Integration of cerebrovascular CO₂ reactivity and chemoreflex control of breathing: mechanisms of regulation, measurement, and interpretation

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Cerebral blood flow (CBF) and its distribution are highly sensitive to changes in the partial pressure of arterial CO₂ (PaCO₂). This physiological response, termed cerebrovascular CO₂ reactivity, is a vital homeostatic function that helps regulate and maintain central pH and, therefore, affects the respiratory central chemoreceptor stimulus. CBF increases with hypercapnia to wash out CO₂ from brain tissue, thereby attenuating the rise in central PCO₂, whereas hypocapnia causes cerebral vasoconstriction, which reduces CBF and attenuates the fall of brain tissue PCO₂. Cerebrovascular reactivity and ventilatory response to PaCO₂ are therefore tightly linked, so that the regulation of CBF has an important role in stabilizing breathing during fluctuating levels of chemical stimuli. Indeed, recent reports indicate that cerebrovascular responsiveness to CO₂, primarily via its effects at the level of the central chemoreceptors, is an important determinant of eupneic and hypercapnic ventilatory responsiveness in otherwise healthy humans during wakefulness, sleep, and exercise and at high altitude. In particular, reductions in cerebrovascular responsiveness to CO₂ that provoke an increase in the gain of the chemoreflex control of breathing may underpin breathing instability during central sleep apnea in patients with congestive heart failure and on ascent to high altitude. In this review, we summarize the major factors that regulate CBF to emphasize the integrated mechanisms, in addition to PaCO₂, that control CBF. We discuss in detail the assessment and interpretation of cerebrovascular reactivity to CO₂. Next, we provide a detailed update on the integration of the role of cerebrovascular CO₂ reactivity and CBF in regulation of chemoreflex control of breathing in health and disease. Finally, we describe the use of a newly developed steady-state modeling approach to examine the effects of changes in CBF on the chemoreflex control of breathing and suggest avenues for future research.

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REGULATION OF CBF WITH PARTICULAR FOCUS ON THE INFLUENCE OF \( P_{aCO_2} \)

The relative constancy of the overall craniospinal volume (203), the cerebrovascular anatomy, and the positional and delay differences of the cerebral circulation relative to the heart contribute to the complexity of intracranial hemodynamics (58, 119, 150, 151, 203) (Fig. 1). Control of cerebral perfusion is linked closely to regulation of intracranial volume; it comprises the arterial cerebrovascular bed, the large cerebral veins, and the processes associated with production and reabsorption of cerebrospinal fluid (70). According to Poiseuille’s law (122) (Eq. 1), CBF is determined by the cerebral perfusion pressure and the cerebrovascular conductance or its reciprocal, cerebrovascular resistance (2). Cerebral perfusion pressure is the difference between blood pressure at the level of the circle of Willis and intracranial pressure, and intracranial pressure, in turn, encompasses central venous pressure and the pressures within the cerebrospinal fluid (Fig. 1). The variable resistance to flow is encountered mostly in the cerebral arteriolar and capillary bed (58). In contrast, the large cerebral arteries and veins are dedicated to blood distribution and storage of blood volume and are, in principle, noncompliant and act merely as a conduit for the pulsatile arterial flow from the aorta to the brain (145). CBF is dynamically adjusted to changes in perfusion pressure, metabolic activity of the brain, humoral factors, and autonomic nerve activity (33). Figure 1 is a simplified diagram of these main regulatory or active mechanisms that interact to maintain \( O_2 \) supply matched to cerebral metabolic demand and protect the brain from changes in cerebral perfusion. This integrative model highlights the interdependence of CBF and many other variables through complex and likely nonlinear relationships. The highlighted areas represent the potential areas, direct and indirect, in which \( P_{aCO_2} \) may influence CBF. The major factors that affect CBF, with particular focus on the modulatory effects of \( CO_2 \), are described below and illustrated in Fig. 2 to highlight the directional influence of these factors on CBF.

**Influence of \( P_{aCO_2} \) on CBF: mechanisms of action.** It is well established that the cerebral vasculature is profoundly affected by \( P_{aCO_2} \) (30). The teleological relevance of the exquisite sensitivity of CBF to changes in \( P_{aCO_2} \) seems to be a vital homeostatic function that helps regulate and maintain central \( pH \) (38) and, therefore, affects the respiratory central chemoreceptor stimulus. The interaction between \( P_{aCO_2} \) and vasodilation/vasoconstriction is normally ascribed to occur at the level of the arterioles and the precapillary sphincters (18, 33, 58). Increased \( CO_2 \) results in a relaxation of the vascular smooth muscle of all cerebral vessels, although the small vessels are the most responsive (213). By contrast, the vasconstrictor effect of hypocapnia is unaffected by vessel size (213). The mechanism(s) behind these actions of \( CO_2 \) has not been entirely elucidated. Some evidence indicates that elevations in \( CO_2 \) and the concomitant change in \( pH \) activate \( K^+ \) channels in the vascular smooth muscle. In support of this, the cerebral endothelial cells express four classes of \( K^+ \) channels: inward rectifying \( K^+ \) channels, \( Ca^{2+} \)-activated \( K^+ \) channels, ATP-sensitive \( K^+ \) channels, and voltage-gated \( K^+ \) channels (99, 134). Of these, ATP-sensitive \( K^+ \) and voltage-gated \( K^+ \) channels are activated by a reduction in \( pH \) (21, 224), suggesting that their contribution to acidosis induced cerebral vasodilation (29, 99). Increases in the open probability of \( K^+ \) channels result in \( K^+ \) efflux and endothelial cell hyperpolarization (64, 89). Hyperpolarizing currents may then be transmitted to the underlying smooth muscle, via myoendothelial junctions (69), where they may elicit vasodilation secondary to closure of voltage-gated \( Ca^{2+} \) channels, a reduction in intracellular \( Ca^{2+} \), and vascular relaxation (89, 101, 134). Hyperpolarization can also be transmitted to neighboring endothelial cells by way of gap junctions, which allow the conduction of a hyperpolarizing current for long distances along the endothelium (89). Thus, \( K^+ \) channels, through their impact on the endothelium and vascular smooth muscle, play a role in coordinating vascular tone in upstream and downstream vessels.

An alternative, or possible complementary, means by which cerebral vasodilation may be mediated is via \( CO_2/pH \)-induced alterations in vasoactive factors. For example, \( CO_2 \)-mediated
cerebral vasodilation and a concomitant increase in CBF may be evoked by the shear stress-mediated release of vasodilatory agents such as nitric oxide (NO) and prostaglandins (107, 153). Evidence for a potential involvement of several other vasodilators, including adrenomedullin and C-natriuretic peptide, a potential candidate for the unknown endothelium-derived hyperpolarizing factor (37, 39), is indirect (157). A recent study in our laboratory examined the cerebral release of a number of these potential candidates in otherwise healthy humans. The findings supported a role for NO and a lesser role for C-natriuretic peptide. Interestingly, the role of NO-mediated cerebral vasodilation in response to hypercapnia, but not hypocapnia, is in agreement with findings from studies of other animals and humans, although this was the first study to directly quantify NO release (as indexed by plasma nitrate) in the human brain. The extent to which NO acts in an obligatory or permissive manner is not known, but it is clear that the role of vasoactive factors is highly complex (82, 189).

Regardless of the underlying mechanism, the time course of the response of the cerebral pial (resistance) vessels to alterations in pH is relatively rapid, with changes in diameter occurring within 10 s, independent of the resting vessel diameter (58). Early reports in humans (181) indicated that the CBF response started within 30 s of the beginning of CO2 inhalation and that ~2 min were required to reach peak values (60). More recent studies (165, 166), consistent with direct microscopic observation of vessels by a cranial window technique, incorporating transcranial Doppler (TCD) and more sophisticated methods to manipulate end-tidal gases, demonstrated that the CBF response to step changes in CO2 in humans was much faster (6 s delay) than that documented in the early reports.

Arterial PO2. The role of arterial PO2 (PaO2) in the day-to-day regulation of CBF seems to be minor, reflected in the findings that, depending on the prevailing PaCO2 (15), a drop in PaO2 below a certain threshold (<40 mmHg) is required for cerebral vasodilation (73). However, although hypoxia per se is a cerebral vasodilator, reflected in a rise in CBF in proportion to the severity of isocapnic hypoxia (41, 225), under normal conditions the hypoxia-induced activation of peripheral chemoreceptor activity leads to hyperventilation-induced lowering of PaCO2 and subsequent cerebral vasoconstriction. Therefore, the cerebrovascular bed receives conflicting signals during exposure to acute hypoxia. The role of PaO2 becomes important on ascent to high altitude (8, 9) and possibly during hypoxemia associated with chronic lung disease (22).

