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Measurement of effective alveolar carbon dioxide tension during spontaneous breathing in normal subjects and patients with chronic airways obstruction

J Jordanoglou, N Koulouris, D Kyroussis, P Rapakoulias, P Vassalos, J Madianos

Abstract

Background **– The measurement of effective alveolar carbon dioxide tension ($P_{A}CO_2$eff) is still a matter of debate. It has, however, become common practice to use arterial instead of alveolar CO_2 tension for computing alveolar oxygen tension (PAO_2) and physiological dead space, not only in normal subjects but also in patients. The purpose of this study was to estimate alveolar CO_2 tension during spontaneous breathing with a new bedside technique which is simple and non-invasive, and to compare these values with arterial CO_2 tension measured in normal subjects and patients with chronic airways obstruction.**

Methods **– The subjects breathed quietly through the equipment assembly (mouthpiece, monitoring ring, Fleisch transducer head) connected to a pneumotachograph and a fast response infrared CO_2 analyser. The method is a computerised calculation of the volume weighted effective alveolar CO_2 tension obtained from the simultaneously recorded expiratory flow and CO_2 concentration versus time curves. An arterial blood sample was taken to measure $PaCO_2$ for comparison during the study.**

Results **– The results showed a mean difference ($PACO_2$eff − $PaCO_2$) of −0·205 kPa in 20 normal subjects and −0·460 kPa in 46 patients. The 95% confidence interval of the bias was −0·029 to −0·379 kPa in normal subjects and −0·213 to −0·707 kPa in patients. The limits of agreement between $PACO_2$eff and $PaCO_2$ were 0·526 to −0·935 in normal subjects and 1·170 to −2·088 in patients.**

Conclusions **– The volume weighted effective alveolar PCO_2 in normal subjects and patients with chronic airways obstruction is lower than the arterial PCO_2 and is recommended as a better estimate in the classical equations for estimating dead space and intrapulmonary shunt.**

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Keywords: alveolar CO_2 tension, alveolar–arterial PCO_2 difference, chronic airways obstruction, spontaneous breathing.

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The estimation of effective alveolar carbon dioxide tension is still a matter of debate because the available methodology is not widely accepted. In most classical calculations alveolar carbon dioxide tension ($PACO_2$) has been assumed to be equivalent to arterial blood CO_2 tension ($PaCO_2$) in normal subjects.[1–10] It has also become common in clinical practice and in research work to use arterial CO_2 tension as a substitute for alveolar CO_2 tension for the computation of alveolar oxygen tension (PAO_2) and of the physiological dead space/tidal volume ratio (VDphys/VT).[1 2 5 6 8–11] The aim of this study was to estimate effective alveolar CO_2 tension during tidal breathing with a new and simple technique and to compare these values with arterial CO_2 tension in both normal subjects and patients with chronic airways obstruction.

Methods

THEORETICAL CONSIDERATIONS

The method is based on the computation of the effective CO_2 concentration in the expired air at the mouth ($FECO_2$eff) and the dead space/tidal volume ratio (VD/VT) on the $\dot{V}E$/time(t) curve by the aid of the effective time (teff) of the FCO_2/t curve. The computed values of $FECO_2$eff and VD/VT are used in Bohr's equation for the estimation of the effective alveolar CO_2 concentration per breath ($FACO_2$eff).

The expiratory flow ($\dot{V}E$/t) and the CO_2 concentration versus time (FCO_2/t) curves are first aligned for the phase lag (Φ). This exists between the two curves as a result of the different response times between the pneumotachograph and the capnograph. The FCO_2 limits of the FCO_2/t curve are determined by the points of zero flow on the $\dot{V}E$/t curve – that is, the beginning and the end of expiration. The initial part of the FCO_2/t curve has zero FCO_2 values and variable duration (t_0). At the end point of t_0 the rate of rise of FCO_2 ($dFCO_2/dt$) is steep, but it decreases progressively until the end of the curve. At this point FCO_2 and $FETCO_2$ are equal (fig 1). In some FCO_2/t curves the end part of the curve reaches a plateau. The area over the FCO_2/t curve [$\int FCO_2 dt(a)$] is confined by the horizontal line at the level of $FETCO_2$ parallel to the time axis, and the vertical line passing through the end point of the time interval (t_0) (fig 1). The ratio of this area divided by $FETCO_2$ equals the effective time of the curve (teff) (fig 1):

