Noninvasive measurement of mean alveolar carbon dioxide tension and Bohr’s dead space during tidal breathing

N.G. Kouloris, P. Latsi, J. Dimitroulis, B. Jordanoglou, M. Gaga, J. Jordanoglou


ABSTRACT: The lack of methodology for measuring the alveolar carbon dioxide tension (PACO₂) has forced investigators to make several assumptions, such as that PACO₂ is equal to end-tidal (PETCO₂) and arterial CO₂ tension (PaCO₂).

The present study measured the mean PACO₂ and Bohr’s dead space ratio (Bohr’s dead space/tidal volume (VD,Bohr/VT)) during tidal breathing. The method used is a new, simple and noninvasive technique, based on the analysis of the expired CO₂ volume per breath (FCO₂) versus the exhaled VT. This curve was analysed in 21 normal, healthy subjects and 35 chronic obstructive pulmonary disease (COPD) patients breathing tidally through a mouthpiece apparatus in the sitting position.

It is shown that: 1) PACO₂ is similar to PaCO₂ in normal subjects, whilst it is significantly lower than PaCO₂ in COPD patients; 2) PACO₂ is significantly higher than PETCO₂ in all subjects, especially in COPD patients; 3) VD,Bohr/VT is increased in COPD patients as compared to normal subjects; and 4) VD,Bohr/VT is lower than the “physiological” dead space ratio (VD,phys/VT) in COPD patients.

It is concluded that the expired carbon dioxide versus tidal volume curve is a useful tool for research and clinical work, because it permits the noninvasive and accurate measurement of Bohr’s dead space and mean alveolar carbon dioxide tension accurately during spontaneous breathing.


The respiratory dead space is the concept in gas exchange derived by the investigators in their effort to determine the effectiveness of ventilation in health and disease. After the description of the dead space by Bohr [1], numerous papers on the subject followed, in which the methodology can be divided into two categories; the noninvasive studies from gas (nitrogen (N₂), Helium (He), carbon dioxide (CO₂)) concentration versus time or volume curves, and the invasive studies in which the arterial CO₂ tension (PaCO₂) instead of the alveolar CO₂ tension (PACO₂) was used [2–15]. In the noninvasive methods, the "anatomical" dead space, i.e. Fowler’s dead space (VD(F)), is determined from the expired gas concentration versus tidal volume or vital capacity curve, which is analysed by geometrical methods. The results obtained by this method may be doubtful since the junction of the phases II and III is difficult to define in disease, especially during tidal breathing. Furthermore, this analysis is based on the assumption that the end-tidal and alveolar CO₂ fractions (PETCO₂ and PACO₂) are identical. However, there is substantial evidence that PETCO₂ is lower than PACO₂ in normal subjects and patients [16–18]. The invasive methods permit the measurement of the "physiological" dead space ratio (physiological dead space/tidal volume (VD,phys/VT)), by using PaCO₂ in Bohr’s equation with the assumption that PACO₂ is equal to PaCO₂, which is valid only in normal subjects.

In previous reports [17, 18], Bohr’s dead space ratio (Bohr’s dead space/tidal volume (VD,Bohr/VT)) and PACO₂ were not measured either simultaneously or within the volume domain. Since VD,Bohr/VT is in the volume domain, theoretically it appeared most appropriate to develop a new technique, i.e. the construction and mathematical analysis of the expired CO₂ volume versus tidal volume curve (FCO₂ versus VT curve). This curve, recorded at the mouth during expiration, has a curvilinear shape and the CO₂ concentrations within the airways are lower than the alveolar one as a result of the "dilution effect" due to the pre-inspired atmospheric air (Appendix 1).

This technique allowed the simultaneous measurement of VD,Bohr/VT and PACO₂. This simple and noninvasive method was applied in 21 normal subjects and 35 chronic obstructive pulmonary disease (COPD) patients breathing tidally through a mouthpiece apparatus. VD,Bohr/VT was compared to VD,phys/VT, and PACO₂ to PaCO₂ and end-tidal carbon dioxide tension (PETCO₂).
Methods