Cerebral autoregulation. Cerebral autoregulation (CA) adjusts cerebral arteriolar caliber, or cerebrovascular resistance, to ensure that CBF levels are matched to metabolic needs, and it comprises two main components: static and dynamic. Static CA keeps CBF constant over gradual and progressive changes in cerebral perfusion (155). Dynamic CA refers to the rapid regulation of CBF in response to changes in arterial blood pressure (BP) that occur in a few seconds (229). Control mechanisms for dynamic CA may differ from those for static CA (45), and data indicate that neural control of cerebral circulation may be more effective under dynamic than steady-state conditions (229). Although the actual range of BP in which CBF is maintained is variable between subjects (104) and was originally based on steady-state CBF data points under different conditions presented in previous publications (104), there have been a number of reports of the influence of CO2 on CA. For example, whereas mild hypercapnia has been shown to impair dynamic CA as estimated by the thigh cuff deflation method (3) and transfer function analysis (10, 24, 150, 228), relative hypocapnia has variable effects on dynamic CA (10, 57, 130). The important point is that if hypercapnia does impair CA, hypercapnia-induced elevations in BP may influence CBF and thereby “mask” the true interpretation of cerebrovascular CO2 reactivity (see Analysis and curve-fitting considerations).

Sympathetic nerve activity. Although the cerebral circulation is richly innervated with sympathetic nerve fibers, the effect of sympathetic nerve activity (SNA) on the regulation of CBF remains controversial (206). The traditional view is that increases in sympathetic activity appear to have a limited effect on the cerebral vasculature of humans, particularly at rest (16, 76). It seems likely that any potential influence of SNA on CBF regulation is masked by the other more powerful regulatory influences on CBF: autoregulation, cerebrovascular CO2 reactivity, and, potentially, cardiac output (Q˙) (110, 195, 206). Recently, however, elegant animal studies incorporating continuous recording of SNA in the superior cervical ganglion (35) concluded that SNA directed to cerebral vessels increases with acute hypertension, but not hypotension, suggesting that it serves a protective function for the cerebral microcirculation, and not a regulatory role for maintenance of systemic arterial pressure. In addition to the influence of SNA on CA (143, 229), there are reports that sympathetic activity influences the reactivity of CBF to PaCO2 (44, 94). Thus, although the influence might be regarded as minor, CO2-induced elevations in SNA have the potential to affect CBF by direct and indirect mechanisms (Figs. 1 and 2).

Cerebral metabolism. The O2 supply to the brain depends on the arterial O2 content and the CBF. Cerebral O2 consumption in normal, conscious, young humans is ~3.5 ml·100 g brain⁻¹·min⁻¹ (172). The rate of O2 consumption of the entire brain of average weight (1,400 g) is therefore ~49 ml O2/min. The magnitude of this rate can be appreciated more fully when it is compared with the average metabolic rate of the whole body, ~250 ml O2/min in the basal state for a 70-kg man. Therefore, the brain, which represents only ~2% of total body weight, accounts for ~20% of the resting total body O2 consumption. Previous studies in humans have shown that cerebral O2 consumption was unchanged with alterations in PaCO2 in the

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**Fig. 2. Directional influence of major factors involved in regulation of CBF. BP, blood pressure; SNA, sympathetic nerve activity.**
range comparable with those measured during cerebrovascular reactivity testing (97, 114, 212). The unchanged cerebral metabolic \( \text{O}_2 \) consumption can be maintained via the increases in \( \text{O}_2 \) extraction.

**Systemic factors.** Although the classical notion is that CBF is maintained over a range of BP, it has more recently been established that CBF is also dependent on \( Q \) (85, 142, 205; for review see Ref. 177). Thus, because SNA and heart rate (HR) are altered during \( Q \) reactivity testing, subsequent changes in \( Q \) may theoretically influence CBF. It should be acknowledged, however, that it is not clear whether these changes in \( Q \) would have direct effects on CBF independent of changes in cerebral perfusion pressure. Although this idea is supported indirectly, it remains counterintuitive, because, according to Poiseuille’s law (Eq. 1) (122), blood flow is the quotient of perfusion pressure and vascular resistance, and changes in \( Q \) are not variables of the equation (202)

\[
F = \frac{(P_1 - P_2)\pi r^4}{8\mu L}
\]

where \( F \) is flow; \( P_1 \) is inflow pressure, \( P_2 \) is outflow pressure, \( r \) is radius, \( \mu \) is viscosity of the fluid, and \( L \) is length (122).

Previous studies, however, have reported a positive relationship between \( Q \) and CBF at normothermia during rest and exercise (83, 142). For example, increases or decreases in \( Q \) with volume expansion or application of lower body negative pressure, respectively, altered CBF velocity in a linear fashion with volume expansion or application of lower body negative pressure. Nonetheless, the mechanism by which \( Q \) affects CBF is unknown, nonneural, flow-mediated mechanisms have been suggested (227). For instance, shear stress related to increasing pulsatile pressure and/or blood flow may modulate the steady-state pressure-flow relationship of the cerebral circulation (173). This may occur via the release of shear stress response cerebrovascular endothelial cells, which in turn results in a decrease in cerebrovascular resistance in the arterioles and elevates CBF (173, 202). Together, although acknowledging that the mechanisms have not been clearly delineated, these findings suggest a direct effect of changes in \( Q \) on CBF.

**CEREBROVASCULAR REACTIVITY TO \( \text{CO}_2 \)**

The term cerebrovascular \( \text{CO}_2 \) reactivity reflects an “index” of the ability of the cerebrovascular bed to dilate or constrict in response to changes in \( \text{Paco}_2 \). For more than 20 years, TCD has been used extensively to study CBF regulation and cerebrovascular \( \text{CO}_2 \) reactivity in otherwise healthy subjects as well as in patients with various forms of cerebrovascular disease. For example, the measurement of cerebrovascular reactivity to \( \text{CO}_2 \) has been applied in clinical practice to evaluate cerebrovascular function [e.g., in patients with carotid artery stenosis (216), hypertension (179), stroke (217), and heart failure (221)], and a related impairment has been linked to cerebral ischemic events (217). Interestingly, links between systemic endothelial function and cerebrovascular \( \text{CO}_2 \) reactivity have been reported (14, 81, 105), indicating a common pathway between these responses. Since TCD measures flow velocity, and not CBF per se, only assessment of changes in flow, rather than absolute values, can be made. Nevertheless, research indicates that middle cerebral artery (MCA) blood flow velocity (MCAv) is a reliable and valid index of CBF (68, 100, 156, 178, 204). Moreover, since determinations of cerebrovascular reactivity are based on stimulus-response principles, absolute CBF values are not as important as reliable and repeatable recordings with short (beat-to-beat) time resolution. For this purpose, therefore, TCD is a well-suited technique in the experimental research and clinical settings. Before we review the evidence linking cerebrovascular \( \text{CO}_2 \) reactivity with ventilatory control, we first provide a discussion of the relevant aspects of cerebrovascular \( \text{CO}_2 \) reactivity to clarify its use, measurement, and related interpretation.

**Regional differences in cerebrovascular \( \text{CO}_2 \) reactivity.** Although there is marked variability in the literature for “normal” cerebrovascular \( \text{CO}_2 \) reactivity (see below), when derived as the average reactivity across the majority of the selected experimental studies, the “global” CBF reactivity to changes in \( \text{Paco}_2 \) is \( \sim 3.8\%/\text{mmHg} \) (72, 77, 95, 170) within the \( \text{Paco}_2 \) range of 35–55 mmHg. On closer examination, however, this reactivity is normally higher in the hypercapnic than hypocapnic range (43, 84, 221, 222). The mechanisms underlying this greater reactivity to hypercapnia than hypocapnia may be related to a greater influence of vasodilator than vasoconstrictive mediators on intracranial vascular tone (157, 199). From a teleological perspective, the normal lower reactivity in the hypocapnic than hypercapnic range might be a protective mechanism to prevent cerebral ischemia during transient drops in \( \text{Paco}_2 \), which are known to occur in a range of physiological (postural change and exercise) and pathophysiological (asthma, syncope, sleep apnea, congestive heart failure, and anxiety attacks) situations. In other words, maintaining oxygenation might be more important than \( \text{pH} \) disturbances. In addition, it is important to note that alterations in CBF reactivity to hypocapnia may be as important as hypercapnic reactivity for breathing stability, especially during sleep, when the wakefulness dive is absent and \( \text{Paco}_2 \) becomes the critical factor in maintaining rhythmic breathing (219).

It should be noted that, partly dependent on the method used to estimate CBF, there is marked inhomogeneity of cerebrovascular \( \text{CO}_2 \) reactivity (137, 160). For example, CBF reactivity is much higher in the gray matter than in the white matter. Thus, although TCD has many advantages because of the noninvasive nature of measurement and continuous recordings with high temporal resolution, TCD normally measures blood velocity in the MCA, an area that transports blood to large brain volumes, including gray and white matter, whereas sophisticated approaches, such as pulsed arterial spin labeling MRI, measure the reactivity of small vessels and capillaries within a purely cortical gray matter area, where hypercapnic \( \text{CO}_2 \) reactivity is much higher (114); potential regional differences in hypocapnic \( \text{CO}_2 \) reactivity have not been reported. Thus, because it is believed that changes in CBF are transmitted accurately to the MCA (1), it seems that the use of TCD may be described as more of an “average” indicator of CBF, whereas greater local resolution can be obtained using MRI.

