

Mixed Venous and Arterial PCO_2

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Summary

The rebreathing method of measuring oxygenated mixed venous PCO_2 ($P\bar{V}CO_2$) was originally introduced as a bloodless way to estimate arterial PCO_2 ($Paco_2$). It has become common practice to subtract 6 mm Hg from the $P\bar{V}CO_2$ to obtain the $Paco_2$, but there are many circumstances in which this leads to an overestimate of the $Paco_2$. Measurements of $P\bar{V}CO_2$ and $Paco_2$ in 19 patients have shown that a better approximation to $Paco_2$ under normal conditions of cardiac output and arterial O_2 saturation is $Paco_2 = 0.8 P\bar{V}CO_2$. These studies also showed that the $P\bar{V}CO_2 - Paco_2$ difference may be much wider, particularly in the presence of arterial unsaturation and a low cardiac output.

The factors governing the venoarterial PCO_2 difference are reviewed and their magnitude is calculated to emphasize the complementary roles of measurements of $P\bar{V}CO_2$ and $Paco_2$ in the assessment of patients with cardiorespiratory disease.

Introduction

Hackney *et al.* (1958) introduced the rebreathing method for measuring mixed venous PCO_2 into clinical practice as a means of estimating arterial PCO_2 . The principle they used was one which was introduced early this century (Plesch, 1909), in which the lung is used as an arotonometer so that the gases during rebreathing reach equilibrium with those in the mixed venous blood. Hackney *et al.* (1958) and Campbell and Howell (1960) examined the accuracy with which rebreathing methods could be used to estimate arterial PCO_2 ($Paco_2$). Both these groups reported that $Paco_2$ was on average 6 mm Hg less than "oxygenated" mixed venous PCO_2 ($P\bar{V}CO_2$), and since their work the subtraction of 6 mm Hg from the rebreathing equilibrium PCO_2 has become an accepted way of estimating $Paco_2$. Theoretical considerations and also our experience, however, indicate that the difference between $P\bar{V}CO_2$ and $Paco_2$ (the $\bar{v} - a$ PCO_2 difference) may be greater than 6 mm Hg. This paper reports on an experimental and theoretical examination of the different but complementary uses of $P\bar{V}CO_2$ and $Paco_2$ measurements.

Terminology

Arterial PCO_2 .—This is measured in samples of arterial blood using the CO_2 electrode or some similar method.

"True" Mixed Venous PCO_2 .—This is the PCO_2 of blood samples from the pulmonary artery (not measured in this study).

"Oxygenated" Mixed Venous PCO_2 .—This is the classical term used to describe the PCO_2 of mixed venous blood in which the haemoglobin is fully saturated with O_2 . The CO_2 content of this blood

is the same as true mixed venous blood but the PCO_2 is higher because oxygenation of haemoglobin decreases buffering capacity and reduces the amount of CO_2 carried as carbaminohaemoglobin—the Christiansen-Douglas-Haldane (C.D.H.) effect (Christiansen *et al.*, 1914). This is the PCO_2 which nearly all "indirect" rebreathing or breath-holding methods aim to measure by using the lungs as an arotonometer (see below).

Rebreathing PCO_2 .—This is recorded during rebreathing of a CO_2 mixture and measured when the CO_2 record shows CO_2 equilibrium between the rebreathing bag, the lungs, and the pulmonary capillary blood (Campbell and Howell, 1960, 1962).

The rebreathing PCO_2 as defined above is taken to be the oxygenated mixed venous PCO_2 . For the bulk of this paper this assumption is accepted, though it is re-examined below.

Material and Methods

Studies were performed on 19 patients, 11 with chronic hypercapnia and 8 with a normal $Paco_2$ (see table). The nature of the procedure was explained to all the patients, the fact that the investigation was for research purposes being pointed out, and their informed consent was obtained.

Spirometric measurements were performed on the day of the study. A Teflon arterial catheter was inserted percutaneously into the brachial artery. The patient sat upright and breathed through a valve box of low dead space. The CO_2 concentration in the mixed expired gas and the end tidal CO_2 were continuously measured to establish a steady state of CO_2 output. After attaining apparently steady-state conditions as indicated by a variation in the expired CO_2 and O_2 concentrations of less than $\pm 0.2\%$ arterial blood was sampled and the rebreathing PCO_2 estimated.