$$teff = \int FCO_2 dt(a) / FETCO_2 \quad (1)$$

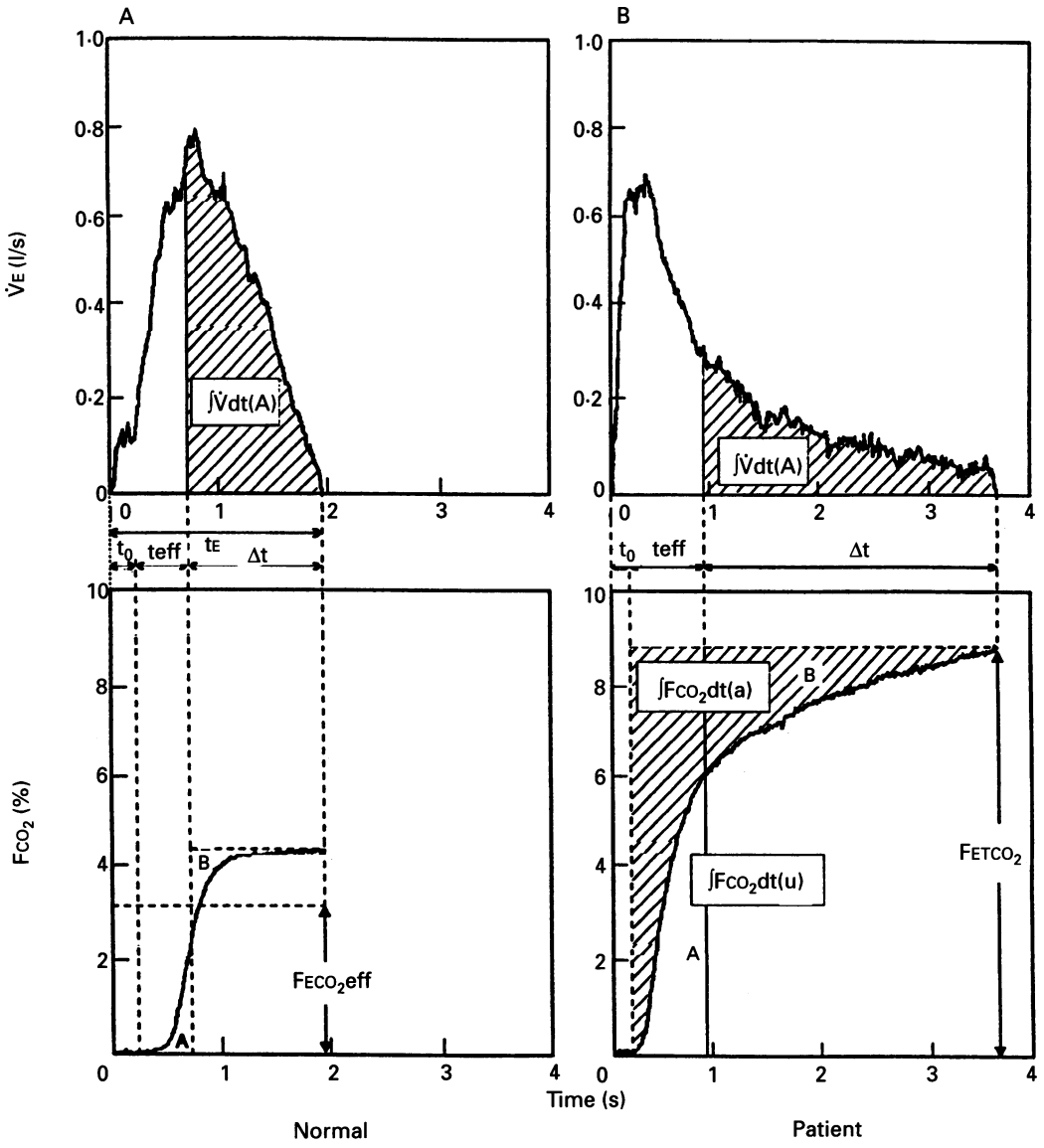

Figure 1 Expiratory flow ($\dot{V}_E$/t) and CO_2 concentration versus time curves (F_{CO_2}/t) recorded simultaneously after correction for the phase lag during spontaneous breathing from (A) a normal subject and (B) a hypercapnic patient with COPD ($\dot{V}_E$ in l/s, F_{CO_2} in %, time in seconds). The expiratory time (t_E) is equal to the sum (t_0+teff+Δt). In the F_{CO_2}/t curves area A=area B (see text). The area enclosed by the F_{CO_2}/t curve [∫F_{CO_2}dt(u)] = (F_{ECO_2}eff × t_E).

