{V}A$) and cardiac output in sheep 4, during exercise (●); venous CO_2 loading (○); exercise plus venous CO_2 unloading (▽); exercise plus venous CO_2 loading (△). Large solid circle represents control value.

in any one animal did not vary by > ±6 mm Hg about the control value.

In contrast to the unique relationship between $\dot{V}A$ and $\dot{V}CO_2$, no such relationship could be demonstrated either between $\dot{V}A$ and $\dot{V}O_2$ (Fig. 3), or between $\dot{V}A$ and cardiac output (Fig. 4). In particular, changes in $\dot{V}A$ as a result of venous CO_2 loading or unloading were achieved with considerably less change in $\dot{V}O_2$ and cardiac output than were comparable changes in $\dot{V}A$ as a result of exercise. Similarly, the changes in $\dot{V}A$ could not be attributed to changes in mixed venous blood gas pressures (Fig. 5), pH, or oxygen saturation. In fact, the same $\dot{V}CO_2$ and $\dot{V}A$ could be achieved by the combination of a high mixed venous PCO_2 and low cardiac output (venous CO_2 loading); or a lower mixed venous PCO_2 and higher cardiac output (exercise). Thus, the unique relationship between $\dot{V}A$ and

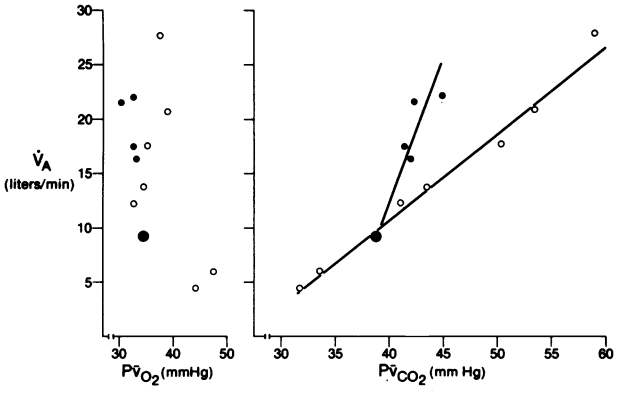

FIGURE 5 Relationship of alveolar ventilation ($\dot{V}A$) and mixed venous O_2 ($P\bar{v}O_2$) and CO_2 ($P\bar{v}CO_2$) pressures in sheep 3, during exercise (●); and during venous CO_2 loading or unloading (○). Large solid circle represents control value. $P\bar{v}O_2$ was relatively constant throughout the various procedures, except during venous CO_2 unloading, when the resulting decrease in $\dot{V}A$ necessitated simultaneous venous O_2 loading through the membrane lungs in order to maintain arterial PO_2 in the normoxic range.

$\dot{V}CO_2$ was not secondary to changes in either mixed venous P_{CO_2} or cardiac output per se.

DISCUSSION

The purpose of this investigation was to compare the ventilatory response to changes in $\dot{V}CO_2$ during exercise with the response to comparable changes in $\dot{V}CO_2$ elicited by infusion of CO_2 into the peripheral venous blood. The major finding of the study was that the relationship of $\dot{V}A$ to $\dot{V}CO_2$ was the same during exercise as during venous CO_2 loading. Therefore, we conclude that under the experimental conditions of this study, the hyperpnea of muscular exercise could be attributed to the increase in $\dot{V}CO_2$ elicited by exercise, and that there was no need to invoke obligatory nonmetabolic stimuli to account for the ventilatory response.

