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

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Abstract

Background – The measurement of effective alveolar carbon dioxide tension ($P_{ACO_2,eff}$) 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 (mouth-piece, 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 P_{aCO_2} for comparison during the study.

Results – The results showed a mean difference ($P_{ACO_2,eff} - P_{aCO_2}$) 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 $P_{ACO_2,eff}$ and P_{aCO_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.

The estimation of effective alveolar carbon dioxide tension is still a matter of debate because the available methodology is not widely ac-

cepted. In most classical calculations alveolar carbon dioxide tension (P_{ACO_2}) has been assumed to be equivalent to arterial blood CO_2 tension (P_{aCO_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 (V_{Dphys}/V_T).^{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 ($F_{ECO_2,eff}$) and the dead space/tidal volume ratio (V_D/V_T) on the $\dot{V}_E/\text{time}(t)$ curve by the aid of the effective time (t_{eff}) of the F_{CO_2}/t curve. The computed values of $F_{ECO_2,eff}$ and V_D/V_T are used in Bohr's equation for the estimation of the effective alveolar CO_2 concentration per breath ($F_{ACO_2,eff}$).

The expiratory flow ($\dot{V}_E/t$) and the CO_2 concentration versus time (F_{CO_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 F_{CO_2} limits of the F_{CO_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 F_{CO_2}/t curve has zero F_{CO_2} values and variable duration (t_0). At the end point of t_0 the rate of rise of F_{CO_2} (dF_{CO_2}/dt) is steep, but it decreases progressively until the end of the curve. At this point F_{CO_2} and F_{ETCO_2} are equal (fig 1). In some F_{CO_2}/t curves the end part of the curve reaches a plateau. The area over the F_{CO_2}/t curve [$\int F_{CO_2} dt(a)$] is confined by the horizontal line at the level of F_{ETCO_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 F_{ETCO_2} equals the effective time of the curve (t_{eff}) (fig 1):

$$t_{eff} = \int F_{CO_2} dt(a) / F_{ETCO_2} \quad (1)$$

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Figure 1 Expiratory flow ($\dot{V}_E/t$) and CO_2 concentration versus time curves (FCO_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, FCO_2 in %, time in seconds). The expiratory time (t_E) is equal to the sum ($t_0 + t_{eff} + \Delta t$). In the FCO_2/t curves area A = area B (see text). The area enclosed by the FCO_2/t curve [$\int FCO_2 dt(u)$] = ($FECO_2 \times t_E$).

The effective time of the FCO_2/t curve permits the transformation of this curve to a square wave, the initial part of which is characterised by ($t_0 + t_{eff}$) and $FCO_2 = 0$, and the rest of it by the time interval $\Delta t = (t_E - t_0 - t_{eff})$ and $FCO_2 = FETCO_2$ (fig 1). In fact, Δt is equal to the ratio [$\int FCO_2 dt(u) / FETCO_2$] where $\int FCO_2 dt(u)$ is the area enclosed by the curve itself, the time axis, and the vertical line passing through the point of $FETCO_2$ (fig 1). The time interval ($t_0 + t_{eff}$) of the transformed FCO_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 ($FCO_2 = 0$) – that is, to the dead space volume [$\int \dot{V}dt(D) = V_D$] (fig 1). The rest of the tidal volume corresponds to the alveolar volume [$\int \dot{V}dt(A) = V_A$] (fig 1). The ratio of the area $\int \dot{V}dt(A)$ divided by the area $\int \dot{V}dt = V_T$ is the ratio of alveolar volume to tidal volume (V_A/V_T). The effective concentration of CO_2 in the expired air ($FECO_2 \text{eff}$) per breath is equal to the ratio of the area $\int FCO_2 dt(u)$ divided by the expiratory time (t_E) (fig 1):

$$FECO_2 \text{eff} = \int FCO_2 dt(u) / t_E \quad (2)$$

According to Bohr's equation the ratio V_A/V_T is equal to the ratio $FECO_2/FACO_2$. Hence, the effective value of the alveolar CO_2 concentration ($FACO_2 \text{eff}$) is equal to:

$$FACO_2 \text{eff} = FECO_2 \text{eff} / (V_A/V_T) \quad (3)$$

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

PCO₂ was measured with a blood gas analyser (ABL; Radiometer, Copenhagen, Denmark).