The effective time of the F_{CO_2}/t curve permits the transformation of this curve to a square wave, the initial part of which is characterised by (t_0+teff) and $F_{CO_2}=0$, and the rest of it by the time interval $\Delta t = (t_E - t_0 - teff)$ and $F_{CO_2} = F_{ETCO_2}$ (fig 1). In fact, Δt is equal to the ratio [∫F_{CO_2}dt(u)/F_{ETCO_2}] where ∫F_{CO_2}dt(u) is the area enclosed by the curve itself, the time axis, and the vertical line passing through the point of F_{ETCO_2} (fig 1). The time interval (t_0+teff) of the transformed F_{CO_2}/t curve corresponds to that part of the tidal volume (integrated area on $\dot{V}_E$/t curve) which does not participate in gas exchange ($F_{CO_2}=0$) – that is, to the dead space volume [∫$\dot{V}$dt(D) = V_D] (fig 1). The rest of the tidal volume corresponds to the alveolar volume [∫$\dot{V}$dt(A) = V_A] (fig 1). The ratio of the area ∫$\dot{V}$dt(A) divided by the area ∫$\dot{V}$dt(=V_T) is the ratio of alveolar volume to tidal volume (V_A/V_T). The effective concentration of CO_2 in the expired air (F_{ECO_2}eff) per breath is equal to the ratio of the area ∫F_{CO_2}dt(u) divided by the expiratory time (t_E) (fig 1):

$$F_{ECO_2}\text{eff} = \int F_{CO_2}dt(u)/t_E \quad (2)$$

According to Bohr's equation the ratio V_A/V_T is equal to the ratio F_{ECO_2}/F_{ACO_2}. Hence, the effective value of the alveolar CO_2 concentration (F_{ACO_2}eff) is equal to:

$$F_{ACO_2}\text{eff} = F_{ECO_2}\text{eff}/(V_A/V_T) \quad (3)$$

STUDY DESIGN

The study was performed in 20 normal subjects (11 men) aged 18–65 (mean 40) years and 46 ambulatory patients (31 men) aged 35–83 (mean 61) years with chronic bronchitis/emphysema or bronchial asthma. All patients were in a stable clinical and functional state and were recruited from the respiratory outpatient clinic. Their lung function data (table 1) were obtained in the seated position with a flow-sensing spirometer (Fukuda; Spiroanalyzer ST300, Japan). Predicted lung function values were those of Morris and coworkers.[18] Arterial

Table 1 Mean (SD) spirometric characteristics of the subjects studied (Fukuda Spiroanalyzer ST300)

	FVC		FEV_1		FEV_1/FVC	FEF_{25-75}	
	l (BTPS)	*% pred*	*l (BTPS)*	*% pred*	*(%)*	*l/s*	*% pred*
Normal subjects (n=20)	3·995 (0·986)	101·01 (10·56)	3·211 (0·950)	97·67 (8·72)	79·44 (6·40)	3·029 (1·397)	87·27 (23·07)
Patients (n=46)	2·685 (1·028)	69·84 (21·08)	1·708 (0·898)	55·85 (25·03)	62·18 (17·13)	1·205 (1·041)	36·15 (28·23)

Normal predicted values obtained from Morris *et al.*[18]

P_{CO_2} was measured with a blood gas analyser (ABL; Radiometer, Copenhagen, Denmark).

The experimental setup used to assess P_{ACO_2} was a flanged plastic mouthpiece connected in series to a Fleisch No 2 flow transducer head (Fleisch, Lausanne, Switzerland) via a metal piece (monitoring ring) on which the CO_2 probe was attached. The pneumotachograph (transducer + amplifier: Gould Godart BV; No. 17212, Bilthoven, Holland) was connected with the Fleisch head via two semirigid plastic tubes, 12 cm in length. The pneumotachograph system (rise time 10–90% = 13 ms) was linear over the range of flows used. An infrared capnograph (Jaeger; CO_2 test III, Wuerzburg, Germany) (rise time 10–90% = 100 ms) was connected to the monitoring ring through a thin polyethene tube (50 cm length, internal diameter 1·2 mm). The mouthpiece assembly had an expiratory dead space of less than 5 ml and minimal resistance to airflow. Calibration of the capnograph was made using a mixture of 4% CO_2 in air before and after each study. The phase lag between the $\dot{V}_E/t$ and F_{CO_2}/t curves was determined by an abrupt change in flow of a gas mixture containing 4% CO_2 generated through the mouthpiece assembly.