Theoretical considerations

The $\text{F}CO_2$ versus $\text{I}T$ curve was derived from the expiratory flow and CO$_2$ concentration versus time tracings measured at the mouth. It was constructed by plotting the exhaled $\text{F}CO_2$ (the integral of CO$_2$ fraction and flow with respect to time ($\text{F}CO_2 = \int \text{FCO}_2 \, \text{V} \, \text{dt}$)) versus the tidal volume (the integral of flow with respect to time ($\text{F}T = \int \text{F} \, \text{dt}$)). The $\text{FET} . \text{CO}_2$ was determined, by computer analysis, from the mean of 10 points of the last segment on the $\text{FCO}_2$ versus time curve, at which the positive slope of the tangent with the horizontal line becomes zero. Beyond these points the curve started to have a consistent negative slope. The height of the mean of these points from the zero line of the curve represents the $\text{FET} . \text{CO}_2$. The mixed expired CO$_2$ fraction ($\text{FE} . \text{CO}_2$) is the ratio of the total expired $\text{V} CO_2$ per breath over $\text{I}T$ (Appendix 1). The analysis of the $\text{FCO}_2$ versus $\text{I}T$ curve is described in detail in the Appendix section.

Study design

The experimental set-up consisted of a flanged semirigid plastic mouthpiece connected in series to a Fleisch No. 2 flow transducer head (Fleisch, Lau-
sanne, Switzerland) via a metal piece (monitoring ring), on which the CO$_2$ probe was attached (mouth-
piece apparatus). The pneumotachograph (trans-
ducer and amplifier: Gould, Godart BV; No. 17212,
Bilthoven, Holland) was connected with the Fleisch head via two semirigid plastic tubes 50 cm in length. The pneumotachograph system (rise time 10 – 90%≈13 ms) was linear over the range of flows used. Volume was obtained by integration of the flow signal. 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 polythene tube (length 50 cm, internal diameter 1.2 mm). The resistance of the mouthpiece apparatus to airflow was negligible. The rise time (10 – 90%) of the capnograph measured at the mouthpiece was $\geq$4.5 times faster than that of the fastest $\text{FCO}_2$ versus time curve ($\text{FCO}_2/\text{I}T$), in normal subjects and COPD patients breathing at a frequency of 10 – 25 min$^{-1}$. Calibration of the CO$_2$ analyser was made using a standard mixture of CO$_2$ (4.0%) in N$_2$. The phase lag between the $\text{FCO}_2$ versus $\text{I}T$ and $\text{V}^\prime$ versus $\text{t}$ signals was determined by an abrupt change in flow of the above gas mixture generated through the experimental set-up. The measurement of the phase lag and the calibration of the CO$_2$ analyser were repeated three times and the mean values were used. Airflow and CO$_2$ signals were monitored on-line on a computer screen and sampled simultaneously at a rate of 150 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 custom-made computer analysis software. $\text{VF}CO_2$ and $\text{I}T$ were expressed in mL body temperature and pressure, saturated (BTPS).

The study was performed in 21 normal subjects and 35 ambulatory COPD patients. Lung function data were obtained in the seated position with a flow-sensing spirometer (Fukuda; Spiroanalyzer ST300, Tokyo, Japan). Anthropometric and routine lung function data are given in table 1. Predicted values were those of Morris et al. [19]. The subjects were studied while seated, breathing room air through the mouthpiece apparatus with a noseclip on, at their own resting $\text{I}T$ and respiratory frequency. Each subject had an initial 10 – 15 min trial run to become accustomed to the apparatus and procedure. After regular breathing had been achieved, a series of breaths over a period of 1 min were recorded. At the end of the recording time, while the subject was still connected to the mouthpiece, an arterial blood sample (>1 mL) was taken for gas analysis. An expert physician using a 21 G needle, performed a quick (5 – 10 s) and direct puncture of the brachial artery. It is highly unlikely that a change in blood gases took place in such a short time interval. If the procedure of gas sampling was not successful after one single effort, the experiment was cancelled. The cancelled experiments were <7.5%. The $P_a . \text{CO}_2$ was measured with a blood gas analyser (CIBA-CORNING; 288 Blood gas system, MA, USA) in 12 normal subjects and in all COPD patients.

The method was experimentally verified in three normal subjects during tidal breathing through different tubes of a known capacity. The dead space of the added tube ($\text{V}_\text{tube}$) was calculated from the difference $\text{V}_\text{D} - \text{V}_\text{D(o)}$, where: $\text{V}_\text{D}$ and $\text{V}_\text{D(o)}$ are $\text{V}_\text{D}$ of the subject breathing through the mouthpiece apparatus with and without the added tube, respectively. Three tubes were used, the capacities ($\text{V}_\text{cap}$) of which were 180, 337 and 504 mL calculated from the equation $\pi r^2 l$ (radius = 3.14, $r$ = radius and $l$ = length of the tube). The capacity of the tube deviated from the measured volume by <2.3% (table 2).