Rebreathing was performed with mixtures of CO_2 and O_2 in a rubber bag of nominal 5-litre capacity. The volume and CO_2 concentration of the gas in the bag were varied to achieve a sustained equilibrium in the rebreathing system. Up to six rebreathings were required to obtain a CO_2 equilibrium fulfilling the criteria set out below; at least half a minute was allowed to elapse between successive rebreathes in order to avoid the competing effects of CO_2 accumulation during rebreathing and the transient stimulus to breathing produced by it. Equilibration of CO_2 was recognized by the appearance of a "plateau" in the record of CO_2 concentration at the mouth; this plateau represents a period during rebreathing when there is no change in the CO_2 concentration of gas passing to and fro between the rebreathing bag and the lungs and which is sustained over several breaths, indicating a lack of net movement of CO_2 either into or out of the system. Previous studies (McEvoy *et al.*, 1973) indicated that the following criteria were necessary to achieve CO_2 equilibrium and a "true plateau."

(a) The CO_2 record should reach plateau conditions within 15 seconds of the onset of rebreathing.

(b) The plateau should be sustained for at least three complete respiratory cycles.

(c) The plateau should not show a tidal fluctuation of more than ± 1 mm Hg.

At least two estimates satisfying these criteria were obtained in 16 patients.

Measurements of CO_2 were made with an infrared CO_2 analyser (Godart Capnograph); the 90% response time of the analyser and sample system was 0.74 second. The analyser was calibrated with gases containing three concentrations of CO_2 in 40% oxygen, previous studies having shown that the rebreathing

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of CO₂ mixtures in oxygen leads to a concentration of 40% oxygen at the end of the rebreathing period. The calibrating gases were analysed with the Lloyd-Haldane apparatus. Oxygen was analysed in the mixed expired gas using a Servomex paramagnetic O₂ analyser, whose accuracy was checked with calibrated gases previously analysed in the Lloyd-Haldane apparatus.

Arterial blood was analysed with a pH meter (Radiometer) and with Severinghaus O₂ and CO₂ electrodes (Radiometer BMS-3). The electrode system was calibrated regularly with gases analysed in the Lloyd-Haldane apparatus and with tonometered blood. The mean (\pm S.D.) differences for duplicate analyses were 0.08 ± 1.10 mm Hg for CO₂ and 0.79 ± 0.50 mm Hg for O₂.

Results

In spite of our care in establishing "steady-state" criteria for CO₂ and O₂ concentrations in the expired gas before rebreathing, when analysing the results it became apparent that several studies had been carried out in an "unsteady state," with high values for the respiratory exchange ratio and arterial pH (see table). These patients are identified in fig. 1 and are omitted from the statistical analyses; wide $\bar{v} - a$ PCO₂ differences were found in these studies.

The differences between mixed venous PCO₂ and arterial PCO₂ varied from 4 mm to 25 mm Hg (table, fig. 1). The difference was greatest at high levels of PCO₂; high values were also associated with the presence of cardiac failure and arterial desaturation (fig. 1). The $\bar{v} - a$ PCO₂ difference for all patients excluding those showing a respiratory exchange ratio of over 1.0 is expressed as: $P_{aCO_2} = 0.68 P_{\bar{v}CO_2} + 7.4$ mm Hg ($r = 0.904$; S.E. 3.01). When the two patients with cardiac failure are excluded the regression equation is $P_{aCO_2} = 0.78 P_{\bar{v}CO_2} \pm 2.5$ mm Hg ($r = 0.904$; S.E. 2.50). These equations suggest that a better approximation to arterial PCO₂ is obtained by taking $0.8 P_{\bar{v}CO_2}$ rather than $P_{\bar{v}CO_2} - 6$.