The measurement of the phase lag and the calibration of the capnograph were repeated three times and the mean values used. The rise time (10–90%) of the capnograph was at least 4·55 times faster than that of the fastest F_{CO_2}/t curve in normal subjects and in patients breathing at a respiratory frequency of 12–18/min.[19,20] Airflow and CO_2 signals were amplified, monitored on line on the computer screen, and sampled simultaneously at a rate of 75 Hz using a computer data acquisition system with a built in 12-bit analogue to digital converter (National Instruments; AT-M10, Austin, Texas, USA). Collected data were stored on computer disk for subsequent analysis with our custom made computer analysis software. These signals were also amplified (Hewlett-Packard; 7700 system, Waltham, Massachusetts, USA) and simultaneously recorded by a pen recorder (Hewlett-Packard; system 7700) onto thermographic paper with the speed of 20 mm/s. End tidal CO_2 concentration (F_{ETCO_2}) was measured at the point on the F_{CO_2}/t curve corresponding to $\dot{V}_E = 0$. Alveolar CO_2 tension was also computed manually from the $\dot{V}_E/t$ and F_{CO_2}/t curves recorded onto the thermographic paper according to equation (3) in order to check the validity of our custom made software computer program. The areas under the $\dot{V}_E/t$ and F_{CO_2}/t curves were measured with a digital planimeter (Hewlett-Packard; 9111A Graphics Tablet) and a desk top calculator (Hewlett-Packard; 85 A). The results obtained by manual and computer analysis in 10 normal subjects were related to each other by the Bland and Altman statistical method[12] (fig 2). It is evident that both methods of computation yielded closely similar results.

Subjects were studied while seated upright in a comfortable chair at least two hours after eating or taking coffee. They were asked to breathe room air through the equipment assembly while wearing a noseclip. Each subject had an initial 10–15 minute trial run to become accustomed to the apparatus and procedure. The pneumotachograph and the capnograph were continuously monitored on line on the computer screen. After regular breathing had been achieved a series of breaths was recorded over a period of one minute. At the end of the recording time an arterial blood sample (>1 ml) was taken for gas analysis. A quick (5–10 second) and direct puncture of the brachial artery was performed by an expert doctor using a 21G needle.

The study was approved by the local ethics committee and all subjects gave informed consent.

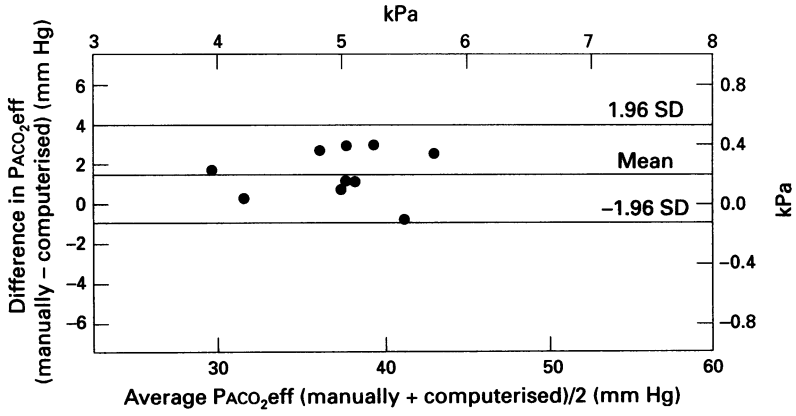

Figure 2 Bland-Altman diagram for the comparison between P_{ACO_2}eff calculated manually and P_{ACO_2}eff measured by computer. Upper limit of agreement (mean + 1·96 SD) = 0·530 kPa; lower limit of agreement (mean − 1·96 SD) = −0·122 kPa.