The study had the approval of the local ethics committee and all subjects gave informed consent.

Table 1. Anthropometric and routine lung function data from 21 normal subjects and 35 chronic obstructive pulmonary disease (COPD) patients

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects</th>
<th>COPD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects n</td>
<td>21</td>
<td>35</td>
</tr>
<tr>
<td>Sex M/F</td>
<td>9/12</td>
<td>28/37</td>
</tr>
<tr>
<td>Age yrs</td>
<td>44 ± 19</td>
<td>60 ± 12</td>
</tr>
<tr>
<td>Weight kg</td>
<td>69 ± 15</td>
<td>73 ± 14</td>
</tr>
<tr>
<td>Height cm</td>
<td>168 ± 10</td>
<td>167 ± 9</td>
</tr>
<tr>
<td>FVC % pred</td>
<td>107 ± 15</td>
<td>80 ± 26</td>
</tr>
<tr>
<td>FEV1 % pred</td>
<td>108 ± 13</td>
<td>57 ± 28</td>
</tr>
<tr>
<td>FEV1/FVC %</td>
<td>82 ± 6</td>
<td>55 ± 14</td>
</tr>
<tr>
<td>FEF25 – 75 % pred</td>
<td>102 ± 27</td>
<td>29 ± 19</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or absolute number. M: male; F: female; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; FEF25 – 75: forced mid-expiratory flow.
Table 2. – The capacity of the added tubes (Vcap=πr²×l), the mean of the measured volume (Vtube, measured) in three normal subjects, and the calculated volume (Vtube, calculated) obtained by the regression equation (footnote) are shown.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Vcap (n=3) mL</th>
<th>Vtube, measured mL</th>
<th>Vtube, calculated mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>180</td>
<td>176</td>
<td>178</td>
</tr>
<tr>
<td>2</td>
<td>337</td>
<td>341</td>
<td>339</td>
</tr>
<tr>
<td>3</td>
<td>504</td>
<td>509</td>
<td>510</td>
</tr>
</tbody>
</table>

Vtube, calculated=−7.3751+1.0275×Vcap (r=0.99).

Results

\( P_{a,CO_2} \) and \( V_{D,Bohr}/VT \) were measured by analysis of the \( FCO_2 \) versus \( VT \) curve obtained from 21 normal subjects and 35 COPD patients during tidal breathing. It is noted that cardiogenic oscillations had no effect on the \( FCO_2 \) versus \( VT \) curve, as this was consistently smooth in all subjects (Appendix 1). \( V_{D,Bohr}/VT \), \( VT \), \( PET,CO_2 \), and \( P_{a,CO_2} \), were obtained for each subject by averaging all breaths during a 1-min data recording period.

The mean within-study, within-day and day-to-day coefficient of variation for \( V_{D,Bohr}/VT \) was 6.5, 6.85 and 7.25% and for \( P_{a,CO_2} \) 1.57, 3.06, and 3.05%, respectively. These were determined in three normal subjects in whom measurements were repeated three times per day for 3 consecutive days.

\( V_{D,Bohr}/VT \) and \( V_{D,phys}/VT \) were not significantly different in the 12 normal subjects. In contrast, this difference was statistically significant in the COPD patients (p<0.001). The \( V_{D,Bohr}/VT \) ratio in COPD patients was significantly higher than in normal subjects (p<0.001), (table 3; fig. 1). \( V_{D,Bohr}/VT \) was higher than the dead space ratio measured from the \( FCO_2 \) versus \( VT \) curve by Fowler’s geometrical method of orthogonal projection (\( V_{D,FY}/VT \)). In normal subjects, mean±SD \( V_{D,FY}/VT \) was 28±8% and in COPD patients, 37±8%. The mean difference between \( V_{D,Bohr}/VT \) and \( V_{D,FY}/VT \) is 5±1% in normal subjects (p<0.001) and 7±2% in COPD patients (p<0.001).