In addition to the noted differences in cerebrovascular \( \text{CO}_2 \) reactivity between white and gray matter, there are marked regional differences of gray matter reactivity. A typical composite blood oxygenation level-dependent (BOLD) MR cere-
brovascular reactivity map in Fig. 3A shows several bilaterally symmetrical regions of negative reactivity (depicted in blue). Moreover, “negative” reactivity in cigar-shaped bands is apparent in the deep white matter of the centrum semiovale, in the white matter about the occipital horns of the lateral ventricles and, to a lesser extent, frontal horns in the genu and splenium of the corpus callosum, and in the posterior limb of the internal capsule. Comparable regional distribution during reactivity was confirmed with the use of composite arterial spin labeling MR (114) (Fig. 3B), indicating that the related changes are not confounded by CO2-induced changes in cerebral blood volume and cerebral metabolic rate of O2 consumption. Thus, an emerging concept is that, even in healthy young subjects, the cerebrovascular CO2 reactivity may reduce blood flow to these regions in its attempt to maintain flow elsewhere in the brain (114). This differential response has aptly been called a “steal” phenomenon. Although this steal phenomenon occurs in those regions where elderly patients most frequently develop white matter disease, or leukoaraiosis (74, 114), and is a strong and independent risk factor for ischemic stroke, it is not clear whether this response might affect ventilatory control.

Regardless of the aforementioned regional difference, it is clear that cerebrovascular CO2 reactivity is influenced by the degree of wakefulness and subsequent neuronal activity. For example, compared with wakeful rest, cerebrovascular CO2 reactivity is reduced during sleep (124) and elevated during exercise (144, 168). These changes are illustrated in Fig. 4. Moreover, recent reports indicate that CBF (14, 42, 43) and cerebrovascular CO2 reactivity show a pronounced circadian rhythm, with low CBF and cerebrovascular CO2 reactivity evident in the early morning compared with late afternoon. The potential implications of these sleep- and circadian-related alterations in CBF reactivity may be underscored by the common (10–40%) nighttime occurrence of strokes (20, 191) and the marked peak of these events in the early morning (115, 118).

Local regulation of cerebrovascular CO2 reactivity. The bulk of cerebrovascular CO2 reactivity occurs within the small arterioles and capillaries, whereas large arteries and veins are dedicated to blood distribution and storage of blood volume. This concept reflects the general notion that arterioles control the majority of cerebrovascular resistance but hold only a minority of total cerebral blood volume. In reality, however, there are no strict borderlines between vessel types based on size, structure, or function, which change smoothly between arterial and venous macro- and microcirculation. It should also be noted that reactivity is not necessarily an active phenomenon (18, 158), either in reactive or counterreactive fashion, but may be combined with possible passive vasodilation due to changes in downstream transmission of intravascular pressure. Also, changes in the number of perfused and nonperfused vessels within the capillary compartment, known as capillary recruitment, have been hypothesized.

METHODOLOGICAL CONSIDERATIONS IN THE ASSESSMENT OF CEREBROVASCULAR REACTIVITY TO CO2

For meaningful physiological interpretation, there are a number of critical considerations about the different means by which cerebrovascular (and ventilatory) responsiveness to CO2 can be assessed. The following is not intended to mandate the details of a particular experimental setup and the testing conditions; rather, we emphasize selected principles of testing that should be followed to enhance comparisons, reproducibility, and accuracy of data collection.

Steady-state vs. rebreathing techniques. A critical consideration in the assessment of cerebrovascular CO2 reactivity is whether to use steady-state or rebreathing techniques (Figs. 5–7). We believe that the rationale for using a steady-state or rebreathing method (or both) should firmly reflect the experimental question that is to be addressed. For example, the incremental change in brain tissue Pco2 is less during a steady-state change in Paco2 than during rebreathing (65, 157); conversely, during rebreathing, any Pco2 gra-
ventilatory sensitivity to \( \text{CO}_2 \), the change in medullary \([\text{H}^+]\) will depend on the extent of cerebrovascular reactivity, an unpredictable response. Unfortunately, at least in humans, it is not possible to make continuous measurements of the medullary (or venous) \([\text{H}^+]\); therefore, marked variability will also exist. There are a number of different ways in which steady-state and rebreathing techniques are assessed (see above).

**Practical considerations.** In addition to consideration of the most appropriate change in \( \text{PaCO}_2 \) and related means to best “fit” the relationship with CBF (see Analysis and curve-fitting considerations), various factors are known to affect CBF and CBF-CO\(_2\) reactivity; therefore, consideration of such influencing factors is critical to improve reproducibility and accuracy in experimental design. Established influencing factors include hydration (63), temperature, diet, caffeine (159), time of day (14, 42, 43), alcohol (25), prior exercise (113, 131), posture (121), age and sex (12), and extent of collaterals with completeness of the circle of Willis (208). Although it is established that changes in \( \text{PaCO}_2 \) per se will not alter cerebral O\(_2\) consumption (97, 114, 212), reports indicate that visual stimulation may profoundly influence CBF and cerebral O\(_2\) consumption (51, 95); therefore, care should be taken to ensure that subjects receive no visual stimulation during cerebrovascular CO\(_2\) reactivity tests. Various medications such as angiotensin-converting enzyme inhibitors and statin may influence normal cerebrovascular responsiveness to changes in \( \text{PaCO}_2 \) (175, 209).

**End-tidal, arterial, or brain \( \text{Pco}_2\)?** In most instances, CBF reactivity is expressed as the percent change in CBF per mmHg change in \( \text{PaCO}_2 \), or end-tidal \( \text{Pco}_2 \), obviating the more invasive \( \text{PaCO}_2 \) measurement. The tight correlation between the percent change in MCAv (54, 84, 117) measured by TCD ultrasonography during end-tidal \( \text{Pco}_2 \) variations has encouraged the use of TCD ultrasonography to measure CO\(_2\) cerebrovascular reactivity. However, several considerations are important when \( \text{PaCO}_2 \) (or end-tidal \( \text{Pco}_2 \)) is used to investigate CBF reactivity.

First, end-tidal \( \text{Pco}_2 \) has been shown to underestimate \( \text{PaCO}_2 \) at rest and to overestimate \( \text{PaCO}_2 \) during hypercapnia (156) and exercise (93). Such alterations in the \( \text{PaCO}_2 \)-end-tidal \( \text{Pco}_2 \) relationship may have implications for the true representation and physiological interpretation of cerebrovascular reactivity to \( \text{CO}_2 \). To address these inaccuracies, regression equations using end-tidal \( \text{Pco}_2 \) and tidal volume have been formulated to provide an estimate of \( \text{PaCO}_2 \) during exercise (93) and during hypercapnia (156) to compensate for the overestimation of \( \text{PaCO}_2 \) by end-tidal \( \text{Pco}_2 \). Results from studies using end-tidal forcing or fixed fraction of inspired \( \text{CO}_2 \) (Fi\(_{\text{CO}_2}\)) change without correction of end-tidal \( \text{Pco}_2 \) to \( \text{PaCO}_2 \) should therefore be treated with caution. Recently, however, prospective targeting of end-tidal \( \text{Pco}_2 \) with low gas flows, via a sequential gas delivery circuit, has been shown to adequately reflect \( \text{PaCO}_2 \) at rest and during various changes in end-tidal \( \text{Pco}_2 \) (86).

Another consideration is that, at least during steady-state testing, cerebrovascular reactivity to \( \text{CO}_2 \) might be even better expressed as a percentage of brain tissue \( \text{Pco}_2 \). For example, early work by Shapiro and colleagues (181) showed a higher correlation of jugular venous \( \text{Pco}_2 \) than \( \text{PaCO}_2 \) with the associated changes in CBF during elevations in \( \text{CO}_2 \), indicating that brain tissue \( \text{Pco}_2 \), rather than \( \text{PaCO}_2 \), provides a better correlate of the physiological stimulus. Conversely, during hypocapnia, experimental data indicate that \( \text{PaCO}_2 \) (or arterial wall \( \text{Pco}_2 \))
may have a more important role than jugular venous PCO2 (180). Recently, we reported that cerebrovascular CO2 reactivity in the hypercapnic and hypocapnic ranges was higher when presented against jugular venous PCO2 than PaCO2. This increase in jugular venous PCO2-CBF reactivity was higher in the hypercapnic than hypocapnic range (97% vs. 24%). It is tempting to speculate that these hypercapnic-hypocapnic reactivity differences may reflect a differential control of CBF via brain tissue PCO2 or PaCO2 during hypercapnia (65, 156, 222) and hypocapnia (135); however, although jugular venous PCO2 is likely to be a closer index of brain tissue PCO2 than PaCO2 (10, 65, 156, 182, 222), it is difficult to clarify the mechanisms involved with knowledge of only arterial-venous PCO2 gradients and no information related to the CO2 flux across the brain. Thus, considerations regarding the differences in end-tidal, arterial, and brain tissue PCO2 have important implications for the true representation and physiological interpretation of cerebrovascular CO2 reactivity.

Appropriate experimental change in PaCO2. In healthy subjects, an acute lowering of CBF is associated with mild symptoms of cerebral hypoperfusion. Mental confusion becomes prominent with 50–60% reduction, and cerebral oxygenation becomes affected (135); thus, for a “safe” range for human experimentation, hypocapnia should be \( <20 \) mmHg. Similar, marked subject discomfort is apparent with administration of \( >15 \) mmHg PaCO2 (10, 65, 156, 182, 222), it is difficult to clarify the mechanisms involved with knowledge of only arterial-venous PCO2 gradients and no information related to the CO2 flux across the brain. Thus, considerations regarding the differences in end-tidal, arterial, and brain tissue PCO2 have important implications for the true representation and physiological interpretation of cerebrovascular CO2 reactivity.