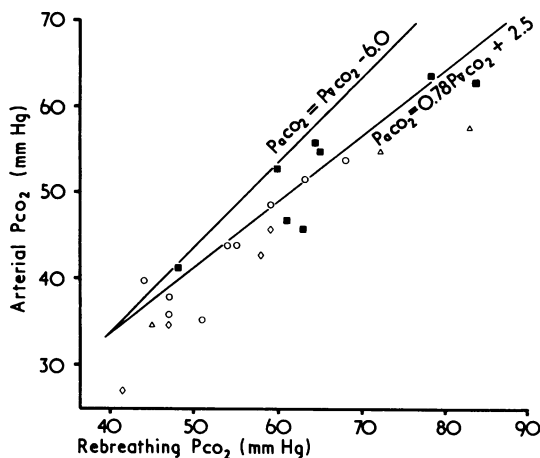


FIG. 1—Experimental results. Symbols other than (O) represent arterial O₂ saturation of less than 0.80 (■), patients with clinical evidence of right heart failure (▲), and studies in which respiratory exchange ratio was above 1.0 (△). Regression equation omits last two groups.

Discussion

The results in our patients in general bore out our experience—that is, the mixed venous PCO₂ was more than 6 mm Hg higher than the arterial PCO₂. Thus we critically re-examined this previously accepted difference.

FACTORS AFFECTING VENOARTERIAL PCO₂ DIFFERENCE

The mixed venous minus arterial PCO₂ difference is determined, firstly, by the venoarterial CO₂ content difference and, secondly, by the CO₂ dissociation curve, which expresses the relationship between CO₂ pressure and CO₂ content. The former represents the balance between pulmonary CO₂ excretion and cardiac output; the latter is influenced by blood haemoglobin, oxygenation, and the level of PCO₂ as detailed below. When taking usual values for these variables found in a healthy subject at rest the mixed venous minus arterial PCO₂ at rest is closer to 10 mm Hg than 6 mm Hg (fig. 2). One or more of the above factors may lead to the difference being increased to over 10 mm Hg. We examined these effects using the CO₂ dissociation curves of McHardy (1967) and Kelman (1967).

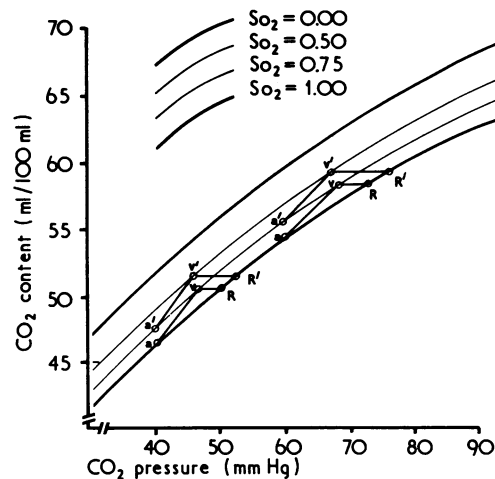


FIG. 2—Carbon dioxide dissociation curves for different values of arterial O₂ saturation (SO₂). Points a, v, and R represent arterial blood, true mixed venous blood, and oxygenated mixed venous blood respectively when arterial blood is fully saturated with O₂; a', v', and R' represent same relationships when arterial O₂ saturation is 0.75. Arteriovenous CO₂ content difference is constant at 4 ml/100 ml. Relationships for two levels of arterial PCO₂, 40 and 60 mm Hg, are shown.

Increasing Blood PCO₂.—The CO₂ dissociation curve is convex upwards; the $P_{\bar{v}CO_2} - P_{aCO_2}$ difference becomes wider for a given venoarterial CO₂ content difference in higher regions of the curve. This is illustrated in fig. 2, which shows that at a P_{aCO_2} of 40 mm Hg the mixed venous PCO₂ is 50 mm Hg for a venoarterial CO₂ content difference of 4 ml/100 ml; when P_{aCO_2} is 60 mm Hg the mixed venous PCO₂ is 72.5 mm Hg, the $\bar{v} - a$ PCO₂ difference increasing to 12.5 mm Hg.

Reduced Arterial Oxygen Saturation (fig. 2).—When the arterial blood is unsaturated the PCO₂ is lower for any given CO₂ content by virtue of the C.D.H. effect (compare a' and a in fig. 2). As the rebreathing method estimates the oxygenated mixed venous PCO₂ the $\bar{v} - a$ PCO₂ rises (compare the horizontal difference a-R with a'-R' in fig. 2). This effect is somewhat greater higher up the dissociation curve; at a P_{aCO_2} of 60 mm Hg the rebreathing PCO₂ is 76 mm Hg, a difference of 16 mm Hg (fig. 2).

