The expiratory capnogram : a measure of ventilation-perfusion inequalities

B . I . HOFFBRAND

From University College Hospital, London

Current methods of estimating ventilation–perfusion imbalance using radioactive gases (Dollery and Hugh-Jones, 1963), although giving regional localization, require exceptional technical resources, as does the single breath technique of West, Fowler, Hugh-Jones, and O'Donnell (1957). These methods also suffer the disadvantage that the respiratory manœuvres involved, such as breath-holding, may of themselves alter the ventilation–perfusion ratios (Briscoe, 1962). The method of Riley, Cournand, and Donald (1951) gives a measure of overall 'wasted' ventilation and perfusion (physiological dead-space and shunt, respectively) and avoids this latter disadvantage but requires arterial blood gas analysis.

The non-uniformity of expired carbon dioxide in emphysema has been known for many years (Roelsen, 1939). This scatter of expired carbon dioxide concentration (expiratory capnogram) is attributable to imbalance between alveolar ventilation and pulmonary capillary perfusion, different areas of lung having different carbon dioxide levels at end-inspiration and emptying asynchronously during expiration (Marshall, Bates, and Christie, 1952 ; Comroe, Forster, DuBois, Briscoe, and Carlsen, 1962). It has been suggested that the expiratory capnogram could be of value in the diagnosis of emphysema (Dornhorst, Semple, and Young, 1953) and of ventilation–perfusion imbalance in general (Comroe *et al.*, 1962). Kelsey, Oldham, and Horvath (1962), analysing the expiratory capnogram qualitatively, found that it was indeed of use in the diagnosis of chronic non-specific lung disease and could relate abnormal curves to certain conventional lung function test abnormalities.

It was decided, in view of the need for a relatively simple test of overall ventilation-perfusion imbalance, to investigate the expiratory capnogram further.

APPARATUS AND METHODS

A rubber mouthpiece, a 2·5 cm. bore steel tube with a right-angle side-piece sampling from the middle of the gas stream, and a wire-mesh pneumotachograph, linear from 0 to 200 l./min., were placed in series. The instrumental dead-space to the fractional sampling tube was 19·5 ml. The linearity of the pneumotachograph was confirmed by repeated recording in series with a rotameter. The gas was sampled at 500 ml./min., at which rate there was an adequate response time, with an insignificant loss through a single full expiration. This sampling rate is also unlikely to exceed the expiratory flow rate, since the lowest flow rate was 2·6 l./min. The sampling tube was connected by a short (3 cm.), thick polythene tube to the intake of the analysis cell of a Godart infra-red capnograph. This instrument had a 90% response time of 0·08 sec. and no shunt sensitivity to water vapour. Calibration graphs for this instrument were constructed using carbon dioxide in air mixtures prepared by rebreathing and analysed by the micro-Scholander method (Scholander, 1947). Carbon dioxide concentration, flow rate, and volume by electrical integration were recorded via a Vicker's respiratory analyser on three channels of an N.E.P. ultra-violet light recorder at a paper speed of 15 mm./sec. The volume calibration was provided by a Palmer spirometer.

Arterial blood samples were obtained early in the investigation. In-dwelling Riley needles were placed in the brachial artery, blood was taken into heparinized syringes, and the arterial Pco_2 was measured in a Severinghaus electrode. In the majority of cases, however, the arterial Pco_2 was determined indirectly from the mixed venous Pco_2, measured by the rebreathing method of Campbell and Howell (1960). The rebreathing procedure was recorded continuously by incorporating the capnograph into the closed circuit. Adequate tidal ventilation was ensured to prevent a false plateau. The arterial Pco_2 was derived from the recorded and directly measured mixed venous Pco_2 by deducting 6 mm. Hg (Hackney, Sears, and Collier, 1958 ; Campbell and Howell, 1960 ; Nicholls and Hoffbrand, 1962 ; see Appendix).

Resting carbon dioxide output was measured using the bag-box circuit of Donald and Christie (1949) and a low resistance one-way valve system, the dead-space of which was 69 ml. The kymographic record corrected for instrumental dead-space gave the minute ventilation and respiratory frequency. The mixed expired carbon dioxide concentration was measured

immediately on the capnograph calibrated as described above. The minute carbon dioxide output was then calculated.

PROCEDURES AND SUBJECTS

The procedures were fully explained and were then performed with the subjects in the resting state, sitting erect and wearing comfortable nose clips.