Analysis and curve-fitting considerations. Steady-state cerebrovascular CO2 reactivity testing (Figs. 5, 6, and 8) has been assessed by least squares linear regression (165, 166, 207), biasymptotic curve analysis (i.e., a tangent-hyperbolic function) (117), a dynamic single-compartment model (165, 166, 207), and an exponential function (56, 59, 60, 77, 125, 152). In addition, with a steady-state change in end-tidal PCO2, the speed (or onset response) of CBF velocity at the transition period of on- and off-CO2 administration can be assessed (165,
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Fig. 7. Typical recording of baseline, hyperventilation, rebreathing, and recovery in 1 subject. HR, heart rate; MSNA, muscle SNA. Note significant increases in ABP and MSNA, concurrent with increase in CBFV during rebreathing. Arrows indicate start and end of hyperventilation and rebreathing periods. Note 1) equilibrium between fraction of inspired CO2 and end-tidal PCO2 (PETCO2) during rebreathing and progressive rise in PETCO2 and 2) progressive increase in MSNA and mean ABP during rebreathing. [Modified from Claassen et al. (40).]

166, 221); the physiological meaning of this response, however, is unclear. Indeed, recent experimental results from our laboratory indicate that the initial CBF response to a step change in PaCO2 is a highly complex response with marked inrasubject variability (Fig. 6).

Numerous studies have also used linear regression to assess CO2 reactivity during modified rebreathing tests (5, 6, 8, 15, 19, 43, 63, 96, 105, 124, 157, 171, 181, 221, 222) (Figs. 5 and 8). However, more research exploring the physiological characteristics of cerebrovascular CO2 reactivity has demonstrated that the relationship between PaCO2 and CBF is nonlinear and might be affected by CO2-induced changes in arterial BP (Fig. 7) (71, 94). On closer examination, during hypercapnia, increases in SNA and HR are well documented, whereas variable changes in BP have been reported. Some studies report an increase (40, 56, 125, 152), while others report no change (71, 94). Methodological differences in duration and intensity of hypercapnia and in the measurement of BP may partly explain the discrepancies between studies.

In addition, the control mechanisms that govern the responses of CBF and arterial BP to CO2 have dynamic properties (40, 125, 126). These studies, among many others, have quantified cerebrovascular CO2 reactivity using linear regression of steady-state responses of CBF to changes in CO2, without incorporation of the effects of BP. The likely reason for this simplicity is that well-controlled experiments and complex modeling methods may not be practical for clinical use (40). To account for the nonlinear CBF-end-tidal PCO2 relationship, the use of cerebrovascular conductance index during this process may reveal direct effects of changes in arterial BP on CBF, leading to a more precise estimation of cerebrovascular CO2 reactivity based on the cerebrovascular conductance-end-tidal PCO2 relationship (40). Despite the mixed reports of the influence of BP, the direct influence of SNA or indirect influence of increases in HR on elevating Q may also influence cerebrovascular CO2 reactivity (see above). For example, even when cerebrovascular CO2 reactivity is expressed using cerebrovascular conductance, the potential influence of SNA is important. Some studies have suggested that increases in SNA attenuate the rise in CBF associated with hypercapnia (44, 94), whereas others have shown no modulating effect (108, 167). More recently, in the highly controlled lamb model, it has been reported that cerebral SNA is withdrawn during rapid-eye-movement (REM) sleep, and, therefore, the CBF response to hypercapnia is augmented (34). Thus, although the influence might be regarded as slight, CO2-induced elevations in SNA have the potential to affect CBF by direct and indirect mechanisms. Moreover, although the modified rebreathing technique may be advantageous in revealing the effects of BP on cerebrovascular reactivity, the lack of sustained (15-s) periods of hypocapnia may preclude useful information gained from assessment of reactivity in the hypocapnic range.

CHEMOREFLEX CONTROL OF BREATHING: INFLUENCE OF CBF

General organization. Breathing is stimulated via a chemoreflex arc, which includes the central and peripheral chemoreceptors, the central nervous system, and the respiratory muscles. The chemoreflexes form the feedback part of a negative-feedback loop (Fig. 9). The loop is completed by the forward part, in which alveolar ventilation controls the uptake of O2 and elimination of CO2. The forward part of the loop relates the dependence of PCO2 and PO2 on ventilation, and, as the alveolar air equation states, the product of ventilation and alveolar PCO2 is proportional to the amount of CO2 eliminated; hence, in any steady metabolic state, PCO2 depends on CO2 production divided by alveolar ventilation (52). This rectangular hyperbolic relationship is referred to as the metabolic hyperbola. PCO2 is the major factor controlling the [H+] sensed by the chemoreceptors, but acid-base status is also involved (Fig. 8). Stimulation of the chemoreceptors results in an increased alveolar ventilation, which results in an increased elimination of CO2 and a fall in PCO2 and [H+] stimulus at the chemoreceptors, hence, the negative-feedback designation of the system.

Central chemoreflex. The central chemoreceptors are stimulated by the [H+] of their local environment in the medulla (scattered within and near the ventrolateral surface of the medulla) (129, 132). Since [H+] is directly dependent on the Pco2 of chemoreceptor tissue, they are often thought of as CO2 receptors, but this simplification can be misleading. Although CO2 passes freely across the blood-brain barrier, H+ ions do not; therefore, central [H+] may differ from arterial [H+]. As a consequence, medullary acid-base conditions determine the Pco2-[H+] relationship at the central chemoreceptors, and the central chemoreceptors are isolated from arterial acid-base disturbances, except as they involve changes in Paco2. The control of central acid-base status to keep central [H+] at normal values may result in differences in the Pco2-central [H+] relationship.
that shift the central chemoreflex ventilatory response to CO₂ (52).

Central PCO₂ is determined by three factors, PaCO₂, medullary CO₂ production, and medullary blood flow, varying directly with PaCO₂ and inversely with medullary blood flow. The time constant for change in central PCO₂ is \( \tau \approx 100 \) s (medullary volume/blood flow), so a full response to any alterations in PaCO₂ and medullary blood flow by central PCO₂ requires \( \approx 5 \) min (3 time constants). Models of the drive to breathe from the central chemoreceptors (Fig. 10) assume that central neural drive increases linearly with \([H^+]\) above a chemoreceptor threshold \([H^+]\) with a constant slope (sensitivity); therefore, sensitivity and threshold determine the response to any particular stimulus.

**Peripheral chemoreflex.** The peripheral chemoreceptors, located in the carotid bodies at the bifurcation of the carotid arteries, are stimulated by arterial \([H^+]\) and hypoxia. They "taste" the blood approaching the brain, signaling the respiratory controller in the medulla via the carotid sinus nerve (a branch of the glossopharyngeal or IXth cranial nerve) (87, 88). In the same way as for the central chemoreceptors, acid-base conditions, in this case in the arterial blood, determine the PaCO₂-[H⁺] relationship at the peripheral chemoreceptors.

Models of the drive to breathe from the peripheral chemoreceptors (Fig. 11) assume that the neural drive to breathe from peripheral chemoreceptors increases linearly with \([H^+]\) above a chemoreceptor threshold \([H^+]\) with a constant slope (sensitivity); therefore, sensitivity and threshold determine the response to any particular stimulus. However, in contrast to the central chemoreceptors, the sensitivity of the peripheral chemoreflex response to \([H^+]\) also depends on PaO₂. Thus, hypoxia acts by increasing the peripheral chemoreceptor response to \([H^+]\); therefore, the receptors are maximally stimulated by a
simultaneous increase in $[H^+]$ and decrease in $PO_2$, in other words, by asphyxia (201).

Traditionally, the peripheral chemoreceptors have been assumed to be hypoxia sensors, driving ventilation independent of $[H^+]$. This assumption is misleading for acute changes; hypoxia affects the peripheral chemoreceptor drives to breathe, but its ultimate influence is strongly dependent on the prevailing $[H^+]$ (103). This aspect of the peripheral chemoreflex has two important implications: 1) hyperoxia reduces the peripheral chemoreflex sensitivity to $[H^+]$ to negligible values in many individuals, and 2) if $[H^+]$ is below the ventilatory recruitment threshold, there is little peripheral chemoreflex response to hypoxia (192). However, in the presence of prolonged continuous or intermittent hypoxia, the chemoreflex may undergo modifications (53).

**Chemoreflex control system.** The central and peripheral chemoreceptor neural drives to breathe sum within the medulla to provide the chemoreflex neural drive to breathe in humans (66, 127, 146, 183), but perhaps not in rats (46). Pulmonary ventilation is unaffected until the total neural drive exceeds a neural drive threshold; therefore, an increase in $PCO_2$ does not increase ventilation until a threshold $PCO_2$ has been exceeded, referred to as the ventilatory recruitment threshold (Fig. 12).
Above the ventilatory recruitment threshold, the ventilatory response to \( P_{CO_2} \) is usually linear, with a slope (sensitivity) varying with \( Po_2 \) (52, 127).