Increased Venoarterial CO₂ Content Difference ($\bar{v} - a$ CCO₂).—When the Fick principle is applied to CO₂ exchange in the lung $\bar{v} - a$ CCO₂ = CO₂ output/cardiac output. Thus in any condition in which the cardiac output is low $\bar{v} - a$ CCO₂ is increased, leading to a rise in the $\bar{v} - a$ PCO₂ difference. The magnitude of this effect is shown in fig. 3 for a cardiac output which is half normal—that is, the $\bar{v} - a$ CO₂ content difference is twice normal at 8 ml/100 ml. At an arterial PCO₂ of 40 mm Hg $P_{\bar{v}CO_2}$ is 60.5 mm Hg, showing a $\bar{v} - a$ PCO₂ difference of 20.5 mm Hg. Thus a fall in cardiac output has a marked influence on the $\bar{v} - a$ PCO₂ difference.

Reduced Haemoglobin Concentration.—A reduced blood

haemoglobin increases the $\bar{v} - a$ PCO_2 difference for any given CO_2 content difference, particularly at low values of PCO_2 . This effect is shown in fig. 4, which indicates that at a haemoglobin level of 10 g/100 ml, an arterial PCO_2 of 40 mm Hg, and a CO_2 content difference of 4 ml/100 ml PvCO_2 is 53 mm Hg or 3 mm higher than at a haemoglobin of 15 g/100 ml.

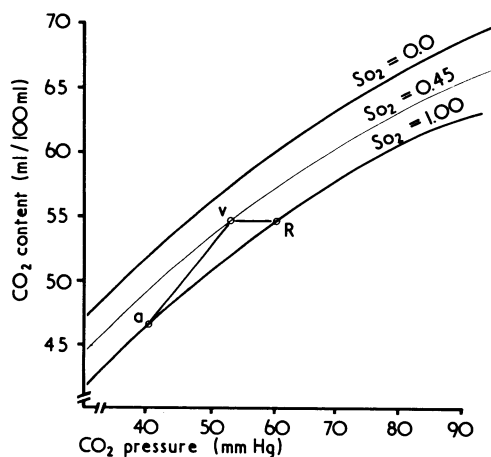


FIG. 3—Effect of increase in arteriovenous CO_2 content difference to 8 ml/100 ml; arterial blood fully oxygenated. Symbols as in fig. 2.

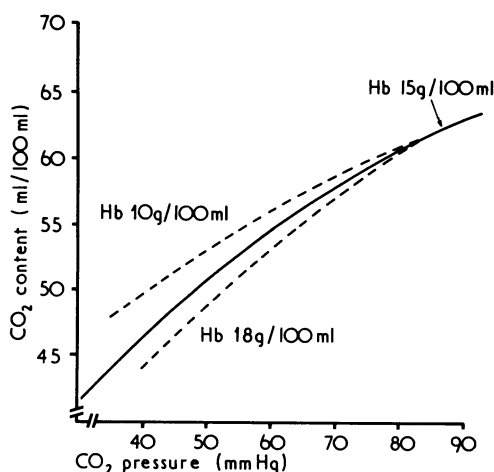


FIG. 4—Carbon dioxide dissociation curves of whole blood showing effect of haemoglobin levels.

We may summarize (fig. 5) by stating, firstly, that if equilibration is obtained with oxygenated mixed venous blood the equilibrium PCO_2 ($\text{P}\bar{\text{VCO}}_2$) will be 10 mm Hg above Paco_2 , given normal cardiac output, O_2 saturation, and haemoglobin; secondly, that the $\text{P}\bar{\text{VCO}}_2 - \text{Paco}_2$ difference is likely to be greater than 10 mm Hg if PCO_2 is high and arterial O_2 saturation is reduced (both being common in respiratory failure); if cardiac output is low (often a complicating factor in clinical practice); and, finally, if there is anaemia. Our studies in patients bore out these considerations (table, fig. 1).

In addition to these physiological factors the difference between mixed venous PCO_2 and arterial PCO_2 may be widened by a number of factors which are more technical than physiological in nature. Furthermore, the previously established difference of approximately 6 mm Hg may be accounted for by such factors.