The experimental setup used to assess PACO₂ 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 CO₂ 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; CO₂ test III, Wuerzburg, Germany) (rise time 10–90% = 100 ms) was connected to the monitoring ring through a thin polyethylene 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% CO₂ in air before and after each study. The phase lag between the $\dot{V}_E/t$ and FCO₂/t curves was determined by an abrupt change in flow of a gas mixture containing 4% CO₂ 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 FCO₂/t curve in normal subjects and in patients breathing at a respiratory frequency of 12–18/min.^{19,20} Airflow and CO₂ 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 CO₂ concentration (FETCO₂) was measured at the point on the FCO₂/t curve corresponding to $\dot{V}_E = 0$. Alveolar CO₂ tension was also computed manually from the $\dot{V}_E/t$ and FCO₂/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 FCO₂/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 method¹² (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.

Results

The effective alveolar PCO₂ (PACO₂eff) value for each individual is the mean PACO₂eff obtained from all breaths during the one minute data collection period. In normal subjects the mean coefficient of variation (CV) of PACO₂eff 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 PACO₂eff 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%

Figure 2 Bland-Altman diagram for the comparison between PACO₂eff calculated manually and PACO₂eff 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.

Table 2 Limits of agreement of PACO_2eff versus PACO_2

	$\text{PACO}_2\text{eff} - \text{PACO}_2$ (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 PACO_2eff within and between days was practically the same as the CV of PACO_2eff for the group of normal subjects.

Among the normal subjects the mean (SD) PACO_2eff was 4.75 (0.59) kPa and PACO_2 was 4.96 (0.45) (Student's paired t test: $t = -2.46$, $p < 0.05$, $n = 20$). In patients PACO_2eff was 5.11 (1.92) kPa and PACO_2 was 5.57 (1.48) ($t = 3.75$, $p < 0.001$, $n = 46$). The variability around the mean of PACO_2eff and PACO_2 was greater in patients than in normal subjects. Regression analysis showed a significant linear relation between PACO_2eff and PACO_2 . In normal subjects this relation was $\text{PACO}_2\text{eff} = -0.081 + 0.129 \text{ PACO}_2$ kPa ($r = 0.77$, $\text{SEE} = 0.383$ kPa, $p < 0.001$) and in patients $\text{PACO}_2\text{eff} = -1.538 + 0.159 \text{ PACO}_2$ kPa ($r = 0.91$, $\text{SEE} = 0.792$, $p < 0.001$). The limits of agreement of PACO_2eff versus PACO_2 were analysed by the method of Bland and Altman¹² (table 2, figs 3 and 4).

Figure 3 Comparison of PACO_2eff with PACO_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 PACO_2eff with PACO_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 ($\text{PACO}_2\text{eff} - \text{PACO}_2$) and the range of limits of agreement were almost double in the patients compared with the normal subjects.

The end tidal PCO_2 (PETCO_2) was lower than the effective alveolar PCO_2 . In normal subjects the mean (SD) difference ($\text{PACO}_2\text{eff} - \text{PETCO}_2$) was 0.427 (0.300) kPa ($n = 20$).

The mean (SD) of the Vd/Vt 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 PACO_2eff and PACO_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 (FECO_2eff) is a weighted mean value between zero and FETCO_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 FCO_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 ($t_0 + t_{\text{eff}}$).

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 Vd/Vt ratio is not correct since, in this case, PACO_2 has to be equal to PETCO_2 .

In normal subjects the values of the Vd/Vt 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 FCO_2/t curve is not parallel to the time axis, resulting in a smaller area than $\int \text{FCO}_2 dt(a)$ and so to a smaller Vd/Vt ratio.

The effective alveolar CO_2 concentration (FACO_2eff) is computed from FECO_2eff and the VA/Vt ratio, and so is liable to errors inherent in the measurement of the areas of the FCO_2/t and of the $\dot{\text{V}}\text{E}/t$ curves. However, such errors must be small since the dispersion of PACO_2eff around the mean for each individual was small in all normal subjects.

The mean coefficient of variation for PACO_2eff , 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 $\dot{\text{V}}\text{E}/t$ curves, or both.^{15,17}

The regression equations showed a strong relation between PACO_2eff and PACO_2 in both normal subjects and patients. There were highly significant differences between PACO_2eff and PACO_2 both in patients and normal subjects.

The difference ($\text{PACO}_2\text{eff} - \text{PACO}_2$) 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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