When \( Po_2 \) is high, the ventilatory response to \( CO_2 \) is due almost entirely to the central chemoreflex in many individuals, although for some a reduced peripheral response remains. When \( P_{CO_2} \) is below the ventilatory recruitment threshold, ventilation is maintained by the waking neural drive independent of the chemoreflexes, which reflects the “state” of the subject. It is referred to as the “waking neural drive,” because it is withdrawn during sleep (66, 146, 183). When this drive is lost during sleep, \( P_{CO_2} \) below the ventilatory recruitment threshold results in apnea; the apnea threshold and the ventilatory recruitment threshold are equal.

The graphic representation of the chemoreflex control of breathing is useful for predicting ventilation and \( P_{CO_2} \) under a variety of conditions. Figure 13 shows one example, that of an individual during sleep at altitude. In this case, the waking neural drive is absent, the peripheral chemoreflex drive is enhanced because of low \( Po_2 \), and the resting \( P_{CO_2} \) is decreased because of the lowering of the chemoreflex threshold with adaptation to altitude (10, 190). As a result, the individual’s equilibrium point is close to the apnea threshold, and, under these conditions, a small decrease in \( P_{CO_2} \) results in a loss of ventilation (52).

**Stability.** The stability of the chemoreflex control system is governed by the sensitivity or gain of the entire control loop, both forward and feedback (chemoreflex) portions (Fig. 9). Increases in loop gain are associated with instability (98, 226). As illustrated by a sleeping individual at altitude (Fig. 13, see Fig. 18), sleep also moves the equilibrium point to increasing \( P_{CO_2} \), which increases the ability of ventilation to change \( P_{CO_2} \); i.e., the sensitivity or gain of the forward part of the loop is increased. The chemoreflex sensitivity (feedback portion of the loop) is also increased due to the hypoxia, so that overall the loop gain, which is the combination of the forward and feed-forward gains, is increased, thereby reducing control system stability. It should also be noted that peripheral chemosensitivity plays a key role in breathing stability (50, 98, 147, 186, 220). Moreover, recent evidence from animal experiments emphasizes that brain tissue \( P_{CO_2} \) (46) may also affect peripheral chemosensitivity in a hypoadaptive manner (47). This possible link between central sleep apnea and CBF control is discussed further (see Role of the carotid bodies in breathing stability).

**Influence of CBF.** The effect of CBF control by \( P_{CO_2} \) should also be considered in an overview of the chemoreflex control of breathing; as \( P_{ACO_2} \) increases, CBF also increases and washes out \( CO_2 \) from brain tissue, reducing the central chemoreceptor stimulus. Any reduction in the sensitivity of CBF to \( P_{CO_2} \), therefore, increases the overall sensitivity of the central chemoreflex response to changes in \( P_{ACO_2} \) (222). On the other hand, if the sensitivity is high in an individual and CBF increases markedly with \( P_{CO_2} \), then the difference between central chemoreceptor \( P_{CO_2} \) and \( P_{ACO_2} \) declines as \( P_{ACO_2} \) increases. Measurement of sensitivity using a steady-state technique (128, 149), which measures the central chemoreflex ventilatory response and the effect of the CBF response, may provide a lower sensitivity of the ventilatory response of the central chemoreflex than the rebreathing technique (52), which measures only the central chemoreflex ventilatory response unaffected by CBF. Nevertheless, in many individuals, this effect is negligible (149).

**Methodological considerations.** Several components of the chemoreflex control system described above must be considered when tests are designed to assess the ventilatory responses to \( CO_2 \) and hypoxia. 1) The location of the central chemoreceptors in medullary tissue means that changes in \( P_{ACO_2} \), will not be fully expressed at the central chemoreceptors for \( \sim 5 \) min (3 time constants of 100 s); however, at least on the basis of two-compartment modeling data, central and peripheral chemoreceptors have a relatively short delay (\( \sim 12–24 \) and \( \sim 6–8 \) s, respectively) (43a). 2) Because hypoxia affects ventilation by changing the sensitivity of the peripheral chemoreflex to \( P_{CO_2} \), the ventilatory response to hypoxia depends on the choice of isocapnia; which is problematic for comparisons (185). 3) Because CBF changes with \( P_{CO_2} \) and hypoxia, the central chemoreceptor \( P_{CO_2} \), as well as its associated time constant, also changes; as a result, the ventilatory response to \( P_{ACO_2} \) may differ from the ventilatory response to brain tissue \( P_{CO_2} \).

These considerations and the fundamental issue of the experimental question dictate the protocol for testing. With consideration 2 in mind, evaluation of the chemoreflexes should consist of measuring the ventilatory responses to \( P_{CO_2} \) at several isoxic \( Po_2 \) levels. Two techniques may be used: steady state and rebreathing.

The steady-state ventilation response relates end-tidal \( P_{CO_2} \) and ventilation and, therefore, provides a measure of the chemoreflex sensitivity, which includes the effect of CBF in mitigating the central stimulus. Techniques such as end-tidal forcing with high gas flows (165, 166, 207) and prospective targeting with low gas flows (185) can be used to change end-tidal \( P_{CO_2} \) while maintaining isoxia. Expression of the full ventilatory response takes several minutes at each end-tidal \( P_{CO_2} \), and, for the isoxic hypoxic responses, care must be taken to limit the accumulated hypoxic exposure time to avoid...
hypoxic ventilatory decline. Obtaining several points on the response, therefore, takes time, and since only a few points on the response are measured, care must be taken to ensure that undetected nonlinearities, such as thresholds, do not affect the measurement of sensitivity (55, 128). With the range of PCO2 limited to hypercapnia, the ventilatory recruitment threshold is not measured, unless special techniques, such as assisted ventilation, are employed (220).

With the modified rebreathing method (52, 128), ventilatory response relates mixed venous PCO2 and ventilation and, therefore, provides a measure of the chemoreflex sensitivity and the ventilatory recruitment threshold without the effect of CBF in mitigating the central stimulus. This method is based on the rebreathing method of Read and Leigh (169) with two modifications. 1) A 5-min period of hyperventilation before rebreathing reduces the arterial and central PCO2 at the start, so that as PCO2 rises during rebreathing, the ventilatory recruitment threshold is discernible. 2) A controlled flow of O2 into the rebreathing bag maintains isoxia, and since the method measures the response within 5 min of hypoxia, it avoids hypoxic ventilatory decline.

The modified rebreathing method rapidly equilibrates arterial, alveolar, and rebreathing bag PCO2 to mixed venous PCO2 at the start of rebreathing and relies on the resting metabolic production of CO2 to slowly increase PCO2 over time; thus tissue PCO2, rather than inspired PCO2, drives the increase, and the slow dynamics of the central response in the latter case are absent. With breathing and Q providing the mixing, end-tidal PCO2, therefore, estimates PA,PCO2, and central PCO2, and the arterial-venous PCO2 difference is reduced sufficiently to negate any effects of CBF changes. However, the rebreathing method may overestimate the CO2 sensitivity if brain CO2 production is greater than whole body CO2 production and central CO2 increases faster than mixed venous CO2. Although modeling shows that this factor is negligible (169), direct experimental evidence for this assumption is lacking. For testing the sensitivity of the central chemoreceptors (i.e., to ensure a defined stimulus), the rebreathing technique is likely to be superior to the steady-state method; however, the latter is arguably less “physiological” in nature when blood gas perturbations are considered (i.e., during sleep apnea). Clearly, there are limitations with rebreathing and steady-state methods that should be considered in the design of the experimental question.

Methodological considerations for the integrated assessment of cerebrovascular and ventilatory control. The range of steady-state and rebreathing techniques have been reviewed for the assessment of cerebrovascular reactivity; many of the same issues apply for the assessment of ventilatory reactivity. It is clear that there are many advantages and disadvantages to the different testing regimens, and attempts at consensus have produced no uniform agreement. Furthermore, the nature of the integrative cerebrovascular and ventilatory responses requires additional comment. For example, as mentioned, with steady-state testing, there is always a PCO2 gradient between the brain tissue, arterial, and venous compartments; this gradient, in part, will be determined by the cerebrovascular and ventilatory reactivity. Therefore, results from steady-state tests of cerebrovascular reactivity that use a fixed change in FICO2 may be interpreted as “ventilatory dependent.” Since end-tidal clamping methods using end-tidal forcing (165, 166, 207) or prospective targeting with low gas flows (185) result in a fixed change in PCO2 independent of ventilation, the cerebrovascular reactivity is likely not to be influenced by related changes in ventilation, and the cerebrovascular reactivity results may be interpreted as “ventilatory independent.” During rebreathing, PCO2 gradients between arterial, venous, and brain tissue compartments are abolished; therefore, assessment of cerebrovascular reactivity with this method may be also be interpreted as ventilatory independent.

INTEGRATION OF CEREBROVASCULAR REACTIVITY TO CO2 AND THE CHEMOREFLEX CONTROL OF BREATHING

A close relationship between changes in CBF and ventilatory output has been shown in animal studies. Results of the first major study on the interrelationship between CBF and ventilation in anesthetized dogs reported in 1928 (176) showed that if CBF was increased from low levels, ventilation increased if the animals were hypoxic but decreased if the animals were breathing room air. It was suggested that the former response was indicative of removal of brain hypoxic depression by the increasing CBF, and the latter response (ventilatory depression) was a consequence of the removal of accumulated brain CO2 and acid metabolites. Other studies investigated the ventilatory responses to acute reductions of CBF by clamping the vertebral artery and/or the common carotid artery (78, 161). After total or partial reduction of CBF, ventilation is usually increased and, depending on the degree of CBF reduction, apnea may develop. However, although brain hypoxia and brain acidosis were evident in these studies, because the animals were anesthetized and the contribution of the carotid chemoreceptors to the ventilatory response was unknown, interpretation of these data is difficult.

