Continuing Medical Education

The chemoreflex control of breathing and its measurement

James Duffin PhD

The chemoreflex control of breathing is described in terms of a graphical model. The central chemoreflex, the ventilatory response to carbon dioxide mediated by the central chemoreceptors, is modelled as a straight-line relation between the ventilatory response and the arterial level of carbon dioxide. The peripheral chemoreflex, the ventilatory response to carbon dioxide and hypoxia mediated by the peripheral chemoreceptors, is broken into two relations. First, a straight-line relation between the ventilatory response and the arterial level of carbon dioxide whose slope (sensitivity) increases as the oxygen level varies from hyperoxic to hypoxic. Second, a rectangular hyperbolic relation between the ventilatory response and the arterial level of oxygen with ventilation increasing with increasing hypoxia. The three ventilatory response relations (one central and two peripheral) add to produce the total chemoreflex ventilatory response which forms the feedback part of the respiratory regulator. The forward part consists of the relation between the arterial level of carbon dioxide and ventilation when ventilation is controlled (the metabolic hyperbola). The forward and feedback parts of the respiratory regulator can be combined so as to predict resting ventilation and carbon dioxide levels under a number of circumstances. Methods of measurement of these chemoreflex ventilatory responses are also described so as to illustrate the physiological principles involved in the model.

Le contrôle chimioréflexe de la respiration est décrit comme un modèle graphique. Le centre chimioréflexe, la réponse respiratoire au CO₂ médiée par les chémorécepteurs centraux sont décrits comme une relation directe entre la réponse respiratoire et les niveaux de CO₂ artériels. Le chimioréflexe périphérique, la réponse ventilatoire au CO₂ et l'hypoxie médiés par les chémorécepteurs périphériques sont subdivisées en deux relations. Premièrement, une relation directe entre la réponse ventilatoire et le niveau artériel de CO₂ dont la pente (sensitivité) augmente avec les variations du niveau d'oxygène d'hyperoxique à hypoxique. Deuxièmement, une relation hyperbolique rectangulaire entre la réponse respiratoire et le niveau artériel d'oxygène avec la ventilation augmentant avec l'augmentation de l'hypoxie. Les trois relations de la réponse respiratoire (une centrale et deux périphériques) s'ajoutent pour produire la réponse respiratoire chémoréflexe totale qui forme la portion de « feedback » du régulateur respiratoire. L'autre partie consiste à une relation entre le niveau artériel de CO₂ et la ventilation lorsque cette dernière est contrôlée (l'hyperbole métabolique). Ces deux parties du régulateur respiratoire peuvent être combinées afin de prédire la ventilation au repos et le niveau de CO₂ dans d'autres circonstances. Des méthodes de mesure et des réponses de ces chémorécepteurs respiratoires sont aussi décrites afin d'illustrer les principes physiologiques impliqués dans ce modèle.

Key words

REFLEXES: chemoreceptor;

VENTILATION: carbon dioxide response, control, hypoxic response.

Departments of Anaesthesia and Physiology, University of Toronto.

Address correspondence to: Dr. J. Duffin, Department of Physiology, University of Toronto, Toronto, Ontario, Canada, M5S 1A8.

This article presents a view of the control of breathing by the central and peripheral chemoreflexes as a graphical model of this feedback regulator, and also presents methods by which the regulator performance may be assessed. It is not a review of the literature relating to either the underlying physiology or models of it, but is intended as a practical approach to understanding. For the background research involved the reader is referred to the review by Cunningham *et al.*¹

In the awake patient, breathing is subject to conflicting demands and conditions. These may include diverse influences such as anxiety hyperventilation, posturally

FIGURE 1 A block diagram of the control of breathing by the chemoreflexes.

induced changes in pulmonary mechanics, and metabolic requirements. While the control of breathing in the anaesthetized patient is somewhat simplified by the elimination or suppression of many of these influences, the physiology of breathing will be further simplified in this article by assuming that breathing is under the sole control of the respiration chemoreflexes.

The term chemoreflexes refers to the effects of the central and peripheral chemoreceptors on pulmonary ventilation. The chemoreflexes form the feedback portion of a control loop. The forward portion, which completes the control loop, refers to the effects that changing pulmonary ventilation has upon the stimuli sensed by the chemoreceptors and is usually termed the metabolic hyperbola because of its shape. The complete control loop is the classical, negative feedback regulator which maintains respiratory homeostasis, pictured in Figure 1.

