The CO₂ response: usefulness and uncertainties

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In 1905, Haldane and Priestley [1] demonstrated the dramatic sensitivity of human ventilation to small increases in arterial carbon dioxide tension (Paco₂), a response now known to be mediated by the intracranial chemoreceptors, with an oxygen-dependent contribution from the peripheral chemoreceptors. Since that time, the response of minute or alveolar ventilation to increases in Paco₂ induced by the inhalation of CO₂ has remained one of the most widely studied relationships in human respiratory physiology. Elucidation of this response is still one of the few techniques available to study respiratory control in man. However, its purpose and limitations are often misunderstood, there is no ideal technique, and doubts have been expressed about its physiological relevance [2, 3].

Until computers became widely available, expired ventilation, measured by means of a gas meter, was one of the few easily measured output variables in man, and more recent attempts to substitute mean inspiratory flow and other components of the respiratory cycle of more relevance to recent models of control of the respiratory cycle [4-6] have still to gain widespread acceptance. The input variable, Paco₂, is usually approximated by end-tidal or alveolar carbon dioxide tension (Petco₂ or Paco₂), measured with great tedium in early studies by Lloyd-Haldane analysis of individual samples of alveolar air.

Carbon dioxide inhalation can be used qualitatively to test for presence or absence of CO₂ sensitivity, and to stress the system as a basis for other studies, or quantitatively to assess chemoreceptor gain under a variety of conditions [7-9]. A background of hyperoxia alveolar oxygen tension (PAO₂ >approx 200 mmHg) functionally inactivates the peripheral chemoreceptors and allows the CO₂ responsiveness of the intracranial chemoreceptors to be studied in isolation. Use of the CO₂ response to study chemoreceptor gains depends on the assumption that Petco₂ changes at the lungs are proportional to changes of H⁺ or carbon dioxide tension (Pco₂) at the chemoreceptors, but the location of this site for the intercranial chemoreceptors is even less certain than it was 20 yrs ago [10]. Following a step change of Pco₂ at the lungs in cats [11], brain extracellular fluid (ECF) H⁺ changes slowly, with a time constant of nearly a minute, and takes 5 min to stabilize, whilst ventilation lags still further, changing in man as a monoexponential with a half-time of 1-1.5 min [12]. The site of chemosensitivity is probably closer to the venous than the arterial side of the cerebral circulation and is, thus, influenced by cerebral blood flow, which increases dramatically as CO₂ increases [13]. The output of the chemoreceptors, thus depends not only on the amplitude of the increase in Paco₂, but also on the rate of change of Paco₂, and the time at which measurement is made. These vary for the different techniques used to determine the CO₂ response.

The traditional steady-state technique usually requires an open circuit [6, 8], and offers great flexibility in manipulation of inspired gases. Inspired CO₂ is held at a fixed level until ventilation reaches a quasi-plateau (usually 6-8 min), and the mean of ventilation over the final minute or two provides one point on the response curve. Successive levels are studied either by returning to eupnoea between each level, or by continuing up the response curve in steps of approximately 1% inspired Pco₂ up to 5-7%. A truly random technique is rarely possible, due to time constraints. Ventilation continues to change for hours and even days after a step of CO₂ [14], and thus it is difficult to define a true steady-state. Moreover, as ventilation increases, increasing amounts of CO₂ are inhaled, imposing a limitation on the range studied. Injection of a fixed amount of CO₂ per breath overcomes this limitation, and produces the same responses as standard inhalation techniques [15]. Because of the time required for one estimation, steady-state techniques are unsuitable for patient studies.

Rebreathing techniques are even more approximate, in that rebreathing from zero inspired CO₂, as used in the study of Tarver et al. in this issue [16] will result in progressively changing Pco₂ gradients across each of the interfaces between the alveolar air and the chemoreceptors, with even less certainty that changes of Paco₂ are proportional to changes of H⁺ at the chemoreceptors. The modification of Read [17], in which the rebreathing bag initially contains Pco₂ at the mixed venous level, ensures that the gradients are abolished, and partly overcomes these objections.

Nevertheless, rebreathing results often differ from those obtained by steady-state techniques. Recent studies in which rebreathing was stimulated [18], have documented criteria for the initial step and subsequent rate of increase of Paco₂ that ensure that rebreathing and steady-state responses are the same. These findings should be taken into consideration in future studies using rebreathing techniques.

Despite improvements in technique, the physiological relevance of these responses must still be questioned. It is generally accepted that the slope of a first degree
regression line fitted to this relationship, when Paco2 is increased between about 5–20 mmHg (0.7–2.7 kPa) above resting in hyperoxia, gives a measure of intracranial chemoreceptor sensitivity, with progressive increase in slope as oxygen tension (Pao2) falls [8] and a horizontal shift in the "fan" of lines in acidemia and alkalaemia [9]. However, breathing 2–6% CO2 is rarely physiologically.