Evidence for the increased sensitivity of ventilation to a change in PaCO2 by reduced CBF and cerebrovascular CO2 reactivity was first provided in highly controlled studies in the unanesthetized goat (36) (Fig. 14). This study demonstrated that when CBF was reduced by 30%, the cerebrovascular response was attenuated, whereas the ventilatory responsiveness to CO2 was increased. This observation suggests that CBF affects ventilation through modification of tissue PCO2 in the region of the medullary chemoreceptor area. With poor brain perfusion, the central chemoreceptor will sense a relatively higher [H+] for a given change of PaCO2, and will correspondingly trigger a more vigorous ventilatory response. However, when CBF was further reduced to 50%, which nearly abolished CBF-CO2 reactivity, there was a marked blunting of the minute ventilation (Ve)-PaCO2 response, possibly as a consequence of hypoxic depression of the respiratory neurons (36). Thus, on the basis of these animal experiments, there seems to be a threshold at which changes in CBF and cerebrovascular CO2 reactivity may lead to differential alterations in the ventilatory responsiveness to CO2.

Experimental evidence for the close relationship between changes in CBF and ventilatory control in humans is mostly based on early studies in a range of pathological conditions. For example, elevations in ventilatory CO2 responsiveness have been found primarily in clinical studies of patients with moderate cerebrovascular disease. Heyman et al. (79) used the steady-state method to determine ventilatory responsiveness to CO2 in a group of patients with chronic bilateral forebrain
In goats, the ventilatory response to CO₂ increased at 70% CBF but is more subject to potential artifacts induced by impairment (steady state vs. rebreathing), because the steady-state method was depressed at 50% CBF, indicating that severe brain ischemia blunts the CO₂ response.

In contrast, North and Jennett (136), using a rebreathing method, found that the ventilatory response to CO₂ was depressed in patients with severe cerebrovascular disease (136, 163, 215). Such changes likely reflect impairment of metabolism of respiratory neurons, as reflected in a marked decline in whole brain O₂ consumption in patients with severe brain ischemia (104). Collectively, on the basis of animal and human pathological studies, there seems to be a threshold at which changes in CBF and cerebrovascular CO₂ reactivity may lead to differential alterations in the ventilatory responsiveness to CO₂.

A number of related experiments utilizing TCD have speculated that a reduction of CBF-CO₂ reactivity may lead to subsequent alterations in ventilatory reactivity to CO₂ (7, 8, 14, 43, 63, 144, 156, 221). Specifically, these studies indicated that a reduced CBF-CO₂ reactivity results in an enhanced ventilatory sensitivity to CO₂ (measured using steady-state methods) via a CBF-related attenuation of brain [H⁺] washout and greater stimulus at the central chemoreceptors. Three important considerations arise: 1) Is there direct evidence for a role of cerebrovascular CO₂ reactivity in the ventilatory response to PaCO₂? 2) Does a change in ventilatory response to CO₂ affect cerebrovascular CO₂ reactivity? 3) Does the commonly used TCD-measured blood flow velocity in the MCA reflect blood flow in the vicinity of the central chemoreceptors?

Is there direct evidence for a role of cerebrovascular CO₂ reactivity in the ventilatory response to PaCO₂? Recent elegant studies have utilized powerful pharmacological manipulation of CBF-CO₂ reactivity to determine the influence of CBF reactivity per se on steady-state ventilatory responsiveness. The pharmacological intervention used in these studies was indomethacin, a potent reversible cyclooxygenase inhibitor that effectively decreases CBF and attenuates the cerebrovascular sensitivity to hypercapnia and hypocapnia (49, 61, 116, 193, 210, 214, 219, 222) without concomitant changes in metabolic rate (222) or plasma catecholamines (31, 61, 116, 193). Such acute reductions in CBF-CO₂ sensitivity result in an elevation in Ve-CO₂ sensitivity under steady-state testing conditions (221). Moreover, as recently discussed elsewhere (219, 222), the direct influence of indomethacin on ventilation (32) (via inhibition of prostaglandins) or the carotid body (90, 123, 218) seems negligible, and recent findings at sea level indicate that indomethacin has no measurable effect on peripheral chemosensitivity in response to transient hypoxia, hypercapnia, or hyperoxia (P. N. Ainslie, unpublished data). This feature makes indomethacin an ideal tool for investigating the effect of CBF on the control of breathing in humans (see Fig. 18; also see INSIGHT FROM MATHEMATICAL MODELING). Together, the aforementioned findings support the notion that cerebrovascular CO₂ reactivity plays a direct role in regulation of the ventilatory response to PaCO₂.

Does a heightened ventilatory response to CO₂ affect cerebrovascular CO₂ reactivity? Although it has not been clearly established, it seems reasonable to suggest that those individuals with a heightened ventilatory response to a step change in PaCO₂ (especially if the carotid bodies are sensitive to CO₂) will limit the increase in arterial and brain tissue PCO₂; therefore, the CO₂ stimulus should be somewhat less than a “low-Vₑ” responder.” The influence of alterations in ventilatory responsiveness on cerebrovascular CO₂ reactivity is likely to be most obvious when tested under conditions of a “steady-state” change in CO₂, rather than by the rebreathing method (see

Fig. 14. Ventilatory (Ve) and CBF responses to CO₂ at 100, 70, and 50% of control CBF in goats. Ventilatory response to CO₂ increased at 70% CBF but was depressed at 50% CBF, indicating that severe brain ischemia blunts the sensitivity of the ventilatory chemoreflex. [Modified from Chapman et al. (36).]
Methodological considerations for the integrated assessment of cerebrovascular and ventilatory control.

Does the commonly used TCD blood flow velocity in the MCA reflect blood flow in the vicinity of the central chemoreceptors? Important in the use of TCD is the issue that changes in MCAv reflect changes in the posterior circulation supplying the medulla (i.e., changes in CBF during CO2 reactivity are likely to cause changes in central chemoreceptor stimulation). As highlighted throughout this review, numerous efforts have been made to establish normal criteria for CO2 reactivity of the cerebral circulation by the use of TCD. Although there has been ample research involving normal values for the anterior half of the circle of Willis, mainly for the MCA, we have found few studies involving these values for the basilar artery (19, 67, 80, 96, 139, 148, 154). Nonetheless, these studies seem to support the notion that MCAv measurement is likely to reflect blood flow in the region(s) of the central chemoreceptors.

In summary, evidence from animal and human studies indicates that the effects of CO2 on CBF provide an important counterregulatory mechanism that serves to minimize changes in brain [H+], thereby stabilizing the breathing pattern in the face of perturbations in PaCO2 (27, 50). An inappropriate CBF response to a given change in CO2, in the hypercapnic or hypocapnic range, may lead to breathing instability, in particular, development of central sleep apnea (CSA).

CSA IN CONGESTIVE HEART FAILURE AND AT HIGH ALTITUDE

The pathogenesis of CSA, also referred to as Cheyne-Stokes respiration, in congestive heart failure and at high altitude remains incompletely understood (26, 28, 50, 109, 111). CSA is an abnormal periodic breathing pattern in which central apneas and hypopneas alternate with periods of hyperventilation that have a waxing-waning pattern of tidal volume that classically has been associated with severe decompensated heart failure (8, 174, 230). The key pathophysiological mechanism(s) leading to Cheyne-Stokes respiration is a fluctuation of PaCO2 above and below the so-called “apneic threshold” (50, 221). In addition to the common occurrence of CSA in patients with congestive heart failure and in healthy individuals after ascent to high altitude, periodic breathing during sleep is almost universal, occurring in >90% of humans (5). A reduction in cerebrovascular CO2 reactivity during wakefulness has been identified in patients with congestive heart failure and CSA; this reduction may affect stability of the breathing pattern (26, 28, 50, 109, 111). More recently, a comparable finding has been shown at high altitude (8). Such reductions in cerebrovascular responsiveness to CO2 that provoke an increase in the sensitivity or gain of the chemoreflex control of breathing may underpin breathing instability during CSA observed in patients with congestive heart failure and on ascent to high altitude (Fig. 15).