The central chemoreflex

The central chemoreceptors respond only to the hydrogen ion concentration of their environment, and therefore this chemoreflex might be expected to be relatively simple to understand. However, the complexities associated with the central chemoreflex are due to the location of the central chemoreceptors, somewhere within the brain tissue in the medulla.² This location has three consequences for the operation of the central chemoreflex.

The first consequence concerns the relation between hydrogen ion concentration and the partial pressure of carbon dioxide. This relation can be expressed as the linear form of the Henderson-Hasselbalch equation shown in Figure 2 (but also see an alternative approach to acid-base chemistry using fundamental physical and chemical principles).³ Because of the blood-brain barrier for polar solutes, hydrogen ion concentration does not easily equilibrate between the central chemoreceptors and

$$[H^+] = \frac{24 P_{CO_2}}{[HCO_3^-]}$$

where:

$[H^+]$ is the Hydrogen ion concentration in nanomoles per litre

P_{CO_2} is the partial pressure of Carbon Dioxide in mm Hg

$[HCO_3^-]$ is the Bicarbonate ion concentration in millimoles per litre

FIGURE 2 The linear form of the Henderson-Hasselbalch equation. Normal resting values are: hydrogen ion concentration = $40 \text{ nmol} \cdot \text{L}^{-1}$, partial pressure of carbon dioxide = 40 mmHg , and bicarbonate ion concentration = $24 \text{ mmol} \cdot \text{L}^{-1}$.

arterial blood, but the partial pressure of carbon dioxide does. In addition, the bicarbonate ion concentration within the tissues of the central chemoreceptors may alter over time and differ from that of arterial blood; usually in such a way as to restore central nervous system hydrogen ion concentration to normal values.⁴ For these reasons, the hydrogen ion concentration sensed by the central chemoreceptors is likely to be more closely related to the arterial partial pressure of carbon dioxide than to the arterial hydrogen ion concentration in the short term (minutes), and furthermore that relationship may be altered by changes in central nervous system bicarbonate ion concentration (hours).

The second consequences of the location of the central chemoreceptors concerns the time course for changes in the partial pressure of carbon dioxide at the central chemoreceptors, relative to such changes in arterial blood.

Because the central chemoreceptors are located in brain tissue which is supplied with blood at a flow of about $0.01 \text{ ml} \cdot \text{sec}^{-1}$ for every ml of tissue, the changes in the partial pressure of carbon dioxide at the central chemoreceptors lag behind those in arterial blood. In experiments where the arterial level of the partial pressure of carbon dioxide is abruptly increased (a step change), the partial pressure of carbon dioxide at the central chemoreceptors gradually increases to a new level following the time course of a wash-in exponential function.⁵ The time constant of this exponential function can be estimated as the reciprocal of the blood perfusion per volume of chemoreceptor tissue, i.e., 100 sec . Since a wash-in exponential process is almost complete in about three time constants, it therefore takes five minutes for the partial pressure of carbon

FIGURE 3 The alveolar ventilation response to arterial carbon dioxide mediated by the central chemoreceptors.

dioxide at the central chemoreceptors to reach its new level.

It should be understood that the partial pressure of carbon dioxide at the central chemoreceptors is not the same as that of arterial blood, even when equilibration is complete, but is close to that of mixed venous cerebral blood. Since changes in cerebral blood flow change the cerebral arterio-venous difference in the partial pressure of carbon dioxide it follows that the relationship between the partial pressure of carbon dioxide in arterial blood and that of the central chemoreceptors will be altered by changing cerebral blood flow. This complication is the third consequence of the central-chemoreceptor location.

For example, suppose that the arterial partial pressure of carbon dioxide is held steady at a normal level and hypoxia occurs. The hypoxia has two effects on ventilation, but the second is more subtle. Hypoxia not only stimulates ventilation via the peripheral chemoreceptors but also stimulates an increased cerebral blood flow.⁶ This latter effect washes carbon dioxide out of the central chemoreceptor tissues so that the cerebral arterio-venous difference in the partial pressure of carbon dioxide is decreased and the partial pressure of carbon dioxide at the central chemoreceptors changes, decreasing towards the arterial value. This decrease withdraws the carbon dioxide ventilatory stimulus from the central chemoreceptors, thus counteracting the hypoxic drive to ventilation, even if arterial carbon dioxide partial pressure is kept constant at a normal value. Another example of the effect of changing cerebral blood flow, this time in response to increasing carbon dioxide, is discussed later, in the measurement section, where estimates of the central chemoreceptor sensitivity to carbon dioxide can be, on average, halved because of the cerebral blood flow effect.⁷

$$P_{a_{CO_2}} - P_{I_{CO_2}} \propto \frac{\dot{V}_{CO_2}}{\dot{V}_A}$$

where:

$P_{a_{CO_2}}$	is the arterial partial pressure of Carbon Dioxide in mm Hg
$P_{I_{CO_2}}$	is the inspired partial pressure of Carbon Dioxide in mm Hg
$\dot{V}_{CO_2}$	is the rate of Carbon Dioxide output in litres per minute
$\dot{V}_A$	is the alveolar ventilation in litres per minute

FIGURE 4 The metabolic hyperbola, the relation between ventilation and carbon dioxide when ventilation is controlled.

The relationship between the partial pressure of carbon dioxide in arterial blood and alveolar ventilation is that shown in Figure 3, when only the central chemoreflex is operating. This straight-line relationship with a threshold of approximately 5.3 kPa (40 mmHg) partial pressure of carbon dioxide and a slope of about $22.5 \text{ L} \cdot \text{min}^{-1} \cdot \text{kPa}^{-1}$ ($3 \text{ L} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$) describes the central chemoreflex part of the feedback loop.

The forward part of the loop describes the relationship between alveolar ventilation and the arterial partial pressure of carbon dioxide when the former is varied. This relation is the metabolic hyperbola for carbon dioxide whose equation is shown in Figure 4. The curve which this equation represents is a rectangular hyperbola whose shape changes with the metabolic production of carbon dioxide. A similar relation exists for oxygen.

If the central chemoreflex relation shown in Figure 3 is combined on one graph with the metabolic hyperbola then Figure 5 is the result, and this graph defines the central chemoreflex control of breathing, that is the regulation of ventilation in an hyperoxic patient at rest. Ventilation and carbon dioxide partial pressure values must satisfy both the central chemoreflex relation and the metabolic hyperbola. The intersection of the forward loop characteristic (the metabolic hyperbola) and the feedback loop characteristic (the central chemoreflex) defines the resting point for the respiratory regulator (circled point in Figure 5), determining the alveolar ventilation and the arterial partial pressure of carbon dioxide.

The central chemoreceptor relation is a straight line characterized by its slope (i.e., sensitivity) and its intercept with the carbon dioxide axis (i.e., threshold). Both of these characteristics may be changed in either direction (increased or decreased) by a number of factors which are too numerous to list here. A few examples

FIGURE 5 The central chemoreflex control of breathing. Solid, straight line: the alveolar ventilation response to arterial carbon dioxide mediated by the central chemoreceptors. Solid, curved line: the changes in arterial carbon dioxide resulting from controlling alveolar ventilation (the metabolic hyperbola). Dashed line: the alveolar ventilation response to arterial carbon dioxide mediated by the central chemoreceptors during anaesthesia. Dotted line: the alveolar ventilation response to arterial carbon dioxide mediated by the central chemoreceptors during metabolic acidosis. The circle indicates the normal equilibrium point.

should suffice to illustrate the use of the graphical model shown in Figure 5.

First, a decrease in central chemoreflex sensitivity such as by anaesthesia⁸ causes a decrease in slope (the dashed line in Figure 5). The change in the intersection point of the metabolic hyperbola and the central chemoreflex in the graphical model demonstrates the well-known observation that because of the shape of the metabolic hyperbola, alveolar ventilation is little decreased, but the arterial partial pressure of carbon dioxide rises markedly. Other factors can also produce this type of respiratory depression such as sleep,⁹ a mild effect, and cerebral hypoxia, whose effects are difficult to quantitate in humans but have been shown in sheep.¹⁰

Second, an increase in the central chemoreflex sensitivity such as by amphetamines causes an increase in slope (not illustrated in Figure 5). The graphical model predicts that ventilation increases a little and the arterial partial pressure of carbon dioxide falls slightly.