\( P_{a,CO_2} \) and \( P_{a,CO_2} \) were compared in 12 normal subjects and in all patients. In the COPD patients, \( P_{a,CO_2} \) was significantly higher than \( P_{a,CO_2} \) (p<0.001). In the 12 normal subjects, the difference between \( P_{a,CO_2} \) and \( P_{a,CO_2} \) was not statistically significant (table 4; fig. 2). In all normal subjects and patients, \( P_{a,CO_2} \) was significantly higher than \( PET,CO_2 \) (table 4, fig. 3). The relationship between \( PET,CO_2 \) and \( P_{a,CO_2} \) is shown in figure 3.

The alveolar-end-tidal \( P_{CO_2} \) ((A-ET) \( CO_2 \)) and the arterial-alveolar \( P_{CO_2} \) ((a-A) \( CO_2 \)) differences were also related to the \( V_{D,Bohr}/VT \) ratio. In all subjects, no statistical relationship was found between (a-A) \( CO_2 \), and \( PET,CO_2 \), and end-tidal \( PET,CO_2 \) carbon oxide tension (kPa), in normal subjects and chronic obstructive pulmonary disease (COPD) patients.

Table 3. – Comparison of dead space ratios, in 21 normal subjects and 35 chronic obstructive pulmonary disease (COPD) patients.

<table>
<thead>
<tr>
<th>Subject type</th>
<th>( V_{D,Bohr}/VT )</th>
<th>( V_{D,phys}/VT )</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0.333±0.090</td>
<td>0.378±0.088</td>
<td>0.135</td>
</tr>
<tr>
<td>COPD patients</td>
<td>0.436±0.097</td>
<td>0.498±0.123</td>
<td>0.001</td>
</tr>
<tr>
<td>p-value</td>
<td>p&lt;0.001</td>
<td>p=0.003</td>
<td></td>
</tr>
</tbody>
</table>

Mean values±SD. \( V_{D,Bohr}/VT \): Bohr’s dead space ratio; \( V_{D,phys}/VT \): physiological dead space ratio; p-value: indicate comparisons of respective rows/columns.

Table 4. – Alveolar (\( P_{a,CO_2} \)) arterial (\( P_{a,CO_2} \)) and end-tidal (\( PET,CO_2 \)) carbon oxide tension (kPa), in normal subjects and chronic obstructive pulmonary disease (COPD) patients.

<table>
<thead>
<tr>
<th>CO2 tension variable</th>
<th>Normal subjects</th>
<th>COPD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects n</td>
<td>21</td>
<td>35</td>
</tr>
<tr>
<td>( P_{a,CO_2} )</td>
<td>4.88±0.48</td>
<td>4.84±0.59</td>
</tr>
<tr>
<td>( PET,CO_2 )</td>
<td>4.60±0.45</td>
<td>4.38±0.84</td>
</tr>
<tr>
<td>( P_{a,CO_2}-PET,CO_2 )</td>
<td>0.28±0.11</td>
<td>0.55±0.22</td>
</tr>
<tr>
<td>( P_{a,CO_2}-PET,CO_2 )</td>
<td>-</td>
<td>0.61±0.83</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD.
A significant regression was found for COPD: $P_{A,CO_2} = 1.38 + 0.64 P_{A,CO_2}$, $r = 0.551$, $n = 35$, $p < 0.001$. Dotted lines represent 95% confidence intervals of regression.

The present study used the expired $V_{CO_2}$ versus $V'T$ curve for the noninvasive measurement of $V'D_{Bohr}/V'T$ and mean $P_{A,CO_2}$ in normal subjects and COPD patients during tidal breathing. According to the results: 1) $V'D_{Bohr}/V'T$ is increased in COPD patients as compared to normal subjects; 2) $V'D_{Bohr}/V'T$ is lower than $V'D_{phys}/V'T$ in COPD patients; 3) $P_{A,CO_2}$ is closely similar to $P_{a,CO_2}$ in normal subjects, whilst it is significantly lower than $P_{a,CO_2}$ in COPD patients; and 4) $P_{a,CO_2}$ is significantly higher than $P_{ET,CO_2}$ in all subjects, especially in COPD patients. This curve overcomes: 1) the assumption inherent in the analysis of the $F_{CO_2}$ versus $V$ curve, i.e. that $F_{a,CO_2}$ is equal to $P_{ET,CO_2}$, and 2) the difficulty in drawing the extrapolated line of the sloping alveolar plateau in disease, especially during tidal breathing.