In patients with congestive heart failure, however, a number of destabilizing factors contribute to fluctuations in PaCO2. First, a low PaCO2, close to the apneic threshold predisposes to the development of central apneas (50); however, this will only occur if the resting PCO2 is decreased because the chemoreflex gain has increased. In support of this, a number of studies have reported that PaCO2 is lower in patients with congestive heart failure and Cheyne-Stokes respiration (75, 92, 112, 133, 198, 223). Naughton et al. (133) and Hanly et al. (75) found lower PaCO2 during wakefulness and non-REM (NREM) sleep in patients of comparable age, left ventricular ejection fraction, PaO2, and lung-to-chemoreceptor circulatory delay with congestive heart failure with Cheyne-Stokes respiration than in patients without congestive heart failure with Cheyne-Stokes respiration. All episodes of Cheyne-Stokes respiration starting during stage 2 sleep were almost always precipitated by hyperventilation in association with arousals from sleep. Furthermore, during Cheyne-Stokes episodes in stage 2 sleep, PaCO2...
fell on average by 1.5 mmHg, which mirrored a 23% rise in $V_E$ (223). A lower resting $P_{CO_2}$ can be the result of chemoreflex feedback gain increases and, also, chemoreflex threshold decreases; total loop gain (and thus stability) is determined in part by the balance of feedback and plant gain (50). For example, if feedback gain alone decreases the resting $P_{CO_2}$, the decrease in plant gain will offset the increase in feedback gain, so that loop gain increases only if the feedback gain increases more than plant gain decreases; if loop gain increases, then stability will be decreased (Fig. 15). Under this condition, a relatively small increase in ventilation would drive $P_{aCO_2}$ below threshold and trigger a central apnea (75). It is unknown how CBF and CBF-reactivity might be altered during sleep in congestive heart failure patients with and without CSA.

Patients with congestive heart failure and Cheyne-Stokes respiration have an unusual response to sleep, in that their $P_{aCO_2}$ levels do not increase in the progression from wakefulness to sleep (112), and, as a consequence, $P_{aCO_2}$ is lower to their apneic threshold during sleep (112). Lorenzi-Filho et al. (111, 112) abolished Cheyne-Stokes respiration in congestive heart failure patients by inhalation treatment with small concentrations of $CO_2$ delivered by a mask. Stabilization of breathing was achieved by a small (~2 mmHg), but significant increase, in transcutaneous $P_{CO_2}$. In contrast, supplemental $O_2$ was not able to raise transcutaneous $P_{CO_2}$ and had no significant impact on the frequency of Cheyne-Stokes respiration. This study reveals the critical importance of small variations in $P_{aCO_2}$: a decline in $P_{aCO_2}$ below the apneic threshold triggers central apneas and Cheyne-Stokes respiration. Arousal, through promotion of hyperventilation, appear to facilitate, rather than provoke, periodic breathing directly. More recently, we reported a reduction of cerebrovascular $CO_2$ reactivity at high altitude compared with low altitude and a greater decrease in CBF and loss of CA during sleep (8). The lowered CBF and impaired CA during sleep at high altitude may cause changes in central chemoreceptor stimulation and, thus, the apneic threshold, which potentially could promote the breathing instability at high altitude. This would seem especially likely if the reduced CBF-$CO_2$ reactivity, especially reductions in the CBF response to hypocapnia, during wakefulness also occurs during sleep. The critical role of the CBF response to hypocapnia during sleep has recently been reported (219). In support of this notion, a strong correlation was found between the severity of CSA and the change in CBF (8). In other words, at high altitude, subjects with the largest decrease in CBF during sleep had the highest number of central events per hour (Fig. 16), suggesting a link between central chemoreceptor stimulation and CBF. More recently, we extended these findings in a placebo-controlled, randomized design ($n = 12$), where indomethacin (100 mg po) and acetazolamide (10 mg/kg iv) were used during wakefulness and before sleep to alter CBF and cerebrovascular reactivity to $CO_2$ (11). These measures and blood gases were obtained before and during each intervention at sea level and high altitude (5,050 m, ~6 days of acclimatization). Sleep, including CBF monitoring, was studied using full polysomnography. Acetazolamide, relative to indomethacin, halved the frequency of CSA ($54 \pm 46$ vs. $101 \pm 28$ events/h, $P < 0.01$) and elevated MCAv more during NREM sleep. These results indicate that reductions in CBF and CBF-$CO_2$ reactivity play a key role in the pathogenesis of CSA at altitude (unpublished observations). Although acetazolamide-induced elevations in MCAv may also provide additional protection against development of CSA, we cannot dissociate this effect from its other known prophylactic benefits (91, 106, 197).

Interestingly, our ongoing studies have shown a potential difference in the influence of indomethacin between sea level and high altitude. For example, in contrast to the findings at sea level, administration of indomethacin (100 mg po) at 5,050 m increased the frequency of CSA during sleep (8). In summary, reductions in CBF and cerebrovascular responsiveness to $CO_2$, which provoke an increase in the sensitivity or gain of the chemoreflex control of breathing, may underpin breathing instability during CSA in patients with congestive heart failure and on ascent to high altitude. However, many other factors are also important in the development of CSA. The integration of these key factors and the related comparison between CSA in congestive heart failure and CSA at high altitude are illustrated in Fig. 15, which shows considerable overlap between the pathogenesis of CSA in congestive heart failure and CSA that develops as a consequence of exposure to high altitude. For example, the reduction in $CO_2$ reactivity results in larger changes in the [H$^+$] presented to the central chemoreceptors (50, 186, 222). The potential changes in CBF-$CO_2$ reactivity are not exclusive to hypercapnia; rather, a reduction in the CBF response to hypocapnia seems to be a critical response. For example, a ventilatory overshoot would lead to a greater fall in $P_{aCO_2}$ so the CBF response within the hypocapnic range (in the context of CSA) is probably more important (or at least equally important) during sleep than the CBF response within the hypercapnic range (219). However, it would seem likely that an inappropriate CBF response in either
range would promote breathing instability. Therefore, a reduced cerebrovascular response to CO₂ (to hyper- or hypocapnia) might directly increase the susceptibility for periodic breathing by increasing the central chemoreceptors’ contribution to loop gain. In support of this concept is the aforementioned study indicating that an indomethacin-induced alteration in the cerebrovascular response to CO₂ is sufficient to change the ventilatory response to CO₂ (Ainslie et al., unpublished observations; 62, 219, 222). However, changes in cerebral responsiveness to CO₂ may only be partly sufficient to destabilize breathing, inasmuch as the carotid bodies play a significant role in the rapid ventilatory response to CO₂ challenge (184, 187, 188) (see Role of the carotid bodies in breathing stability: interactions with central chemoreceptor stimulation and CBF). Finally, within the hypocapnic range, input from the central chemoreceptors would actually be reduced owing to a maintained CBF (from a reduced CBF sensitivity) (219).

**Role of the carotid bodies in breathing stability: interactions with central chemoreceptor stimulation and CBF.** Although we have emphasized the influence of CBF in determining the PCO₂ stimulus at central chemoreceptors, it is the degree of hypocapnia sensed at the carotid bodies that seems critical for the development of a central apnea, especially during NREM sleep (184, 187, 188). Moreover, the carotid bodies are an important determinant in breathing stability at rest through tonic inputs and, possibly, through compensation for a reduced central CO₂ sensitivity (50, 98, 147, 186, 220). However, there may be a marked degree of interaction between the peripheral and central chemoreceptors (46–48, 219). For example, elegant animal studies using an in situ dual-perfused preparation demonstrated that a single bout of hypoxia or hypercapnia elicited a larger phrenic response when the brain stem was held at 25 mmHg PCO₂ than at 50 mmHg PCO₂. More recently, this study was extended to show that the peripheral chemoreceptors were more responsive to the lower brain stem PCO₂, whether the peripheral chemoreceptors received stimuli that increased (hypercapnia or hypoxia) or decreased activation (hyperoxia or hypocapnia). These findings clearly demonstrate a negative interaction between brain stem and peripheral chemosensitivity in animals, and if such an interaction occurs in humans, it may contribute to increased controller gain associated with sleep-related breathing disorders. Moreover, because brain stem PCO₂ affects the degree of peripheral chemosensitivity (48), these findings again highlight the critical importance of CBF reactivity in determining the brain PCO₂. Thus it seems possible that the interactions of CBF reactivity that determine brain PCO₂ at the level of the central chemoreceptors might have a significant influence on peripheral chemosensitivity.

It is tempting to speculate that any conditions that result in chronic hypocapnia (e.g., congestive heart failure and high altitude) and related alterations in cerebrovascular CO₂ reactivity may result in different degrees of hypocapnia in the central and peripheral compartments and, subsequently, breathing instability. Consistent with this notion, Xie et al. (219) recently suggested that the predominant role of peripheral vs. central chemoreceptors in causing apnea may be explained, in part, by preservation of PCO₂ and [H⁺] at the central chemoreceptors by hypocapnia-induced cerebrovascular constriction. In their study, indomethacin-induced reduction of cerebrovascular CO₂ led to higher CBF during hypocapnia, leading to instability and related apnea (219). Another interpretation of these novel findings is that, after indomethacin administration, brain PCO₂ would likely be higher, and, therefore, on the basis of the aforementioned animal studies, the tonic input from the peripheral chemoreceptors would be less and, therefore, may affect breathing stability (48).