Third, the apparent threshold of the central chemoreflex can be decreased by compensated metabolic acidosis¹ (the dotted line in Figure 5). The actual threshold for the central chemoreflex in terms of central chemoreceptor hydrogen ion concentration does not change, but because central chemoreceptor bicarbonate ion concentration is decreased, a greater hydrogen ion concentration results at normal arterial partial pressures of carbon dioxide, as the equation of Figure 2 predicts. Therefore the threshold of

the central chemoreflex expressed as arterial carbon dioxide partial pressure is decreased in compensated metabolic acidosis. The graphical model shows that the new system equilibrium is at a slightly increased ventilation and a markedly decreased arterial partial pressure of carbon dioxide.

A similar, but less marked, decrease in apparent central chemoreflex threshold can occur if cerebral blood flow decreases. In this case, because of the decreased removal of carbon dioxide, the carbon dioxide partial pressure in cerebral mixed venous blood and the tissues of the central chemoreceptor increases for the same arterial partial pressure of carbon dioxide. Ventilation is therefore greater for the same arterial partial pressure of carbon dioxide resulting in a decrease in the apparent threshold of the central chemoreflex expressed as arterial carbon dioxide partial pressure.

Fourth, just as a compensated metabolic acidosis produces a decrease in the apparent threshold of the central chemoreflex, so a compensated metabolic alkalosis produces an increase in the apparent threshold (not illustrated in Figure 5). The reasoning is similar, and the graphical model predicts a new system equilibrium at a slightly decreased ventilation and a markedly increased arterial partial pressure of carbon dioxide.

This simple model of respiratory control is useful for the hyperoxic patient but does not include the effects of hypoxia. The inclusion of the peripheral chemoreflex adds considerable flexibility and effectiveness to the respiratory regulator at the cost of increased complexity.

The peripheral chemoreflex

The peripheral chemoreceptors are located in the carotid bodies¹¹ and are complex sensors for both hypoxia and hydrogen ion concentration. Both the carbon dioxide partial pressure and the hydrogen ion concentration of arterial blood can affect the hydrogen ion concentration in the carotid body and thereby affect respiration. The peripheral chemoreceptor responses to hypoxia and hydrogen ion concentration are not simply superimposed by addition, but exhibit a multiplicative effect, so that the responses to the combined stimuli are greater than the sum of their individual responses. In addition to such interaction, the responses are further complicated by the existence of a threshold for the hydrogen ion concentration, below which no stimulation occurs, and the fact that the response to hypoxia is non-linear (rectangular hyperbolic). All of these factors tend to complicate the graphical description for the peripheral chemoreflex.¹²

Usually the peripheral chemoreceptors are thought of as primarily hypoxia sensors,¹³ with secondary effects on the hypoxic response caused by hydrogen ion concentration. Figure 6 illustrates this view by showing the

FIGURE 6 The alveolar ventilation response to changes in arterial oxygen at several constant levels of arterial carbon dioxide mediated by the peripheral chemoreceptors.

relationship between alveolar ventilation and the partial pressure of oxygen in arterial blood at several constant levels of carbon dioxide partial pressure. The interaction is shown by the changing hypoxic responses at super-threshold levels of carbon dioxide partial pressure, and the threshold for the partial pressure of carbon dioxide is indicated by the unchanging hypoxic response below 5.3 kPa (40 mmHg).

This view of the peripheral chemoreflex has some disadvantages however. First, the form of the interaction between hypoxic and hydrogen ion stimuli is not apparent from the response characteristics shown. Second, the emphasis of the response is on hypoxia, but the rectangular hyperbolic shape of the relation shows that the peripheral chemoreceptors are relatively insensitive at normoxic and mildly hypoxic levels. The third disadvantage is that the more sensitive responses to super-threshold hydrogen ion in normoxia and moderate hypoxia are not readily apparent. While the graph does show that ventilation increases with increasing arterial partial pressures of carbon dioxide, the form of this relation is not shown, nor is there an appreciation of the sensitivity of this response.

For these reasons, it may be preferable to view the peripheral chemoreceptors as primarily hydrogen ion sensors, with a secondary role for hypoxia in both enhancing the sensitivity to hydrogen ions and providing an independent weak response to hypoxia. In this view the complete peripheral chemoreflex response shown in

FIGURE 7 The alveolar ventilation response to arterial carbon dioxide at several constant levels of arterial oxygen mediated by the peripheral chemoreceptors.

Figure 6 is broken into primary and secondary responses which add together to make the whole.