EXPIRATORY CAPNOGRAM   With the subjects breathing through the mouthpiece-sampling-tube-pneumotachograph series, resting tidal ventilations were recorded. When these were constant, a full expiration was made on instruction from the resting end-inspiratory position at a steady unhurried rate. Carbon dioxide concentration, flow rate, and volume were recorded simultaneously. The records of all full expirations preceded by a significantly non-resting inspired volume were discarded. In no case did it prove impossible to obtain suitable traces due to lack of cooperation. The procedure was usually repeated one or more times after an interval of 3 to 5 minutes' rest, the subjects remaining seated and unconnected to respiratory apparatus.

The analysis of the records was based on the single breath nitrogen test for uneven distribution of inspired gas (Comroe and Fowler, 1951). The gas in the anatomical dead-space is contained within the first 750 ml. of an expirate, the succeeding volume then consisting of 'alveolar gas'. Change in the composition of this gas over an arbitrary, constant volume is a measure of its non-uniformity (Comroe *et al.*, 1962). In the present study, the carbon dioxide concentration of the expirate at volumes of 750 and 1,250 ml. (A.T.P.S.) was measured, allowing for the instrumental time lag. The rise in concentration over this 500 ml. was converted into partial pressure (capnogram slope) using the ambient dry gas pressure. In some subjects the total full expiration was less than 1,250 ml. in volume, usually due to lung disease. The results in these cases are not considered in the present paper.

PHYSIOLOGICAL DEAD-SPACE   These procedures were performed 10 minutes after the last expiratory capnogram, the subjects sitting resting in the interim. The arterial P_{CO_2} was measured directly in a few subjects on blood taken during the middle minute of a three-minute expired gas collection. In the majority of subjects, the arterial P_{CO_2} was determined indirectly from the mean of mixed venous P_{CO_2}s measured before and after the three-minute expired gas collection. The carbon dioxide output and arterial P_{CO_2} enabled the alveolar ventilation to be calculated by Bohr's equation. The physiological dead-space ventilation (B.T.P.S.) was then determined from this and the minute ventilation, and the ratio dead-space : tidal ventilation (V_D/V_T) was derived.

SUBJECTS   Expiratory capnograms were recorded and the ventilation studies performed on 35 subjects. Five were normal volunteers ; the rest had a variety of cardiopulmonary disorders and included 11 unselected cases of chronic bronchitis. In one case the tests were done before and after an episode of pulmonary infarction, giving a total of 36 experiments.

To establish normal values the expiratory capnogram was recorded in a further 15 normal subjects. None of the normal subjects had chest symptoms and all had normal simple spirometry.

RESULTS

RELATION OF EXPIRATORY CAPNOGRAM AND VENTILATION

All subjects   The initial reading of the capnogram slope was plotted against V_D/V_T and showed (Fig. 1) a highly significant correlation ($r = 0.67$; $P < 0.0025$). The estimated S.D. of a predicted value of V_D/V_T is 0.019. There is a linear relationship up to a capnogram slope value of about 6 mm. Hg. For values above this level there is no further increase in V_D/V_T.

Figure 2 shows a similar but less significant correlation between capnogram slope and physiological dead-space ventilation ($r = 0.46$; $P < 0.005$).

Patients with chronic bronchitis   Figure 1 shows that the greatest capnogram slope values were found in the patients with chronic bronchitis. Figure 3 shows a close relationship between the capnogram slope and mixed venous P_{CO_2} in these 11 unselected cases ($r = 0.89$; $P = 0.0025$). A plot of these parameters in the other 25 experiments gave a completely random scatter.