Hackney *et al.* (1958) studied 60 patients with heart or lung disease and found that $\text{P}\bar{\text{VCO}}_2 - \text{Paco}_2$ varied from 1 to 11 mm Hg even when Paco_2 was high; in one of their patients

Paco_2 was 90.8 mm Hg and $\text{P}\bar{\text{VCO}}_2$ only 1 mm Hg higher. Such a venoarterial PCO_2 difference implies an impossibly high resting cardiac output and must be explained largely on technical factors.

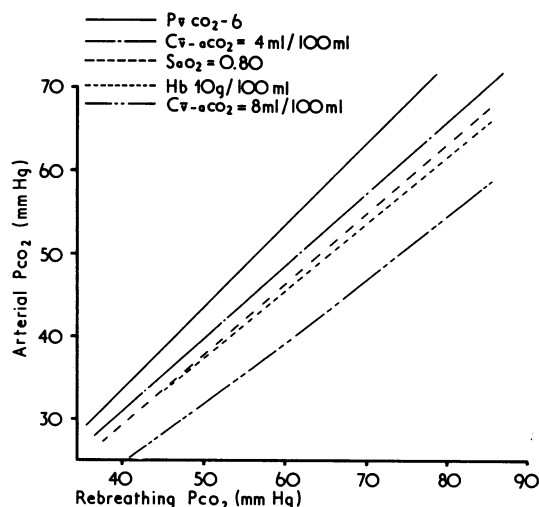


FIG. 5—Theoretical relationship between $\text{P}\bar{\text{VCO}}_2$ and Paco_2 at normal resting venoarterial CO_2 content difference ($\text{C}\bar{\text{v}} - \text{a}\text{CO}_2 = 4$ ml/100 ml), Hb of 15 g/100 ml, and O_2 saturation of 0.95 (—) showing (1) effect of doubling $\text{C}\bar{\text{v}} - \text{a}\text{CO}_2$ to 8 ml/100 ml (— — —) keeping Hb and O_2 saturation constant, (2) effect of lowering SaO_2 saturation to 0.80 keeping Hb 15 g/100 ml and $\text{C}\bar{\text{v}} - \text{a}\text{CO}_2$ at 4 ml/100 ml (— · — · —), and (3) effect of lowering Hb to 10 g/100 ml keeping $\text{C}\bar{\text{v}} - \text{a}$ at 4 ml/100 ml and arterial O_2 saturation at 0.95 (- - - - -).

In the rebreathing techniques described by Collier (1956) care was taken to avoid the effects of recirculation during rebreathing, but an early and brief CO_2 "plateau" appears from later work to lead to an underestimate of $\text{P}\bar{\text{VCO}}_2$ (Jones *et al.*, 1967). Thus the plateau PCO_2 values reported by Hackney *et al.* (1958) often may have represented transient equilibration between the bag CO_2 and the alveolar CO_2 without equilibration with mixed venous CO_2 ; this would be expected to lead to a $\text{P}\bar{\text{VCO}}_2$ value closer to alveolar and thus arterial PCO_2 than the true venous PCO_2 .

Campbell and Howell (1960) shared Collier's concern to avoid overestimation of $\text{P}\bar{\text{VCO}}_2$ through the recirculation of blood with high CO_2 content and accepted rebreathing plateau which did not last beyond 10 seconds (Campbell, 1974). In their 15 patients, 11 of whom had lung disease, Campbell and Howell found a mean difference between $\text{P}\bar{\text{VCO}}_2$ and Paco_2 of 6.1 mm Hg when Paco_2 ranged from 16 to 73.5 mm Hg. For the same reasons we now believe that the measurements of $\text{P}\bar{\text{VCO}}_2$ using their method also lead to underestimates. This is supported by a figure in their paper which shows a rebreathing plateau which lasts for only one complete breath and represents a "phase reversal" of CO_2 (a pattern in CO_2 analysed at the mouth which changes from the CO_2 being higher in the rebreathing bag than in the lungs to one in which the CO_2 is higher in the lungs than in the bag). This phase-reversal pattern occurs long before recirculation could have raised the true $\text{P}\bar{\text{VCO}}_2$; to be certain of equilibrium with pulmonary capillary blood a plateau should last for at least two complete respiratory cycles and until at least 15 seconds after the start of rebreathing. We know that recirculation in a resting subject is unimportant until after 15 seconds (Sowton *et al.*, 1958), and in our experience it is unusual to obtain plateau conditions before 10 seconds in most patients with severe airway obstruction.

