Carbon Dioxide Rebreathing and Mouth Occlusion Pressure Measurements

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The use of carbon dioxide as a stimulant in the evaluation of respiratory function is long established. In 1908, Haldane and Poulton observed the effects upon the breathing of subjects enclosed in a small wooden chamber. Techniques for inducing hypercapnia are today widely used in physiological and pharmacological research. Recent development may lead to renewed application of these methods to patients with diseased lungs. The technique described in this article permits separation of drug and disease effects upon structures involved in the process of breathing. One may now attempt to differentiate between respiratory depression due to effects upon the central nervous system and adverse effects principally affecting the lungs. An obvious clinical use for these new approaches would be to identify the patient with chronic bronchitis and a poor ‘drive to breathe’ who might be at serious risk of under-ventilation during an exacerbation of his condition. There are, unfortunately, a number of important problems inherent in the use of these procedures. It is the purpose of this simple review to highlight some of these weaknesses, especially for anyone beginning or contemplating such work.

CARBON DIOXIDE REBREATHING

A major technical advance was Read and Leigh’s (1967) rebreathing method for the production of progressive hypercapnia. In this, the subject rebreathes a mixture containing carbon dioxide and oxygen from a small closed circuit for several minutes. Simple bag-in-box arrangements are often used to measure ventilation, and carbon dioxide levels at the mouth are conventionally analysed with a rapid-acting infra-red device (Fig. 1). Thus, ventilation can be noted at several levels of CO₂ stimulation and a graph drawn (Fig. 2). The response line is described in terms of its slope (S, or ‘sensitivity’) and its extrapolated horizontal axis intercept (B, or ‘threshold’).

This approach had the advantages of speed and apparent simplicity, with the physiological attractions of a dynamic test that stressed the feedback control loop shown in Fig. 3.

It could be predicted that after a short period of equilibration between the subject and the circuit, lung and blood levels of CO₂ would rise in constant relation to those delivered to the medullary chemoreceptor (Read and Leigh,
Fig. 1. An example of the arrangement of apparatus used to measure ventilatory and \( \frac{dP}{dt} \) max responses when rebreathing. The rubber bag is suspended in a rigid container, and the minute volume, tidal volume and respiratory frequency are derived by means of the displacement of air from around the bag into a spirometer or through a flowhead (as shown). The starting volume of the rebreathing circuit is ideally equal to (vital capacity plus one litre) (Milic-Emili, 1975).

Fig. 2. Idealised result from a re-breathing experiment. There is a ‘dog-leg’ between resting levels of activity going on to a linear response at higher levels of stimulation here expressed as end-tidal PCO\(_2\).
1967), thus ‘opening-up’ the loop between response (ventilation) and stimulus (CO₂).

Compared with classical steady-state methods, rebreathing techniques give results with similar values for S (although B is shifted to the right) but the changes in slope produced by acid-base alterations are dissimilar (Cameron et al., 1972).

A high degree of co-operation and passivity is required of the subject in these experiments, and although this may be obtained from an experienced cohort of well-motivated subjects it is not always possible with patients. Inspection of the ventilation tracing will show deviations from the linear response due to voluntary efforts, swallowing and other interference. The sensory distractions provided by music through headphones and blindfolding may be helpful.

The volume and gas mixture used in the rebreathing circuit are crucially important. If too large a circuit is used the rate at which carbon dioxide accumulates will be affected by the initial level of ventilation. ‘Open-loop’ conditions between stimulus and response will not be present (that is to say the earlier pattern of breathing into the circuit may determine the stimulus rather than the converse). Likewise a CO₂ : O₂ mixture approaching mixed venous CO₂ levels (e.g. 6 : 94) is used rather than 100 per cent oxygen, so that an equilibrium plateau is rapidly attained and briefly held before the characteristic steady rise in levels over the three to four minutes of the rebreathing run.

This method is generally acceptable to normal people who are usually moderately breathless after the run and often complain of an evanescent bursting headache. Breathless patients may find the added dyspnoea less acceptable. There is some evidence that the vasodilatation caused by carbon dioxide could steal blood from areas of cerebral ischaemia in cases of stroke, thereby worsening the condition (Brawley et al., 1967).
Derivation of Results

Special care is needed in the derivation and handling of results. Many workers discard the earlier part of the recording and then note carbon dioxide levels with the corresponding ventilation at timed intervals to give 5 to 10 pairs of data.

A greater number of points (40 to 50) may improve reproducibility (Strachova and Plum, 1973) but considerably detracts from the feasibility of the method unless assisted by computer. Some have merely used graphical techniques to determine the slope, S, but it is preferable to calculate the least squares regression of ventilation upon carbon dioxide and to accept this as satisfactory only when there is a high correlation between the two sets of variables. There is still debate regarding the linearity of the response. The main practical guideline is the need to avoid the ill-defined dog-leg between resting values and slope. Variation in B is magnified by minor changes in S and in any event can only be a hypothetical index of true threshold. The take-off point of the response line from basal levels may be a truer ‘threshold’ (Borgstrom and Bulow, 1967) but cannot be accurately defined because of errors produced by measuring resting ventilation using mouthpiece and noseclip.