**EXERCISE**

The mechanism(s) subserving ventilatory control during exercise remain(s) controversial (17, 23, 164, 211); however, traditionally, these mechanisms are proposed to include elements of proportional feedback, central and carotid chemosensory, and feedforward systems, central command, and muscle reflex (211). Exercise increases ventilation via the respiratory chemoreflex and also modifies the ventilatory response to CO₂ (144); however, it remains unclear how exercise-induced alterations in the respiratory chemoreflex might influence dynamic CBF regulation, in particular, cerebrovascular reactivity to CO₂. This intriguing question has been examined in only two studies, which showed that, during exercise, cerebrovascular CO₂ reactivity at the operating point is enhanced (144, 168) (Fig. 4A). During such exercise, cerebrovascular CO₂ reactivity to hypercapnia has been shown to be elevated during exercise, whereas it was unchanged during hypocapnia (144). Meadows et al. (124) reported that sleep decreased cerebral CO₂ reactivity, suggesting that the level of cerebral activation influences the cerebrovascular reactivity to CO₂. Exercise-induced physiological changes (e.g., autonomic neural control) may also modify the cerebral CO₂ reactivity (4, 140). Ogoh et al. (144) reported that, under conditions of hypercapnia and exercise, the total respiratory loop gain was markedly reduced, whereas cerebrovascular CO₂ reactivity was increased. More recently (141), using exponential regression modeling, we extended these initial findings and examined the interaction between the onset responses of the respiratory chemoreflex and CBF at rest and during dynamic exercise. Our findings indicate that, at rest, the faster “washout” of CO₂ via hypercapnia-induced cerebral vasodilation results in a reduced activation of the central chemoreflex and subsequent slower onset response of V̇E. In contrast, during exercise, despite higher rates of increasing PaCO₂, there was no change in the onset response of CBF, and, therefore, reduced washout of CO₂ may act to augment the onset response of V̇E (141). Together, these findings indicate that, despite an attenuated chemoreflex system controlling ventilation, elevations in cerebrovascular reactivity might help maintain CO₂ homeostasis in the brain during exercise. The extent to which this relationship might be influenced by factors such as exercise intensity, duration, fitness, and aging is not known.

The major implications of alterations in CBF-CO₂ reactivity during exercise might well be related to cerebral oxygenation and muscular energetics: if central [H⁺] can be mitigated using increased CBF over an increase in ventilation, energy might be spared for muscular exercise. For example, cerebral hypoxia has been proposed as a critical factor limiting exercise performance (138, 196). This recent report (196) demonstrated that the hypoxia-induced peripheral chemoreflex activity led to marked reductions in PaCO₂, which were related to subsequent reductions in MCAv and cerebral oxygenation. Interestingly, the influence of the reductions in PaCO₂ were much stronger from moderate to high (75–100% of maximal intensity) work rates (196), indicating a distinct point from rising end-tidal PCO₂ and MCAv (during moderate-intensity exercise) to falling
end-tidal PCO2 and MCAv (at maximal intensity). These findings are consistent with another recent study (13) that showed a greater lowering of MCAv and cerebral oxygenation during hypoxic exercise after acclimation to intermittent or continuous hypoxia; these changes were mediated by a greater chemoreflex-induced hypocapnia, rather than a compromise in dynamic cerebral autoregulation or alterations in MCAv-CO2 reactivity.

Thus, during strenuous or hypoxic exercise, hyperventilatory responses to PCO2 for modified rebreathing and steady-state (SS) testing methods. Steady-state method responses show effect of cerebrovascular reactivity during isoxic conditions of hyperoxia and hypoxia, the steady-state method responses show the effect of cerebrovascular reactivity (Eqs. 2 and 3), central-arterial PCO2 difference (normally ~10 mmHg) varies with medullary blood flow. For example, an increase in Paco2 of 10 mmHg above 40 mmHg results in an 8-mmHg reduction in central-arterial PCO2 difference because of an increase in medullary blood flow (Eq. 3). With a normal central chemoreflex sensitivity of 3 l/min·mmHg−1, ventilation response is reduced by 6 l/min. Combining these equations

\[
\begin{align*}
\text{PbCO2} &= \text{Paco2} + \text{VCO2} \left( K \left[ Q_c + Q_s^* (\text{Paco2} - \text{Paco2}_r) \right] \right) \\
\text{PbCO2} &= 40 + 3/0.005* [55 + Q_s^* (\text{Paco2} - 40)]
\end{align*}
\]

(4)

(5)

\[
\begin{align*}
\text{Equation 5} & \text{ was incorporated into the chemoreflex model and used to predict the effect of cerebrovascular reactivity on the isoxic ventilatory responses to PCO2}; \text{ in effect, the model compares steady-state with modified rebreathing responses (Figs. 17 and 18, Tables 1 and 2). As illustrated in Fig. 17, during isoxic conditions of hyperoxia and hypoxia, the steady-state method responses show the effect of cerebrovascular reactivity (Eq. 5). In contrast, the modified rebreathing method responses show the effect of equalizing the central-arterial PCO2 difference to the mixed venous PCO2 and, therefore, K is slope of the linearized CO2 dissociation curve (0.005 ml·ml−1·mmHg−1).
\end{align*}
\]

For cerebrovascular reactivity

\[
\begin{align*}
\dot{Q} &= Q_c + Q_s^* (\text{Paco2} - \text{Paco2}_r) \\
\text{where } \dot{Q} &\text{ is resting central blood flow (55 ml·min}^{-1} \cdot 100 \text{ g}^{-1}), Q_c \text{ is central blood flow sensitivity (2 ml·min}^{-1} \cdot 100 \text{ g}^{-1} \text{·mmHg}^{-1}), \text{ and } \text{Paco2}_r \text{ is resting PCO2.}
\end{align*}
\]

As demonstrated by Eqs. 2 and 3, central-arterial PCO2 difference (normally ~10 mmHg) varies with medullary blood flow. For example, an increase in Paco2 of 10 mmHg above 40 mmHg results in an 8-mmHg reduction in central-arterial PCO2 difference because of an increase in medullary blood flow (Eq. 3). With a normal central chemoreflex sensitivity of 3 l/min·mmHg−1, ventilation response is reduced by 6 l/min. Combining these equations

\[
\begin{align*}
\text{PbCO2} &= \text{Paco2} + \text{VCO2} \left( K \left[ Q_c + Q_s^* (\text{Paco2} - \text{Paco2}_r) \right] \right) \\
\text{PbCO2} &= 40 + 3/0.005* [55 + Q_s^* (\text{Paco2} - 40)]
\end{align*}
\]

(4)

(5)

Equation 5 was incorporated into the chemoreflex model and used to predict the effect of cerebrovascular reactivity on the isoxic ventilatory responses to PCO2; in effect, the model compares steady-state with modified rebreathing responses (Figs. 17 and 18, Tables 1 and 2). As illustrated in Fig. 17, during isoxic conditions of hyperoxia and hypoxia, the steady-state method responses show the effect of cerebrovascular reactivity (Eq. 5). In contrast, the modified rebreathing method responses show the effect of equalizing the central-arterial PCO2 difference to the mixed venous PCO2 and, therefore,
Table 1. Predicted values for hyperoxic sleeping subject with and without indomethacin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Control</th>
<th>Indomethacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>[H⁺], nmol/l</td>
<td></td>
<td>42.0</td>
<td>42.2</td>
</tr>
<tr>
<td>Central</td>
<td></td>
<td>42.0</td>
<td>42.2</td>
</tr>
<tr>
<td>Arterial</td>
<td></td>
<td>41.0</td>
<td>39.8</td>
</tr>
<tr>
<td>Resting PCO₂, mmHg</td>
<td></td>
<td>46.1</td>
<td>44.2</td>
</tr>
<tr>
<td>Resting ventilation, l/min</td>
<td></td>
<td>6.6</td>
<td>7.0</td>
</tr>
<tr>
<td>Apnea threshold, mmHg</td>
<td></td>
<td>40.0</td>
<td>40.0</td>
</tr>
<tr>
<td>CO₂ reserve, mmHg</td>
<td></td>
<td>6.1</td>
<td>4.2</td>
</tr>
<tr>
<td>Hypocapnic gain, l·min⁻¹·mmHg⁻¹</td>
<td></td>
<td>1.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Plant gain, mmHg·l·min⁻¹</td>
<td></td>
<td>6.9</td>
<td>6.3</td>
</tr>
<tr>
<td>Loop gain</td>
<td></td>
<td>7.5</td>
<td>10.6</td>
</tr>
</tbody>
</table>

[H⁺]. H⁺ concentration.

subsequently greater elevations in rebreathing Ve·venous PCO₂ sensitivity than the steady-state Ve·PaCO₂ sensitivity. The “Chemo” responses show the effect of eliminating the cerebrovascular reactivity and assuming a constant 10-mmHg central-arterial PCO₂ difference. Next, we considered the influence of indomethacin on cerebrovascular CO₂ reactivity during sleep (Fig. 18). These findings from our mathematical model support recent experimental data during wakefulness (222) and sleep (219, 222). Moreover, the related elevations in hypocapnic Ve sensitivities underscore the potential importance of a stable CBF reactivity in the hypacapnic and hypercapnia ranges. An inappropriate CBF reactivity in either range may be a critical factor leading to breathing instability. The preliminary findings from our newly described steady-state modeling approach have significant potential to provide unique and complementary insight into the effects of changes in CBF on the chemoreflex control of breathing.

FUTURE DIRECTIONS

Over the last century, extensive progress has been made in the study of CBF, respiratory, and cardiovascular control. The further utilization, development, and refinement of our newly described steady-state modeling approach to quantify the effects of changes in CBF on the chemoreflex control of breathing may also provide unique and complementary insights.

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