Results

The effective alveolar P_{CO_2} (P_{ACO_2}eff) value for each individual is the mean P_{ACO_2}eff obtained from all breaths during the one minute data collection period. In normal subjects the mean coefficient of variation (CV) of P_{ACO_2}eff was 6·0% (range 4·1–9·9) and in patients was 7·9% (range 2·4–23·0) within one study session.

The reproducibility of the method for assessing P_{ACO_2}eff was checked in terms of CV in three normal subjects in whom measurements were repeated three times per day for three consecutive days. Within day CV was 5·7% (range 4·2–7·4) and day to day CV was 5·8%

Table 2 Limits of agreement of $P_{ACO_2}eff$ versus P_{aCO_2}

	$P_{ACO_2}eff - P_{aCO_2}$ (kPa)	
	Normal subjects (n=20)	*Patients (n=46)*
Mean (SD) of the differences	−0·205 (0·373)	−0·460 (0·832)
Limits of agreement		
Upper	0·526	1·170
Lower	−0·935	−2·088
95% confidence interval of the bias	−0·029 to −0·379	−0·213 to −0·707

(range 3·7–10·1). It is evident that the CV of $P_{ACO_2}eff$ within and between days was practically the same as the CV of $P_{ACO_2}eff$ for the group of normal subjects.

Among the normal subjects the mean (SD) $P_{ACO_2}eff$ was 4·75 (0·59) kPa and P_{aCO_2} was 4·96 (0·45) (Student's paired *t* test: t = −2·46, p<0·05, n=20). In patients $P_{ACO_2}eff$ was 5·11 (1·92) kPa and P_{aCO_2} was 5·57 (1·48) (t = 3·75, p<0·001, n=46). The variability around the mean of $P_{ACO_2}eff$ and P_{aCO_2} was greater in patients than in normal subjects. Regression analysis showed a significant linear relation between $P_{ACO_2}eff$ and P_{aCO_2}. In normal subjects this relation was $P_{ACO_2}eff = -0·081 + 0·129\ P_{aCO_2}$ kPa (r=0·77, SEE=0·383 kPa, p<0·001) and in patients $P_{ACO_2}eff = -1·538 + 0·159\ P_{aCO_2}$ kPa (r=0·91, SEE=0·792, p<0·001). The limits of agreement of $P_{ACO_2}eff$ versus P_{aCO_2} were analysed by the method of Bland and Altman[12] (table 2, figs 3 and 4).

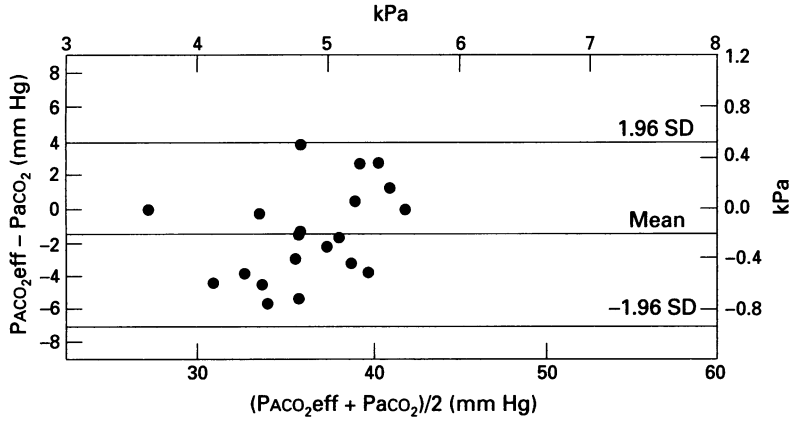

Figure 3 Comparison of $P_{ACO_2}eff$ with P_{aCO_2} by the Bland-Altman method in 20 normal subjects (see also table 2). Upper limit of agreement (mean + 1·96 SD) = 0·526 kPa; lower limit of agreement (mean − 1·96 SD) = −0·935 kPa.