Variation in Results

(a) Inter-individual variation. There is a very wide variation in responsiveness to high levels of carbon dioxide between healthy individuals. This was recognised by Lindhard (1911) who wrote, ‘the excitability of the respiratory centre has for different individuals quite a different value’. Rebuck and Read (1971) described a fourteen-fold range of S, and other workers have found a similar spread of values (Lyall and Cameron, 1974). Data from a group of normal young people examined personally shows a comparable situation (Fig. 4).

Much of the variation seen results from differing tidal volumes between individuals when rebreathing, although ‘poor’ responders do not increase respiratory frequency as much as do others (Rebuck et al., 1974; Shaefer, 1958; Lyall et al., 1976). Genetic factors seem likely to be important; similar sensitivities were seen in identical twins (Leitch et al., 1975). A larger study of both mono- and dizygous twins suggested that genetic influences principally controlled the tidal volume, whereas the frequency component of the response was more related to environmental and psychological factors (Arkinstall et al., 1974). Racial influences were suggested by a study of New Guinea tribesmen, none of whom had high sensitivity, although normal values were found in Nigerians (Beral and Reed, 1971; Patrick, 1975). Endocrine factors such as progesterone levels and thyroid function are important (Lyons et al., 1959; Zwillich et al., 1975).

Data may be corrected for individual size by dividing the ventilatory response (expressed as litres/min/unit rise in CO₂) by body surface area, body weight or vital capacity (Avery et al., 1963; Agostini and Mead, 1964; Lyall and Cameron,
This last factor cannot readily be used in patients with abnormal lung volumes. Variance in results between normal adult subjects is only slightly reduced by this manoeuvre (Table 1). An alternative approach to skewed data of this type is logarithmic transformation (Hamilton, 1976).

Table 1. Between-subject variation in slopes ($S$) of responses to $CO_2$ rebreathing. Data from selected series, expressed as co-efficients of variation CV (standard deviation as a percentage of mean).

| Ventilatory Response(s) | (a) CV$\%$ | (b) CV$\%$ after correction of $S$ for vital capacity | (c) CV$\%$ after log transformation of individual values |
|-------------------------|------------|-----------------------------------------------------|------------------------------------------------------|
| Read and Leigh (1976)   | 45.6       | –                                                   | –                                                   |
| Rebuck and Read (1971)  | 73.4       | –                                                   | –                                                   |
| Irsigler (1975)         | 47.0       | 42.0                                                | –                                                   |
| This series             | 60.0       | 58.4                                                | 22.8                                                |

Table 1 continued...

| Slope of $dP/dt$ Max. Response | (a) CV$\%$ | (b) CV$\%$ after correction of $S$ for vital capacity | (c) CV$\%$ after log transformation of individual values |
|-------------------------------|------------|-----------------------------------------------------|------------------------------------------------------|
| Matthews and Howell (1975)    | 44.6       | –                                                   | –                                                   |
| This series                   | 37.2       | –                                                   | 16.2                                                |
No pathological significance is attached to very high levels of responsiveness in normal persons, whereas it has been postulated that those with low sensitivity might be prone to respiratory acidosis if faced with the burden of chronic bronchitis in later life (Lane and Howell, 1970; Clark and Cochrane, 1972; Matthews and Howell, 1976).

This wide variation in the normal leads to difficulty when comparing different groups, for example in drug trials, and in this case necessitates the careful use of within-subject controls. It would be quite possible to obtain statistically significant differences between groups if the control sample used happened to have high values, as might be seen when using a group of fit young doctors for this purpose.

(b) Intra-individual variation. Within-subject variation is perhaps the main practical weakness of the method. The absolute values for S may vary by up to 49 per cent of the mean in one person when measured repeatedly (Read and Leigh, 1967). For repeated studies in the same individuals over a period of time, coefficients of variation of 7.0 to 36.6 per cent have been reported (Strachova and Plum, 1973). It follows that the interpretation of small alterations or apparent trends in responsiveness must be guarded, even if a statistical case can be made for changing sensitivity (Menendez-Cordova et al., 1976). It is also important to know the reproducibility of a particular individual’s response before going on to examine the effects of drugs or other influences upon respiratory control. Both biological and technical factors seem likely to be responsible for this inconstancy, which emphasises the need for standardisation of procedure between laboratories.

MOUTH OCCLUSION PRESSURE MEASUREMENTS

(P 0.1 and dP/dt max)

If the lungs are mechanically abnormal there cannot be an efficient transformation of respiratory muscular work into gas movement (Cherniack, 1959). Thus, rebreathing experiments in subjects with airways obstruction might not differentiate between those who could not increase ventilation as a result of pulmonary factors and those who had true central insensitivity.