Lowering of Paco_2 due to transient hyperventilation may be associated with arterial puncture even when great care is taken to minimize anxiety or discomfort. As body CO_2 stores are large the fall in mixed venous PCO_2 lags behind the fall in

Clinical and Experimental Data on Patients Studied

Case No.	Age (Years)	Sex	Body Surface Area (m ²)	Diagnosis	Hb (g/100 ml)	% Predicted FEV ₁	Sao ₂	P \bar{V} CO ₂ (mm Hg)	Paco ₂ (mm Hg)	P \bar{V} CO ₂ - Paco ₂ (mm Hg)	Respiratory Exchange Ratio (R.Q.)
1	45	F.	1.30	Bronchiectasis, recurrent cardiac failure	17.4	17	0.91	83	58	25	0.94
					17.2	20	0.94	72	55	17	0.83
2	50	M.	1.66	Chronic bronchitis	17.5	46	0.93	58	43	15	1.09
					17.3	20	0.86	65	53	12	0.90
3	53	M.	1.75	Chronic bronchitis	17.2	24	0.91	68	54	14	0.75
					17.2	14	0.76	84	65	19	—
4	74	M.	1.77	Chronic bronchitis	15.5	26	0.83	64	56	8	0.85
					12.5	20	0.90	59	46	13	1.13
5	71	M.	1.94	Chronic bronchitis	16.4	32	0.93	54	44	10	0.86
					18.1	31	0.81	63	46	17	0.80
6	58	M.	2.08	Chronic bronchitis	17.0	40	0.86	65	55	10	0.77
					17.2	48	0.93	63	52	11	0.97
7	62	M.	2.13	Chronic bronchitis	16.6	20	0.91	59	49	10	1.00
					11.2	19	0.75	78	64	14	0.90
8	66	M.	1.49	Chronic bronchitis	17.3	51	0.88	60	53	7	0.85
					16.3	43	0.88	61	47	14	0.89
9	66	M.	1.77	Chronic bronchitis and emphysema	15.5	77	0.95	55	44	11	0.76
					17.0	40	0.86	65	55	10	0.77
10	72	M.	1.84	Chronic bronchitis	17.2	48	0.93	63	52	11	0.97
					16.6	20	0.91	59	49	10	1.00
11	54	M.	2.12	Chronic bronchitis	11.2	19	0.75	78	64	14	0.90
					17.3	51	0.88	60	53	7	0.85
12	58	M.	1.86	Chronic bronchitis and mitral stenosis	16.3	43	0.88	61	47	14	0.89
					15.5	77	0.95	55	44	11	0.76
13	56	M.	1.97	Chronic bronchitis, emphysema	15.3	75	0.95	42	27	15	1.27
					15.4	19	0.94	45	34.5	10.5	1.00
14	61	M.	1.65	Chronic bronchitis, mitral stenosis, cardiac failure	15.4	19	0.94	45	34.5	10.5	1.00
					12.9	64	0.93	44	40	4	0.74
15	50	M.	1.74	Bronchiectasis	16.1	59	0.93	47	34.5	12.5	1.12
					18.0	19	0.74	48	41.5	6.5	0.85
16	59	M.	1.80	Chronic bronchitis	18.0	19	0.74	48	41.5	6.5	0.85
					11.8	84	0.96	47	38	9	0.84
17	49	M.	1.88	Chronic bronchitis and pulmonary fibrosis	13.0	87	0.94	47	36	11	0.91
					11.8	84	0.96	47	38	9	0.84
18	48	F.	1.54	Pulmonary fibrosis	13.0	87	0.94	47	36	11	0.91
					13.0	87	0.94	47	36	11	0.91
19	53	F.	1.74	Mitral incompetence	13.0	87	0.94	47	36	11	0.91
					13.0	87	0.94	47	36	11	0.91

Paco₂, leading to an increased difference between P \bar{V} CO₂ and Paco₂. Such hyperventilation will also lead to high values for the respiratory exchange ratio and arterial pH as found in several of our patients (table). Finally, a true difference may exist between the rebreathing PCO₂ and the PCO₂ in venous blood. There is evidence that such a difference may exist during exercise (Jones *et al.*, 1967, 1969) but at rest it is insignificant and certainly cannot be more than 2 mm Hg even in patients with chronic airway obstruction and respiratory failure (McEvoy *et al.*, 1973).