It has long been appreciated that there is a direct relationship between metabolic rate and ventilation during exercise (1–4). However, the problem in linking these two physiological variables has been that during mild to moderate exercise, ventilation can increase without a measurable change in classical metabolic respiratory stimuli (P_{CO_2}, P_{O_2}, pH) at their principal sites of chemoreception (aortic, carotid, and medullary chemoreceptors) (1–4). This paradox has resulted in a search for either other chemoreceptors or other (nonmetabolic) stimuli that might contribute to ventilation during exercise. The search for other chemoreceptors has focused on both the exercising muscles and on the mixed venous (i.e., pulmonary) circulation; but to date no convincing physiological or histological evidence of such receptors has been produced (4). Furthermore, the present data argue against a role for tissue chemoreceptors, since the ventilatory response to venous infusion of CO_2 was the same as the response to exercise. The data also indicate that changes in $\dot{V}A$ were not a unique function of mixed venous P_{CO_2} or P_{O_2} (or pH or oxygen saturation), and therefore suggest that receptors in the pulmonary circulation were not critical to the response. The search for alternate (i.e., nonmetabolic) drives to breathing during exercise has focused principally on neural stimuli arising in the motor cortex or in the exercising limbs; and on thermal, hemodynamic, and humoral stimuli such as increased adrenal secretion of catecholamines (1–4). A variety of studies have demonstrated or implied a contribution by such stimuli to the hyperpnea of exercise under certain conditions (4–11); whereas other attempts to identify nonmetabolic respiratory drives during exercise have failed (4, 12–15, 32). The present findings do not exclude the possibility that such stimuli are capable of increasing ventilation under appropriate conditions. However, the findings indicate that nonmetabolic stimuli are not mandatory to account for the hyperpnea of exercise, and in particular for the isocapnic hyperpnea that is generally (1–4), but not always (32), a feature of mild to moderate levels of work. Rather, the findings indicate that the ventilatory response to exercise can be accounted for solely by the associated increase in $\dot{V}CO_2$ (Fig. 1), whether the response is isocapnic or hypercapnic (Fig. 2). This conclusion is in agreement with the concepts of exercise ventilation formulated by a number of previous investigators, particularly Bainton (32), and Wasserman and colleagues (16).

The present study has not identified the specific stimulus linking $\dot{V}A$ to $\dot{V}CO_2$ during exercise or venous CO_2 loading. Simultaneous changes in $\dot{V}O_2$, cardiac output, and mixed venous P_{CO_2} do not appear to be responsible (Figs. 3–5). Similarly, mean Pa_{CO_2} may not be increased, despite considerable increases in $\dot{V}A$ (Fig. 2), and is therefore unlikely to be the critical stimulus. An alternate possibility to account for the isocapnic hyperpnea is that of oscillation of Pa_{CO_2} about its mean value, as first suggested by Yamamoto and Edwards (17). It has been well documented that under normal conditions, Pa_{CO_2} and arterial pH oscillate during each respiratory cycle about their mean values (33, 34). The magnitude (and probably instantaneous rate) of such oscillations are increased when mixed venous-arterial P_{CO_2} differences are increased, such as during venous CO_2 loading (34, 35). It has not been established that such oscillations do in fact provide a stimulus to ventilation, but there is some experimental support for the possibility (36, 37). Furthermore, it is of interest that the oscillations in arterial P_{CO_2} and pH are detected by the carotid body chemoreceptors and reflected in their neural output, even under normoxic conditions (38–40). We have recently demonstrated in awake sheep that denervation of the carotid bodies abolishes the isocapnic hyperpnea of venous CO_2 loading and of muscular exercise (unpublished data). These latter observations indicate a major role for the carotid chemoreceptors in the response of $\dot{V}A$ to changes in $\dot{V}CO_2$, and suggest that differences in chemoreceptor activity among different subjects or animals may determine whether the response is isocapnic or hypercapnic (Fig. 2). In addition, the observations are compatible with the possibility that the response depends, at least in part, on chemoreceptor detection of oscillations in Pa_{CO_2} about its mean value. Clearly the precise identification of the specific CO_2-related stimulus linking $\dot{V}A$ and $\dot{V}CO_2$ is of the utmost importance, since it appears to be capable of producing the entire ventilatory response to exercise. In fact, as we have demonstrated recently, the stimulus is fundamental to the very generation of an effective respiratory rhythm even at rest (27).

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