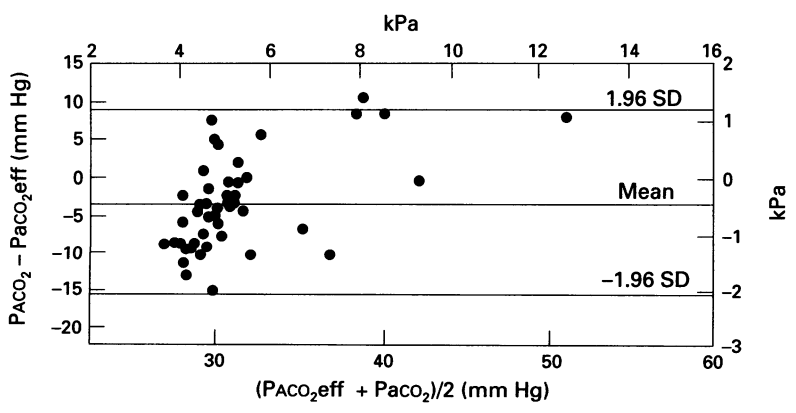

Figure 4 Comparison of $P_{ACO_2}eff$ with P_{aCO_2} by the Bland-Altman method in 46 patients with COPD (see also table 2). Upper limit of agreement (mean + 1·96 SD) = 1·170 kPa; lower limit of agreement (mean − 1·96 SD) = −2·088 kPa.

The mean of the difference ($P_{ACO_2}eff - P_{aCO_2}$) and the range of limits of agreement were almost double in the patients compared with the normal subjects.

The end tidal P_{CO_2} (P_{ETCO_2}) was lower than the effective alveolar P_{CO_2}. In normal subjects the mean (SD) difference ($P_{ACO_2}eff - P_{ETCO_2}$) was 0·427 (0·300) kPa (n=20).

The mean (SD) of the V_D/V_T ratio measured with our method in the normal subjects was 0·403 (0·070) (n=20) and in the patients 0·478 (0·082) (n=46), (t = −3·58, p<0·001), while this ratio measured from $P_{ECO_2}eff$ and P_{aCO_2} was 0·433 (0·082) in normal subjects (n=20) and 0·536 (0·079) in patients (n=46), (t = −5·20, p<0·001).

Discussion

The effective CO_2 concentration in the expirate ($F_{ECO_2}eff$) is a weighted mean value between zero and F_{ETCO_2} according to equation (2). In order to separate the physiological dead space from the alveolar volume for the application of Bohr's equation the F_{CO_2}/t curve was transformed to a square wave by using the effective time of this curve.[13 14] In this way the ideal CO_2 front with respect to time within the airways may be located at the end point of the time interval (t_0 + teff).

This principle for measuring the dead space volume is similar to that for the estimation of the so called "anatomical dead space volume".[13 14] The difference between our method and the earlier one is the simple mathematical approach for the determination of the effective time, as opposed to the geometrical approach with the declining plateau used in the past. Furthermore, the use of the CO_2 concentration versus volume curve for the estimation of the V_D/V_T ratio is not correct since, in this case, P_{aCO_2} has to be equal to P_{ETCO_2}.

In normal subjects the values of the V_D/V_T ratio computed by our method are greater than those obtained by the old methods because the line of backwards extrapolation of the last part of the real F_{CO_2}/t curve is not parallel to the time axis, resulting in a smaller area than $\int F_{CO_2}dt(a)$ and so to a smaller V_D/V_T ratio.

The effective alveolar CO_2 concentration ($F_{ACO_2}eff$) is computed from $F_{ECO_2}eff$ and the V_A/V_T ratio, and so is liable to errors inherent in the measurement of the areas of the F_{CO_2}/t and of the $\dot{V}_E/t$ curves. However, such errors must be small since the dispersion of $P_{ACO_2}eff$ around the mean for each individual was small in all normal subjects.

The mean coefficient of variation for $P_{ACO_2}eff$, which reflects the precision of the measurement, was 6% (range 4·1–9·9%) in normal subjects and 2·4–23·0% in patients. This finding may be explained by the wide range of time constants within the lungs of the patients, or by the breath by breath variation of their $\dot{V}_E/t$ curves, or both.[15 17]

The regression equations showed a strong relation between $P_{ACO_2}eff$ and P_{aCO_2} in both normal subjects and patients. There were highly significant differences between $P_{ACO_2}eff$ and P_{aCO_2} both in patients and normal subjects.