The primary response is the ventilatory response to hydrogen ion concentration whose sensitivity is controlled by the level of hypoxia. It is this dependence of sensitivity on hypoxia that models the interaction of the two stimuli. The secondary response is the ventilatory response to hypoxia which is independent of hydrogen ion concentration and therefore carbon dioxide partial pressure. This division of the responses also emphasizes the relative importance of the responses with respect to their control of ventilation. The primary response to hydrogen ion concentration when hypoxia is present is very powerful, but the secondary response alone is weak.

The peripheral chemoreceptor response to hydrogen ions is linear, like that of the central chemoreceptors, but the sensitivity is controlled by hypoxia in a non-linear way, which constitutes the interaction between these two stimuli. Figure 7 shows the relationship between alveolar ventilation and the partial pressure of carbon dioxide in arterial blood at several constant levels of oxygen partial pressure. The straight-line relations, with a threshold of approximately 5.3 kPa (40 mmHg) describe the primary part of the peripheral chemoreflex response.

To this primary part must be added the secondary hypoxic response. This secondary response has already been shown in Figure 6 as that for sub-threshold hydrogen ion concentration, and is shown alone in Figure 8.

The complete peripheral chemoreflex characteristic can therefore be obtained by adding the responses shown in Figures 7 and 8. The rectangular hyperbolic relation of Figure 8 not only serves to define the secondary peripheral chemoreflex response, but also serves to define the

FIGURE 8 The alveolar ventilation response to changes in arterial oxygen alone (arterial carbon dioxide below threshold) mediated by the peripheral chemoreceptors.

relation between the sensitivity of the hydrogen ion response and hypoxia. The vertical axis of this graph can therefore be calibrated in both alveolar ventilation and sensitivity units.

It can readily be seen from this description of the peripheral chemoreflex characteristic that its major function is as an asphyxia sensor and that the effectiveness of either hypoxia or hydrogen ions alone as stimuli is poor. The peripheral chemoreflex, like the central chemoreflex can be altered by many factors and these can be incorporated into the graphical model as before to predict the changes in resting ventilation. For example, as in the case for the central chemoreflex, if the threshold for hydrogen ions is expressed in terms of carbon dioxide partial pressure, then acid-base disturbances can change it. It should also be realized that the partial pressure of oxygen in the arterial blood may not necessarily reflect the amount of oxygen available for metabolism such as in carbon monoxide poisoning. Finally, the local blood flow through the carotid body is under complex local and autonomic control so that the partial pressures of blood gases at the chemoreceptive sites may differ from those of arterial blood. For example, agents such as halothane¹⁴ and alcohol¹⁵ which depress the peripheral chemoreceptor sensitivity may do so by altering blood flow within the

FIGURE 9 The chemoreflex control of breathing. Straight lines: the alveolar ventilation response to arterial carbon dioxide mediated by the central and peripheral chemoreflex. Curved line: the changes in arterial carbon dioxide resulting from controlling alveolar ventilation (the metabolic hyperbola). The circle indicates the normal equilibrium point.

carotid body since both of these agents increase blood flow in peripheral tissues.

The complete graphical model

The prediction of ventilation from any set of chemoreceptor stimuli can be accomplished by adding the ventilation contributions of Figures 3, 7 and 8. However, to this value must be added one more contribution to ventilatory drive: that commonly referred to as the "neural" drive. This drive to breathe is independent of chemoreceptor stimuli and although usually low, varying slightly with the state of alertness, can increase to significant levels during pain or exercise.

Figure 9 shows the sum of the individual chemoreflex responses plotted as ventilation versus carbon dioxide lines at constant levels of oxygen. With the inclusion of the resting metabolic hyperbola it is possible to predict the ventilation and carbon dioxide levels for a patient at rest for any given level of oxygen. For example at a partial pressure of oxygen of 13.3 kPa (100 mmHg) the iso-oxic ventilation response line intersects the metabolic hyperbola at about 5.5 kPa (41 mmHg) partial pressure of carbon dioxide and a ventilation of about 7 L·min⁻¹ (circled point in Figure 9). This point is the equilibrium point for the respiratory regulator as discussed before for Figure 5. It should be understood that the responses pictured are those of an average subject, and that individuals may vary from this average quite markedly.

The determination of an individual's ventilatory responses is within the capabilities of hospital-based re-

search but requires experienced personnel. Evaluation of both the central and peripheral chemoreflex ventilatory responses to carbon dioxide separately, and the peripheral chemoreflex response to hypoxia requires the employment of different techniques. These techniques are described in the following section so as to elucidate further the principles of the chemoreflex control of breathing, to explain the differences between steady-state and re-breathing measured ventilatory sensitivities to carbon dioxide, to enable the reader to judge critically research reports, and as an encouragement to the clinical researcher.