The rate of rise of expired P_{CO_2} is partly related to the P_{CO_2} gradient between mixed venous blood and alveolar gas (DuBois, Fowler, Soffer, and Fenn, 1952). However, in the cases of chronic bronchitis, there was in fact a poor correlation ($r = 0.21$; $P = 0.53$) between the capnogram slope and (mixed venous P_{CO_2} minus the mean P_{CO_2} of expired gas between 750 and 1,250 ml. of
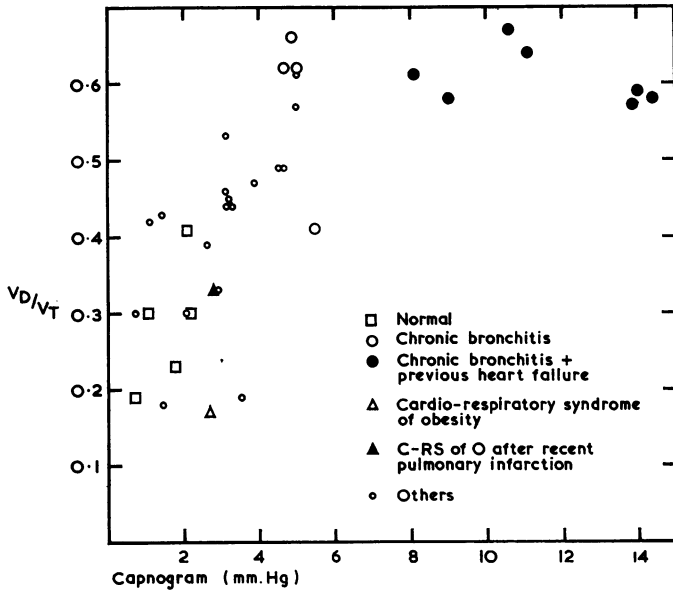
FIG. 1. *Relationship of V_D/V_T and the capnogram slope in 36 experiments in 35 subjects, normal and with a variety of cardiorespiratory conditions.*
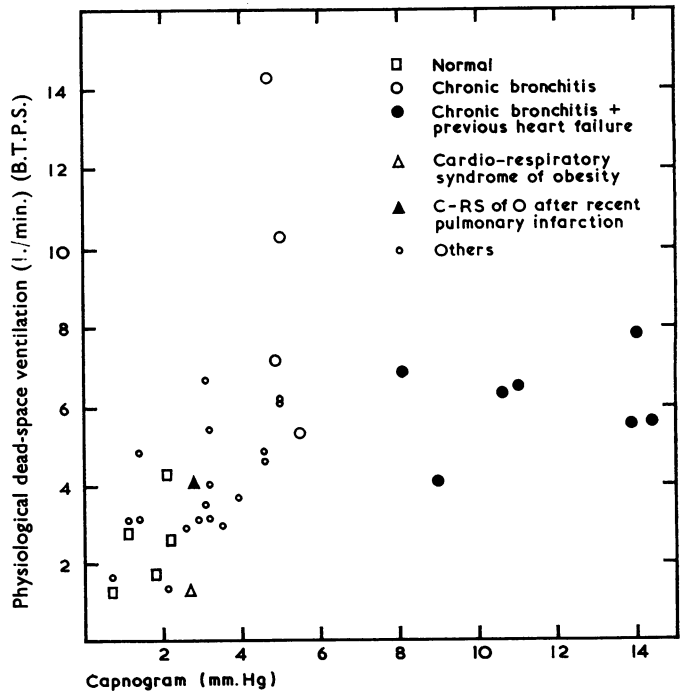

FIG. 2. *Relationship of the physiological dead-space ventilation and the capnogram slope in 36 experiments in 35 subjects, normal and with a variety of cardiorespiratory conditions.*

FIG. 3. *Relationship of the mixed venous* PCO_2 *and the capnogram slope in 11 unselected patients with chronic bronchitis, with and without previous heart failure. The results in a patient with the cardiorespiratory syndrome of obesity, who had recently been in heart failure, are also shown for comparison. The calculated regression line for the cases of chronic bronchitis,* $x = -8.655 + 0.310y$, *is shown.*
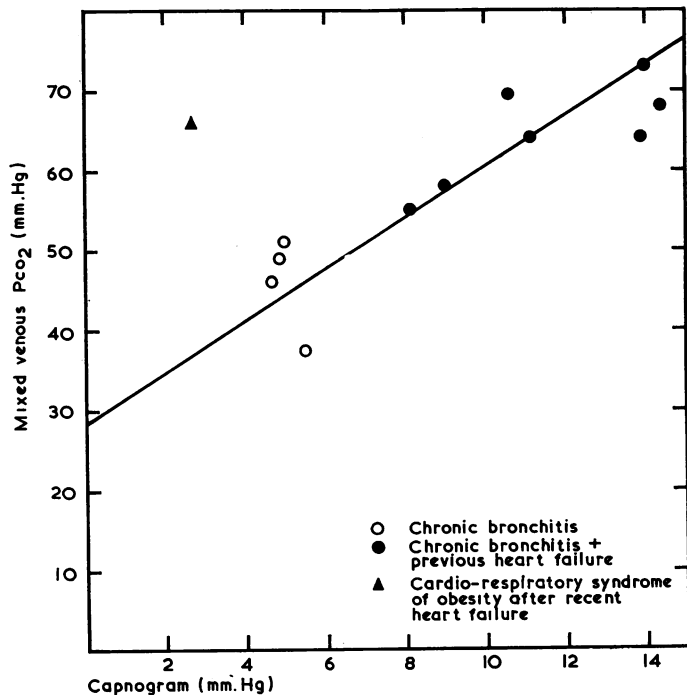
expirate), using this latter parameter as the average mixed venous–alveolar PCO_2 difference.