The difference ($PACO_2eff - PaCO_2$) was close to that obtained using the two stage helium washout technique.[21]

We conclude that (1) effective alveolar PCO_2 ($PACO_2eff$) can be estimated simply in the laboratory or at the bedside without any special manoeuvre on the part of the subject. The subject breathes freely without any appreciable resistance through the mouthpiece assembly which has no two way valve; (2) $PACO_2eff$ is significantly different from $PaCO_2$ in both normal subjects and patients, but in normal subjects the difference between the alveolar and arterial CO_2 tension is relatively smaller; and (3) this estimate of $PACO_2eff$ should be used in the theoretical calculation of dead space and CO_2 shunt.

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1 Sykes MK, McNicol MW, Campbell EJM, eds. *Respiratory failure.* Oxford: Blackwell Scientific Publications, 1969: 51, 314.
2 Engel LA. Intraregional gas mixing and distribution. In: Engel LA, Paiva M, eds. *Gas mixing and distribution in the lung.* New York: Marcel Dekker, 1985:326–7.
3 Enghoff H. Volumen inefficax, bemer Kungen zur Frage des schadlichen Raumes. *Ups Lakaref* 1938;**44**:191–218.
4 Boyhus A. Respiratory dead space. In: Fenn WO, Rahn H, eds. *Respiration. American Physiological Society,* 1964: 699–714.
5 Asmussen E, Nielsen M. Physiological dead-space and alveolar gas pressures at rest and during muscular exercise. *Acta Physiol Scand* 1956;**38**:1–21.
6 Otis AB. Quantitative relationships in steady-state gas exchange. In: Fenn WO, Rahn H, eds. *Respiration.* American Physiological Society, 1964:681–98.
7 Anthonisen NR, Fleetmann JA. Ventilation: total, alveolar, and dead space. In: Fishman AP, Fahri LE, Tenney RM, Geigen SR, eds. *Handbook of physiology. The respiratory system. American Physiological Society,* 1987:113–29.
8 Hlastala MP. Ventilation. In: Crystal RG, West JB, Barnes PJ, Cherniack NS, Weibel ER, eds. *The lung.* 1st edn. New York: Raven Press, 1991:1211–3.
9 Cerretelli P, di Prampero PE. Pulmonary gas exchange. In: Crystal RG, West JB, Barnes PJ, Cherniack NS, Weibel ER, eds. *The lung.* 1st edn. New York: Raven Press, 1991: 1566.
10 Riley RL, Lilienthal JL, Proemmel DD, Franke RE. On the determination of the physiologically effective pressures of oxygen and carbon dioxide in alveolar air. *Am J Physiol* 1946;**147**:191–8.
11 Luft UC, Loeppky JA, Mostyn EM. Mean alveolar gases and alveolar-arterial gradients in pulmonary patients. *J Appl Physiol* 1979;**46**:534–40.
12 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;i:307–10.
13 Fowler WS. Lung function studies II. The respiratory dead-space. *Am J Physiol* 1948;**154**:405–16.
14 Fowler WS. Lung function studies III. Uneven pulmonary ventilation in normal subjects and in patients with pulmonary disease. *J Appl Physiol* 1949;2:283–99.
15 Hugh-Jones P, Barter CE, Hime JM, Rusbridge MM. Dead space and tidal volume of the giraffe compared with some other mammals. *Respir Physiol* 1978;**35**:53–8.
16 Bouhuys A. Distribution of inspired gas in the lung. In: Fenn WO, Rahn H, eds. *Respiration. American Physiological Society,* 1964:715–33.
17 Sanchis J, Diez-Betoret JL, Canet J, Casan P. Pneumotachographic recording of ventilatory pattern. In: Benito S, Net A, eds. *Pulmonary function in mechanical ventilated patients.* New York: Springer-Verlag, 1991:9–22.
18 Morris AH, Kanner RE, Crapo RO, Gardner RM. *Clinical pulmonary function testing: a manual of uniform laboratory procedures.* 2nd edn. Salt Lake City: Intermountain Thoracic Society, 1984.
19 Shykoff BE, Swanson HT. A model-free method for mass spectrometer response correction. *J Appl Physiol* 1987;**63**: 2148–53.
20 Clayton GB. Understanding operational amplifier performance parameters. In: Clayton GB, ed. *Operational amplifiers.* 2nd edn. London: Butterworths, 1979:16–99.
21 Jordanoglou J, Tatsis G, Danos J, Gougoulakis S, Orfanidou D, Gaga M. Alveolar partial pressures of carbon dioxide and oxygen measured by a helium washout technique. *Thorax* 1990;**45**:520–4.