Measurement of the central chemoreflex

To measure the central chemoreflex the technique of choice is the rebreathing method as first proposed by Read,¹⁶ not only because of its short duration and low stress, but also for accuracy. Briefly, the method is as follows.

The subject rebreathes from a bag filled with an hyperoxic gas mixture containing carbon dioxide at a partial pressure which is approximately twice the estimated arterio-venous difference above the end-tidal value (i.e., about 6.7 kPa (50 mmHg) in a normal resting patient). The bag volume should be only slightly greater than the largest tidal volume to be measured. Alveolar and hence arterial carbon dioxide levels are estimated by end-tidal levels from continuous measurement. Ventilation can be determined in a number of ways, one of which is to enclose the rebreathing bag in a rigid box connected to a spirometer. By these means it should be possible to obtain breath-by-breath measurements of both ventilation and end-tidal carbon dioxide level. Figure 10 illustrates a possible apparatus.

As the rebreathing begins, the partial pressure of carbon dioxide in the bag, lungs, and arterial blood, quickly equilibrates with the mixed venous level. The mixed venous level of carbon dioxide serves as an estimate of the large tissue storage level. The equilibration must occur before recirculation, and can be observed as a constant value of the end-tidal carbon dioxide despite breathing. After recirculation, because the subject and bag are a closed system, the level of carbon dioxide begins to rise at a rate determined by resting metabolism, and continues to rise until the subject is disconnected from the bag after about four minutes.

The rebreathing method assumes that the central chemoreceptors are initially at the same level of carbon dioxide as the mixed venous blood, and that the rate of rise is the same. Breathing and circulation are assumed to maintain the level of carbon dioxide in the bag, the alveolar space and the mixed-venous blood at the same partial pressure. Hence an end-tidal measurement should

FIGURE 10 A block diagram illustrating a possible experimental apparatus for the rebreathing method (see text for details).

provide a good estimate of the central chemoreceptor level of carbon dioxide. Since the peripheral chemoreceptors are not sensitive to carbon dioxide in hyperoxia, the ventilation measured is the response to the carbon dioxide mediated by the central chemoreceptors. The method avoids the problem of cerebral blood flow increase with carbon dioxide which occurs with the steady-state method where the estimate of sensitivity is, on average, half that obtained by the rebreathing method.⁷

Measurement of the peripheral chemoreflex

An assessment of the peripheral chemoreflex is more complex and depends upon the stimulus to be altered. If the response to carbon dioxide is to be measured then the central chemoreflex will also be present since there is no convenient way of eliminating it. If the response to hypoxia alone is to be measured then the central chemoreflex can be assumed to be absent when the carbon dioxide level is below the central chemoreceptor threshold.

The peripheral chemoreflex ventilatory response to hypoxia (Figure 8) can be determined by steady-state methods by altering the inspired fraction of oxygen and observing ventilation and both oxygen and carbon dioxide levels. Since the peripheral chemoreceptors respond rapidly, and the body's oxygen stores are small relative to the carbon dioxide stores, little equilibration time is

FIGURE 11 Experimentally determined breath-by-breath responses to carbon dioxide using rebreathing with prior hyperventilation (see text for details). Crosses: hyperoxic rebreathing. Squares: rebreathing at a constant level of hypoxia (9.3 kPa; 70 mmHg).

necessary, but time must be allowed for carbon dioxide levels to fall below threshold. Since the latter changes will not occur until hypoxia is sufficient to provide a ventilation greater than normal resting levels, the normoxic range of the response to hypoxia will not be accurate because of the continuing presence of both the peripheral and central chemoreceptor responses to carbon dioxide. This problem is a nuisance rather than proving detrimental to the estimate of the response to hypoxia because the rectangular hyperbolic shape of the response demonstrates that the hypoxic sensitivity is low for normoxic levels.

Care must be taken to measure good estimates of arterial oxygen partial pressure, either by direct blood sampling, or derived from pulse oximetry. End-tidal sampling is acceptable only if the A-a gradient in the partial pressure of oxygen is a few mmHg. It should also be understood that the response to hypoxia cannot be properly estimated if the carbon dioxide level is above the threshold of the central chemoreceptors, even if means are provided to maintain constant alveolar levels, because of the alteration in cerebral blood flow with hypoxia,⁶ and hence alteration in the level of carbon dioxide at the central chemoreceptors.