At a steady state, regardless of the actual value of the $V'/Q'$ ratio, the $CO_2$ molecules within the residual air define $F_{CO_2}$. This is dependent on the dynamic equilibrium within the alveolar space between the inflow and outflow of the $CO_2$ molecules, and the overall $V'/Q'$ ratio of the lungs at the existing functional residual capacity. A portion of the $CO_2$ molecules is exhaled with the $V'T$ constituting the expired $V_{CO_2}$ per breath. During expiration, these molecules move out from the alveolar space mainly by bulk movement but also by diffusion, and at the same time they are replaced by $CO_2$ molecules originating from blood through the alveolar membrane. The concentrations of the $CO_2$ molecules within the airways, diluted by pre-inspired atmospheric air, are lower than the alveolar concentration. As a result of
the "dilution effect", the $V_{CO2}$ versus $VT$ curve gets the curvilinear shape recorded at the mouth (Appendix 1).

The analytical procedure of the $V_{CO2}$ versus $VT$ curve was verified, both theoretically and practically i.e. 1) The measurement of the volume of the added tubes with a deviation of $<2.3\%$ from the capacity of the tubes denotes the validity and the accuracy of the described method. The added tube affects the entire $V_{CO2}$ versus $VT$ curve and its volume was calculated from the change of $V_{D,Bohr}$. 2) The nonsignificant difference in normal subjects between $P_{A,CO2}$ and $P_{a,CO2}$ is strong evidence for the accuracy of the method. 3) The Equations 9 and 10 in Appendix 1, derived from the $V_{CO2}$ versus $VT$ curve, are identical to those widely accepted in the literature [1–18]. 4) The measurement of the volume of the added tube, i.e. $V_{CO2}(A)$ and $V_{CO2}(B)$, is $<0.4\%$, i.e. $V_{CO2}(A)=V_{CO2}(B)$. This equality means that the points $b$, $d$ and $a$ are correctly positioned and not arbitrarily taken (Appendix 1, 3). Furthermore, the mean deviation of the area $A(A)$ from the area $A(B)$ is very small (Appendix 3).

The repeatability of the measurements for $V_{D,Bohr}/VT$ was $\sim7\%$ and for $P_{A,CO2}$ $\sim3\%$. However, the increase of the coefficient of variation of the $VT$ per se beyond the value of $16\%$ reduces the repeatability especially of $V_{D,Bohr}/VT$.

$V_{D,Bohr}/VT$ is considered as an index of maldistribution of the expired air within the lungs, i.e. within the space between the inner surface of the alveolar membrane and the mouth. The $V_{D,phys}/VT$ is influenced not only by the mechanisms of uneven ventilation, but also by the mechanisms of inhomogeneous distribution of $Q'$. In normal subjects, in whom $P_{a,CO2}$ is approximately equal to $P_{A,CO2}$, the difference between $V_{D,phys}/VT$ and $V_{D,Bohr}/VT$ was not statistically significant. This may be a true result or is more likely due to the small number of observations (power of paired t-test=0.201). In the COPD patients, in whom $P_{a,CO2}$ was higher than $P_{A,CO2}$, the difference between the two dead space ratios was considerable (table 3).

$P_{a,CO2}$ in normal subjects was not significantly different from $P_{A,CO2}$. However, in COPD patients ($a$-$A$) CO$_2$ was significantly higher than in normal subjects (table 4). This may be explained as follows. An increased $P_{A,CO2}$ in regions with low $V'/A'Q'$ ratio is followed by an increase of the end-capillary PCO$_2$ ($P_{C,CO2}$) locally, while in regions with a high $V'/A'Q'$ ratio, the decrease of $P_{A,CO2}$ is accompanied by a local decrease of $P_{C,CO2}$. If the arterial blood is composed mainly from blood perfusing regions with a low $V'/A'Q'$ ratio, $P_{a,CO2}$ will be increased. At the same time, when the exhaled $VT$ contains air coming mostly from regions with high $V'/A'Q'$ ratio, $P_{A,CO2}$ will be decreased. The combination of these two conditions probably results in the increased ($a$-$A$) CO$_2$ in patients with COPD. This is compatible with the results obtained, i.e. that the ($a$-$A$) CO$_2$ is not statistically related to $V_{D,Bohr}/VT$ in the subjects studied. In contrast, ($A$-$ET$) CO$_2$ is significantly related to $V_{D,Bohr}/VT$ in all subjects, due to the existing inhomogeneity of ventilation, especially in the COPD patients. The ($A$-$ET$) CO$_2$ was higher in COPD patients than in normal subjects (table 4). In addition, $P_{A,CO2}$ was linearly related to $PET_{CO2}$ and $P_{A,CO2}$ was higher than $PET_{CO2}$ in all subjects (fig. 3). The ($A$-$ET$) CO$_2$ difference was strongly related to $V_{D,Bohr}/VT$ in normal subjects and COPD patients, as is described in Equation 11 (Appendix 1).