Further evidence was obtained to suggest that the close relationship between the capnogram slope and mixed venous PCO_2 in chronic bronchitis is not simply due to a PCO_2 gradient between mixed venous blood and alveoli. A patient with CO_2 retention (mixed venous $PCO_2 = 66$ mm. Hg) due to the cardiorespiratory syndrome of obesity was found to have a normal capnogram slope. By analysis of the residual variance the likelihood that these results would be found in the population with chronic bronchitis studied here is less than one in a hundred (see Fig. 3).

NORMAL VALUES OF CAPNOGRAM SLOPE   The expiratory capnogram was recorded 33 times in the 20 normal subjects with a mean value capnogram

TABLE

COMPARISON OF CAPNOGRAM SLOPE IN NORMAL
SUBJECTS AGED OVER AND UNDER 50 YEARS

	Age	
	> 50 Years	< 50 Years
Number	6	14
Mean age (yrs)	58·1	28·9
Mean capnogram slope (mm. Hg)	2·3	1·5
S.D.	0·78	0·60

slope of 1·84 mm. Hg (S.D. = 0.62, range 0·7 to 3·0). The Table shows a comparison of the initial capnogram readings in the normal subjects aged over and under 50 years. There was a significant difference (t = 2·238 ; p < 0·025). No difference was found on comparing the readings of the seven smokers and seven non-smokers, aged under 50 years.

REPRODUCIBILITY OF THE CAPNOGRAM SLOPE AND THE BREATH-HOLDING EFFECT   Three consecutive values of the capnogram slope were obtained in 24 subjects, both normal and with CO_2 retention. There was no systematic difference between successive readings. The S.D. within patients was 0·82, giving 95% confidence limits of a single reading of ±1·61.

During the finite time taken for expiration, no fresh inspired air reaches the alveoli. This factor, together with the progressively decreasing lung volume and a continued venous return to the lungs, increases the PCO_2 in the alveoli and thus in the expired air (DuBois *et al.*, 1952). An analysis was made of the duration of the 500 ml. expirates in the 24 subjects with three consecutive capnograms. The mean effect on the capnogram slope was an increase of 0·26 mm. Hg for every second of expiration from 750 to 1,250 ml. There

was, however, a considerable difference between patients, the change in the slope with time varying from $-15\cdot4$ (a result that can be given by only minor experimental variations and is due to an artefact of the method) to $1\cdot1$ mm. Hg/sec. Allowing for the between patients differences, the S.D. within patients is reduced to $0\cdot61$, a significant improvement over the averaged correlation ($p<0\cdot025$).

The presence of airway obstruction thus increases the capnogram slope by a breath-holding effect, slowing the rate of expiration. The time taken over the 500 ml. expirate was 3 to 5 sec. in the subjects with chronic bronchitis, compared with about 1 sec. in the others. Thus increased airway resistance may have contributed up to about $1\cdot5$ mm. Hg of the value of the capnogram slope in these patients. There was, however, no correlation between this slope and conventional measures of airway resistance such as forced expiratory volume.

DISCUSSION

The factors responsible for the rise in expired Pco_2 have been analysed by DuBois *et al.* (1952) and expressed in algebraic form. Berengo and Cutillo (1961) give a detailed mathematical analysis of the expiratory capnogram recorded in 15 subjects, dividing the capnogram into four phases separated by inflexion points. These workers found a high degree of correlation, excluding certain 'pathological' subjects, between the slope of the fourth or 'alveolar phase' and physiological dead-space. The rise in expired Pco_2 over a fixed volume as in the present study, rather than time, also correlates well with physiological dead-space ventilation but is even more closely related to V_D/V_T. With values for the capnogram slope above 6 mm. Hg, there is no further increase in V_D/V_T or physiological dead-space ventilation. Alveoli whose ventilation–perfusion ratios are low and thus make little contribution to dead-space ventilation must be responsible for these higher values and were presumably the cause of the lack of correlation between the 'alveolar phase' slope and physiological dead-space in Berengo and Cutillo's 'pathological' subjects. Although in ventilated alveoli there is no sharp dividing line between physiological dead-space and physiological shunt, these parameters merely reflecting total contributions of a spectrum of ventilation–perfusion ratios, the effect is predominantly one of increased shunt only with ratios below $0\cdot8$ (Briscoe and Cournand, 1962).