The peripheral chemoreflex ventilatory response to hypoxia and carbon dioxide (Figures 7 and 8; added) can be determined by rebreathing methods, and is perhaps more important than the response to hypoxia alone because usually these stimuli occur in combination. The determination requires two rebreathing tests, one as described before, to measure the ventilatory response to

carbon dioxide mediated by the central chemoreceptors, and one to measure the combined responses. Subtraction provides the separation.

Two methods can be used to measure the combined ventilatory responses to carbon dioxide and hypoxia. Both are modifications to the rebreathing technique. The simplest method is to use an initial bag mixture of carbon dioxide and air. As rebreathing starts, both carbon dioxide and oxygen levels equilibrate to the mixed-venous levels. As rebreathing continues, carbon dioxide levels rise and oxygen levels fall, both are assumed to be the same at the peripheral and central chemoreceptors and in the respired air. Performed as for the hyperoxic rebreathing, this hypoxic technique estimates the ventilatory response to carbon dioxide at a constant level of oxygen partial pressure of about 6.7 kPa (50 mmHg).¹⁵

The second rebreathing method which can be used is to maintain a constant level of oxygen by controlling the oxygen level in the bag. Supplying the metabolically consumed oxygen does, however, introduce a small error in central carbon dioxide estimation because of the arterio-venous difference produced. The advantage of this method is that several rebreathing experiments at different constant levels can produce a family of ventilatory responses.

With both of these rebreathing methods it is necessary to subtract the hyperoxic ventilatory response to carbon dioxide of the central chemoreceptors in order to obtain the response of the peripheral chemoreceptors alone. It should also be noted that these methods neglect the effect of any hypoxic depression of the central chemoreceptors. Figure 11 shows both hyperoxic and hypoxic rebreathing experiments done after five minutes of hyperventilation so as to reveal the thresholds for each chemoreceptors.¹⁷ Since the central chemoreceptor threshold is higher than the peripheral chemoreceptor threshold by about the arterio-venous difference at rest, then the two thresholds will be reached at about the same arterial level of carbon dioxide partial pressure in normal resting individuals.

Finally, it must be emphasized that because these rebreathing methods rely on the assumption that central chemoreceptor hydrogen ion concentration rises at the same rate as that of mixed venous blood, they are inapplicable to exercising subjects where such is not the case.

The physiological concepts embodied in the graphical model of the chemoreflex control of breathing presented here, and the methods of measurement of the chemoreflexes themselves have been developed and refined over the past 20 years. They now constitute an established view of respiratory regulation which has stood the tests of experiments, and can function as a basis for further

exploration of the underlying physiology and its alteration by such factors as disease, pharmacological interventions, sleep, exercise and anaesthesia.