$P_{A,CO2}$ is $V_{CO2}/VA$ times the factor (barometric

![Fig. 4.](image-url)
pressure-47), as conventionally referred to in the literature. It is mentioned that the measured value of $PA,CO_2$ per breath is a mean value from all the regions of the lungs with different $V'/A'$ ratios. Furthermore, the values of $PA,CO_2$ shown in the Results section are mean values from all breaths during the 1-min sampling period.

It is concluded that the carbon dioxide output versus tidal volume curve obtained during tidal breathing with minimal cooperation on the patient’s part, is useful in clinical practice and research work. It allows, with accuracy and precision, the noninvasive measurement and monitoring of the mean alveolar carbon dioxide tension and Bohr’s dead space volume. The alveolar carbon dioxide tension can be safely used instead of the arterial one in normal subjects, but not in chronic obstructive pulmonary disease patients. In all subjects, end-tidal carbon dioxide tension cannot be used instead of alveolar carbon dioxide tension.

Appendix

1. The expired carbon dioxide volume versus tidal volume curve

The simplified analysis of the $VCO_2$ versus $VT$ curve, presented in geometrical terms, is as follows. The total area under the $VCO_2$ versus $VT$ curve ($E$) is equal to the area of the triangle $bce$. In either side of the line $bc$ (hypotenuse) the areas $K$ and $M$ are equal to each other (fig. 4). Accordingly, the volume segment $be$ ($V_{be}$) on the $VT$ axis is equal to (fig. 5):

$$V_{be} = 2E/VCO_2$$

(1)

The angle $cbe$ represents the average slope ($F_{de}$=$VCO_2/V_{be}$) of the $VCO_2$ versus $VT$ curve (figs. 4 and 5). $FET,CO_2$ is measured directly at the end of the $FCO_2$ versus time curve. The ratio $VCO_2/FET,CO_2$ determines the volume segment $de$ ($V_{de}$) on the horizontal axis (fig. 5), i.e.

$$V_{de} = VCO_2/FET,CO_2$$

(2)

The line $cd$, the volume segment $id$ and the curve itself confine the one-sided area $D$, which is equal to the area of the triangle $bcd$ (fig. 5), i.e.

$$D = \frac{1}{2} VCO_2 \times (V_{be} - V_{de})$$

(3)

where: ($V_{de}-V_{de}$) is the base (volume segment $bd$=$V_d$) of the triangle $bcd$. The area $D$ denotes that a part of $VCO_2$ ($VCO_2(d)$) is expired at the end-tidal concentration ($FET,CO_2$), which is expired CO$_2$ and $V_d$ is the volume segment $bd$ ($=V_{de}-V_d$). The gas volume $VCO_2(d)$ (gas volume segment $xVBE$) is calculated from Equation 4. The segment $iu$ contains no CO$_2$ gas ($=V_d$) and it represents the upper airways dead space volume. The volume segment $iu$ represents the transitional volume ($V_A$), $V_{D,Bohr}$: Bohr’s dead space, $V_A$: alveolar ventilation.

$$V_A = (VCO_2 - VCO_2(d))/FET,CO_2$$

(5)

$V_{D,Bohr}$ is equal to:

$$V_{D,Bohr} = \frac{V_{CO_2}}{FET,CO_2} \times V_d$$

(6)

The gas volume $VCO_2$, as already described, is expired in two parts, the initial one ($VCO_2(d)$) with a mean concentration $F_d$ and the rest ($VCO_2-VCO_2(d)$) with concentration equal to $FET,CO_2$ (fig. 6). The meeting point (y) of these two slopes ($F_d$ and $FET,CO_2$) lies on the line $cd$ and the gas volume segments $xd$, $ya$ and $ee'$ are equal to each other ($=VCO_2(d)$) (figs. 5 and 6). The volume segment ye' is equal to the segment ae, and represents the alveolar part of the $VT$ with which the gas volume ($VCO_2-VCO_2(d)$) is expired at the end-tidal concentration ($FET,CO_2$), i.e.