The high degree of correlation between the capnogram slope and mixed venous Pco_2 in chronic bronchitis suggests that these parameters are directly related and that they are not just independent measures of the severity of lung damage. The relationship could be explained if progressive reduction in alveolar ventilation (increasing mixed venous Pco_2) selectively affected areas of low ventilation–perfusion ratios, and tended in the absence of compensatory changes in distribution of perfusion to increase inequalities and thus the capnogram slope. Helium washout studies (Briscoe, 1952) suggest that in chronic bronchitis a large part of the lung air-space is poorly ventilated. This 'slow space' is over-perfused relative to ventilation, the overall ventilation–perfusion ratio being about $0\cdot4$ (Briscoe and Cournand, 1962). Any factors reducing alveolar ventilation, such as increased airway resistance or respiratory centre depression, are likely to affect primarily the less freely ventilated 'slow space'. As the 'slow space' occupies a large fraction of the functional residual capacity and thus of the pulmonary capillary bed, compensatory changes in perfusion will be difficult to achieve with a maintained pulmonary blood flow, and the fall in ventilation will reduce the ventilation–perfusion ratios further. It should be added that Briscoe's (1952) helium wash-out data suggest that the 'slow space' is homogeneously ventilated, a factor that would tend to iron out the non-uniformity of expired CO_2.

In the present cases of chronic bronchitis all those with a capnogram slope greater than 6 mm. Hg (and thus with physiological shunts) have been in heart failure, although none were in failure at the time of investigation. This is in agreement with observations that cor pulmonale in chronic bronchitis is related to abnormalities of the blood gases and to the greatest ventilation–perfusion inequalities (Fletcher, Hugh-Jones, McNicol, and Pride, 1963). That the cardiac failure found with respiratory insufficiency is not inevitably associated with ventilation–perfusion inequalities was demonstrated by the patient with the cardiorespiratory syndrome of obesity, whose capnogram slope was normal.

Methods of estimation of ventilation–perfusion imbalance based on expired CO_2 patterns have been criticized as too insensitive (Arnott, 1963). However, the present method has proved sufficiently sensitive to detect the increased ventilation–perfusion imbalance that occurs with advancing age (Read, 1959) and to distinguish groups of patients with carcinoma of the bronchus with and

without chronic bronchitis (Hoffbrand, Gillam, and Heaf, 1965). The discriminatory ability of the test will, moreover, be improved when the mean of multiple readings is used.

SUMMARY

A quantitative test of ventilation–perfusion imbalance based on the single breath expired carbon dioxide curve (expiratory capnogram) is described. The rise in Pco_2 in 500 ml. of 'alveolar' expirate (capnogram slope) is related, to a value of 6 mm. Hg, to dead-space ventilation. Values of capnogram slope greater than this are attributed to alveoli with low ventilation–perfusion ratios, which contribute a physiological shunt.

In patients with chronic bronchitis the capnogram slope is closely related to mixed venous Pco_2. The significance of this finding is discussed.

It is concluded that the expiratory capnogram can provide a simple, sensitive, reproducible, and clinically significant test of ventilation–perfusion imbalance, which warrants further investigation.

APPENDIX

Theoretical analysis indicates a reasonably fixed arteriovenous Pco_2 difference at rest, despite varying cardiac output (Suskind and Rahn, 1954). This difference has been shown to be about 6 mm. Hg and to be independent of CO_2 retention or dead-space ventilation (Hackney *et al.*, 1958 ; Campbell and Howell, 1960). These findings were confirmed in a separate study in this laboratory (Nicholls and Hoffbrand, 1962).

In the present investigation there was no significant difference between the mixed venous Pco_2 values measured before and after the three-minute rebreathing period. The mean difference, irrespective of sign, was 1·57 mm. Hg (S.D. = 1·02 ; range of first minus second +5·0 to −2·2). These findings show good reproducibility of the rebreathing method as well as a constant carbon dioxide output by the subjects.

All direct arterial Pco_2 estimation methods have, even with optimum techniques, random errors with standard deviations of about 1·5 mm. Hg (Thornton and Nunn, 1960). The sources of possible error are many, and it is doubtful whether in practice such accuracy is obtained. The indirect estimation of arterial Pco_2, using the method of Campbell and Howell (1960) with the precautions discussed in the present paper, is considered from the results obtained here to be eminently accurate enough for research purposes. The freedom of the patient from anxiety and discomfort associated with arterial puncture further commends to no small degree the indirect approach to the arterial Pco_2.

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