References

- 1 *Cunningham DJC, Robbins PA, Wolff CB.* Integration of respiratory responses to changes in alveolar partial pressures of CO₂ and O₂ and in arterial pH. *In:* Cherniack NS, Widdicombe JG (Eds.). *Handbook of Physiology, Section 3, The Respiratory System, Volume II, Control of Breathing, Part 2.* Bethesda: Am Physiol Soc 1986; 475–528.
- 2 *Eugene BN, Cherniack NS.* Central chemoreceptors. *J Appl Physiol* 1987; 62: 389–402.
- 3 *Stewart PA.* Modern quantitative acid-base chemistry. *Can J Physiol Pharmacol* 1983; 61: 1444–61.
- 4 *Bledsoe SW, Hornbein TF.* Central chemosensors and the regulation of their chemical environment. *In:* Hornbein TF (Ed.). *Regulation of Breathing, Part I.* New York: Marcel Dekker 1981; 347–428.
- 5 *Nunn JF.* Appendix F. The exponential function. *In:* Nunn JF (Ed.). *Applied Respiratory Physiology.* Cambridge: Butterworths 1967; 516–27.
- 6 *Santiago TV, Edelman NH.* Brain blood flow and control of breathing. *In:* Cherniack NS, Widdicombe JG (Eds.). *Handbook of Physiology, Section 3, The Respiratory System, Volume II, Control of Breathing, Part I.* Bethesda: Am Physiol Soc 1986; 163–79.
- 7 *Berkenbosch A, Bovill JG, Dahan A, De Goede J, Olevier ICW.* The ventilatory CO₂ sensitivities from Read's rebreathing method and the steady-state method are not equal in man. *J Physiol* 1989; 411: 367–77.
- 8 *Nunn JF.* Respiratory aspects of anaesthesia. *In:* Nunn JF (Ed.). *Applied Respiratory Physiology.* Cambridge: Butterworths 1967; 350–78.
- 9 *Phillipson EA.* Control of breathing during sleep. *Am Rev Resp Dis* 1978; 118: 909–39.
- 10 *Phillipson EA, Bowes G, Townsend ER, Duffin J, Cooper JD.* Carotid chemoreceptors in ventilatory responses to changes in venous CO₂ load. *J Appl Physiol* 1981; 51: 1398–403.
- 11 *Fidone SJ, Gonzales C.* Initiation and control of chemoreceptor activity in the carotid body. *In:* Cherniack NS, Widdicombe JG (Eds.). *Handbook of Physiology, Section 3, The Respiratory System, Volume II, Control of Breathing, Part 2.* Bethesda: Am Physiol Soc 1986; 247–312.
- 12 *Cunningham DJC.* Studies on arterial chemoreceptors in man. *J Physiol* 1987; 384: 1–26.
- 13 *Delapiano MA, Hescheler J.* Evidence for a PO₂-sensitive K⁺ channel in the type-I cell of the rabbit carotid body. *FEBS Lett* 1989; 249: 195–8.
- 14 *Duffin J, Triscott A, Whitwam JG.* The effect of halothane and thiopentone on ventilatory responses mediated by the peripheral chemoreceptors in man. *Br J Anaesth* 1976; 48: 975–81.
- 15 *Duffin J, Jacobson ER, Orsini EC.* The effect of ethanol on the ventilatory responses mediated by the peripheral chemoreceptors in man. *Can Anaesth Soc J* 1978; 25: 181–9.
- 16 *Read DJC.* A clinical method for assessing the ventilatory response to carbon dioxide. *Australasian Annals of Medicine* 1967; 16: 20–32.
- 17 *Duffin J, McAvoy GV.* The peripheral-chemoreceptor threshold to carbon dioxide in man. *J. Physiol* 1988; 406: 15–26.

Multiple-choice questions

- 1 The time constant for changes in ventilation with respect to sudden changes in inspired carbon dioxide is approximately:
 - A 1 sec
 - B 10 sec
 - C 100 sec
 - D 10 min
 - E 20 min
- 2 Under anaesthetic-induced respiratory depression which of the following does not pertain?
 - A Arterial carbon dioxide rises slowly.
 - B Arterial oxygen falls slowly.
 - C The peripheral chemoreceptors take over ventilatory drive from the central chemoreceptors.
 - D Ventilation remains about the same as normal.
- 3 Administering oxygen to a spontaneously breathing patient causes — in respiration.
 - A No change.
 - B A transient stimulation.
 - C A transient depression.
- 4 When arterial oxygen tension is low, the ventilatory response to carbon dioxide is — than in normoxia.
 - A Slower.
 - B Faster.
 - C The same.
- 5 Oxygen tensions change at a different rate from carbon dioxide tensions because:
 - A the oxygen storage volume is smaller.
 - B the oxygen storage volume is greater.
 - C oxygen is metabolized at a different rate than carbon dioxide.

- D none of the above because the statement is incorrect.

6 The central chemoreceptors:

- A are sensitive to changes in arterial hydrogen ion concentration.
- B are more sensitive during hypoxia.
- C are responsible for the immediate increase in ventilation upon inhaling carbon dioxide.
- D are sensitive to changes in hydrogen ion concentration in medullary brain tissue.

7 The peripheral chemoreceptors are:

- A very sensitive to hypoxia when arterial carbon dioxide tensions are low.
- B responsive to changes in arterial hydrogen ion concentration.
- C responsible for most normal resting ventilation.
- D slow to respond to stimuli.

8 Concerning the regulation of respiration:

- A The peripheral chemoreceptors respond to an increase in arterial oxygenation by increasing their sensitivity to arterial carbon dioxide.
- B The blood-brain barrier permits the establishment of a carbon dioxide partial pressure gradient between arterial blood and brain tissue.
- C The chemoreflex system is designed primarily to keep brain carbon dioxide levels constant.
- D The central chemoreceptors increase ventilation during hypoxia.