The response, line is probably not linear over the whole range, and flattens off at higher values. Thus, the slope may be different if measured from a different starting value, or over a different part of the curve.

In early studies, the response at and just above resting was rarely studied, due to the breath-by-breath variability in this region, which was assumed to be due to the influence of "higher centre" noise, in the absence of the stabilizing effect of the chemoreceptors. Subject awareness of increase in ventilation at the higher levels of inspired CO2 was also offered as at least a partial explanation for day-by-day shifts in the slope and position of the response curves. This effect can be minimized by averaging the responses to small repeated changes in Paco2, [12, 19]. However, recent studies have shown that resting breathing patterns remain unchanged and unique to an individual over many years, even into stage IV sleep [20], suggesting that breathing may be less random and susceptible to higher centre influence than had previously been supposed.

The lower end of the CO2 response curve is flattened into a "dogleg" region in which CO2 responsiveness is greatly reduced or absent [7, 21]. Young described a region of increased instability at the junction of the "dogleg" and the steep part of the CO2 response curve, suggesting a possible change of mechanism at this point [21] Young is referred to in Cunningham's Review. The work was done by Young while working for Cunningham. Airway chemosensitivity, although of small quantitative importance [22], may also have an increased role in this region. Animal experiments show CO2 sensitivity maintained down to about 1 kPa [23], so that this "dogleg" probably reflects some form of central gating, rather than true loss of chemoreceptor sensitivity. In man, apnoea or unstable breathing patterns can be induced by small reductions in Paco2 below the resting level both in sleep [24, 25], and sometimes in the awake state [26–28]. Venous CO2 unloading by haemodialysis [29, 30], and ensemble averaging of ventilatory responses to transient CO2 pulses during recovery from voluntary overbreathing [19], suggest that the apnoeic threshold for Paco2 may be up to 10 mmHg (1.3 kPa) below the resting level, but with wide individual variation.

The normal "resting" control point probably lies just around the corner on the "dogleg" [30] and, in that the role of the intracranial chemoreceptors is probably to limit natural rises of Paco2, the normal operating range for this feedback control probably lies on this much flatter transitional zone. It is questionable, therefore, whether the slope of the CO2 response curve at much higher Paco2 levels is relevant to control of normal breathing. It may be more physiologically valid to measure the response immediately above resting, something which is rarely attempted. In exercise, it is uncertain whether the intracranial chemoreceptors have any role at all, and the CO2 response may have even less relevance here.

There are other uncertainties about CO2 response. The fact that there is a slope at all, reflects the inability of the control system to fully correct for the imposed increase in Paco2. It has still not been satisfactorily established if, or why, venous loaded CO2 (as in exercise) results in more complete feedback, and a steeper slope, than inhaled CO2. Recent studies of venous CO2 loading in haemodialysis (De Backer, personal communication) suggest that they are the same. Another factor, rarely considered, is the role of post-stimulus potentiation or "after discharge" [32], which will have a variable effect depending on the technique used to increase CO2. Functional residual capacity is rarely measured, but hyperinflation, such as occurs in obstructive lung disease, will increase ventilation [33], and may affect the slope of the response.

In lung disease the situation is even more complex. Because of gas exchange disruption and increased impedance, both Paco2 and ventilation may fail to reflect, respectively, the true input and output at the respiratory centres, requiring other measures, such as arterial or transtracheal Pco2, as inputs, and mouth occlusion pressure (P0.1) or diaphragmatic electromyographic activity (EMG) as outputs. Blood gas abnormalities at rest change the starting point of any determination and, assuming that the response curve is not linear over its range, make comparison between subjects difficult. In the study by TARISF et al. [16] use is made of the fact that the subjects are on a ventilator to normalize the eucapnic starting values to a fixed point (but not necessarily to the subjects, fixed point) to allow comparison of responses. Because of the uncertainties discussed above, their qualitative findings that patients with acute respiratory failure retain roughly normal CO2 sensitivity is valid, but any quantitation of the contribution of CO2 to ventilation in this situation must be interpreted with more caution.

It could be argued that respiratory disease affects the lungs and not the brain stem, and in the absence of neurological lesions, and allowing for chronic acid-base disturbances, there may be no reason to expect anything other than normal chemoreceptor function in these patients. However, sleep deprivation, such as occurs in many patients with respiratory disease, reduces the slope of the CO2 response without alteration of resting values and pattern of ventilation [34], but more recent studies suggest that this effect may be clinically unimportant [35].

References