Links have been shown between phrenic nerve activity and the diaphragmatic electromyogram (EMG_dj), between total electrical activity of muscle and the force of isometric contraction, and between EMG_dj activity and the negative inspiratory pressure generated in the trachea of animals (Evanich, 1974; Altose et al., 1973; Evanich and Lourenço, 1974; Zubillaga et al., 1976). An increase in negative inspiratory pressures with increasing carbon dioxide levels occurs in cats (Lynne-Davis et al., 1971). Thus, if inspiration from functional residual capacity is arrested by a tap, or shutter device, diaphragmatic contraction is initially almost isometric against the occluded airway. Slight rarefaction of the thoracic gas is the only result. The negative pressure so created has therefore been used as an index
of central respiratory neuronal discharge in intact man (Whitelaw et al., 1975; Altose et al., 1976).

The application of the occlusion will disrupt the pattern of that breath (and possibly subsequent non-occluded breaths) after the load is appreciated by the subject (Kryger et al., 1976). Measurement of the recorded mouth occlusion pressure (MOP) is therefore made in very early inspiration, for example at 0.1 seconds into the occluded breath (P 0.1). Alternatively, the maximum rate of inspiratory pressure development (dP/dt max) is derived electronically (Matthews and Howell, 1975) and is thought to yield similar information. Technically P 0.1 is measured by surreptitiously closing a tap in the inspiratory part of the circuit during the expiration preceding the breath to be examined. This arrest of inspiration is uncomfortable; dP/dt max is generated against a lightly spring-loaded valve which briefly occludes each breath and is more acceptable to the subject. Both these methods are much simpler than older approaches to the problem of central chemosensitivity and drive such as the measurement of inspiratory mechanical work rate (Lane and Howell, 1970).

In practice, MOP and ventilation are noted at intervals during stimulated breathing and in normal persons rise closely together. Data for MOP values are handled in the same manner as measurements of ventilation. Between-subject variation in MOP sensitivities is rather smaller than that seen for ventilatory responsiveness (Table 1). This is of interest if MOP is accepted as a more proximal guide to central sensitivity. Like ventilation, MOP sensitivities show a unimodal distribution, having less asymmetry. In patients with normal carbon dioxide sensitivity but airflow limitation, ventilation is unable to rise when compared with the increases seen in mouth occlusion pressure (Matthews and Howell, 1976).

The addition of mouth occlusion pressure measurement to rebreathing methods has been promoted as a clinically useful test of the central drive to breath. By this means it has been shown that methoxyflurane depresses ventilation by acting on the lungs, leaving central sensitivity unharmed (Derenne et al., 1976). Data on the use of respiratory stimulants in respiratory failure could usefully be obtained by this approach.

Current interest focuses on the relationship between lung volumes and mouth occlusion pressure, since, in addition to the degree of motor neural activity, the force developed by contracting skeletal muscles is affected by their resting length. The effect of increased lung volume is to cause diaphragmatic flattening, with muscle fibre shortening and a reduction in mechanical efficiency (Marshall, 1962; Woldring, 1965; Pengelly et al., 1971). Normal subjects with a large functional residual capacity show a smaller increase in MOP per unit increase in carbon dioxide than do others (Shaffer et al., 1976). In addition, the inhalation of CO2 can of itself lead to increases in lung volume (Rodarte and Hyatt, 1973). Diseases such as bronchial asthma are associated with an increased lung volume which has obvious implications for their study (Woolcock and Read, 1966).
CONCLUSION

These new measurements are at an early stage in their evolution. Measurement of mouth occlusion pressure seems likely to inherit the difficulties of interpretation seen with studies of ventilation alone. Furthermore, the complex relationship between neuronal activity, lung volume and inspiratory pressure generation requires clarification.

Particular care should be taken when sampling populations and comparing sets of results, because of the great problem of variability found by all workers in this field.

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BRICKS AND MORTAR

London’s housing problem is far from new. Benjamin Disraeli, as Prime Minister, received a Memorial on the Dwellings of the Poor from the College. The memorial had been proposed by Dr Anstie who founded The Practitioner. It read ‘That your memorialists, in the daily exercise of their profession as physicians, are brought much into contact with the poorer classes of the population, and are deeply interested in everything that concerns the welfare of those classes, not only on account of the poor themselves, but also because the evils engendered among them often affect the whole of society. That it is well known to your memorialists at over-crowding, especially in unwholesome and ill constructed habitations, originates disease, leads to drunkenness and immorality and is likely to produce discontent among the poorer portion of the population.’

The memorial pointed out the distress of those whose homes were demolished under the authority of various Railway and Improvement Acts and considered that private enterprise was powerless to provide the necessary homes; it was for the Government to remedy the evils. All this has a modern ring, as does the Government’s action. It set up a Royal Commission to study the Housing of the Working Classes.