The fact that many mechanisms may effect the prediction of Paco₂ from measurements of P \bar{V} CO₂ may at first sight appear to reduce the value of measurements of P \bar{V} CO₂ in clinical practice. We do not believe that this is so. The two measurements really are complementary. Under conditions in which the difference between them may be increased or unpredictable it can by no means be taken as axiomatic that the arterial PCO₂ is preferable on either technical or physiological or clinical grounds. It is true that the rebreathing method for measuring P \bar{V} CO₂ and estimating Paco₂ was introduced at a time when the estimation of arterial blood gases was time consuming and beset by appreciable technical error. By contrast blood-gas electrodes are now commonplace in all hospitals in which seriously ill respiratory patients are cared for and the measurement of mixed venous PCO₂ may be thought to have lost its value. The following points may, however, be adduced to improve the appreciation of their relative technical, physiological, and clinical places. The measurement of P \bar{V} CO₂ is simple, rapidly performed by relatively unskilled personnel, and may be repeated often. The reproducibility and accuracy are close to those obtained in measurements of Paco₂. From the physiological point of view P \bar{V} CO₂ is less apt to be affected by transient hyperventilation. The argument that P \bar{V} CO₂ is affected by mechanisms additional to those influencing Paco₂ may be turned to advantage through an understanding of their importance. For example, the contribution of a low cardiac output to the total clinical picture in a patient with respiratory failure may be recognized through its effect on CO₂ transport. Though arterial PCO₂ unquestionably

reflects respiratory function mixed venous PCO₂ reflects the sum total effects of all mechanisms clearing CO₂ from extracellular fluid and is a better approximation to the PCO₂ of the extracellular fluid.

Thus the clinical importance of measurements of P \bar{V} CO₂ is based on the following reasoning. Firstly, in patients in whom Paco₂ is not greatly raised—that is, those in whom alveolar ventilation is not greatly impaired—P \bar{V} CO₂ will give an accurate estimate of Paco₂, which is not much influenced by transient hyperventilation. Secondly, in patients in respiratory failure the P \bar{V} CO₂ reflects the adequacy of all CO₂ transport mechanisms—alveolar ventilation, pulmonary gas exchange, cardiac output, and carriage of CO₂ in blood. Furthermore, provided adequate criteria of equilibration are met it will never lead to an underestimate of Paco₂; a raised P \bar{V} CO₂ will thus direct attention to all mechanisms rather than to alveolar ventilation alone. Finally, when used in conjunction with measurements of Paco₂ it will allow some assessment of the adequacy of cardiac output.

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References

- Campbell, E. J. M., and Howell, J. B. L. (1960). *British Medical Journal*, 1, 458.
 Campbell, E. J. M., and Howell, J. B. L. (1962). *British Medical Journal*, 2, 630.
 Campbell, E. J. M. (1974). Unpublished.
 Christiansen, J., Douglas, C. G., and Haldane, J. S. (1914). *Journal of Physiology*, 48, 244.
 Collier, C. R. (1956). *Journal of Applied Physiology*, 9, 25.
 Hackney, J. D., Sears, C. H., and Collier, C. R. (1958). *Journal of Applied Physiology*, 12, 425.
 Jones, N. L., *et al.* (1967). *Clinical Science*, 32, 311.
 Jones, N. L., *et al.* (1969). *Journal of Applied Physiology*, 27, 356.
 Kelman, G. R. (1967). *Respiratory Physiology*, 3, 111.
 McEvoy, J. D., Jones, N. L., and Campbell, E. J. (1973). *Journal of Applied Physiology*, 35, 542.
 McHardy, G. J. R. (1967). *Clinical Science*, 32, 299.
 Plesch, J. (1909). *Archiv für experimentelle Pathologie und Therapie*, 6, 380.
 Sowton, E., *et al.* (1968). *Cardiovascular Research*, 2, 341.