$$(VCO_2 - VCO_2(d))/FET,CO_2$$

(6)
This is divided into two portions, the initial volume $V_0$ (=volume segment $iu$) and the transitional volume $V_tr$ (=volume segment $ua$) (figs. 5 and 6). The volume $V_0$ is the initial part of the $V_T$ with no CO2 gas in it. The transitional volume contains the gas volume $V_{CO2}(d)$ and is equal to (figs. 5 and 6):

$$V_{tr} = V_T - V_0 - V_A$$  \hspace{1cm} (7)

and

$$V_T/V = 1 - (V_0/V_T) - (V_A/V_T)$$  \hspace{1cm} (8)

The volume $V_0$ is directly measured by the computer as the volume segment from the beginning of expiration (point i) to point u, at which CO2 gas starts appearing in the expired air.

$V_A$ is calculated from Equation 5. If $F_{CO2}$ is considered as zero in $V_{D,Bohr}$ ($V_0 + V_T$), then all the $V_{CO2}$ per breath should be expired with the $V_A$ (fig. 6). So, the mean alveolar $F_{CO2}$ is calculated from the equation:

$$F_{A,CO2} = V_{CO2}/V_A$$  \hspace{1cm} (9)

By substituting in Equation 9 the term $V_{CO2}$ by its equal $F_{E,CO2} \times V_T$, the equation for the $V_A/V_T$ ratio is the following:

$$V_A/V_T = F_{E,CO2}/F_{A,CO2}$$  \hspace{1cm} (10)

where $F_{E,CO2}$ is the mixed expired CO2 fraction (= $\Sigma V_{CO2}(d)/V_T$) (angle $cie$) (fig. 4). Since the $V_A$ is smaller than the volume segment $V_{de}$ by the volume segment $da$ ($V_{da}=V_{CO2}(d)/F_{ET,CO2}$), $F_{A,CO2}$ is greater than $F_{ET,CO2}$ (fig. 6), i.e.

$$F_{A,CO2} - F_{ET,CO2} = V_{CO2}(d)/V_A$$  \hspace{1cm} (11)

Equation 11 is derived from Equations 5 and 9.

2. Relationship between the expired carbon dioxide versus tidal volume and carbon dioxide fraction versus tidal volume

The gas volume versus $V_T$ curve (lower curve) and the corresponding gas concentration versus $V_T$ curve (upper curve) are obtained from a single breath of a COPD patient (fig. 7). In the upper curve ($F_{CO2}$ versus $V_T$ curve), the vertical line $dd'$ corresponds to the point $d$ of the lower curve. The line $dd'$ separates the $F_{CO2}$, versus $V_T$ curve to the areas $A$ and $B$, which are equal to each other. It is evident that $V_D(F)$, measured by Fowler’s technique of orthogonal projection, is smaller than $V_{D,Bohr}$ by the volume segment $V_{da}$. It is mentioned that if $V_{CO2}(d)$ is zero, $V_D(F)$ is equal to $V_{D,Bohr}$. In the upper curve ($F_{CO2}$ versus $V_T$ curve), the drawing of the line of the “sloping alveolar plateau” is very difficult. However, if the last part of the $F_{CO2}$ versus $V_T$, which by no means is a straight line, is extrapolated, $V_D(F)$ becomes even smaller as compared to $V_{D,Bohr}$ by the volume segment $V_{da}$ (fig. 7).

3. Verification of the method

The analysis of the $VCO2$ versus $V_T$ curve was verified as follows: 1) In three normal subjects breathing tidally through tubes of known capacity ($V_{cap}$) interposed between the mouthpiece and the monitoring ring, the dead space volume was measured without ($V_{D(0)}$) and with the added tube ($V_D$). The difference $V_D-V_{D(0)}$ was compared with the capacity of the added tube (Results). 2) The gas volume $V_{CO2}(A) (=F_{A,CO2}\times V_A)$ was compared to the volume $V_{CO2}(B) (=F_{tr}\times V_T+F_{ET,CO2}\times V_A)$ (fig. 6). The error between $V_{CO2}(A)$ and $V_{CO2}(B)$ was calculated from (1 - $V_{CO2}(B)/V_{CO2}(A)$)$\times 100$ (Results). 3) The area $A(A) (=\frac{1}{2}V_A\times V_{CO2}(d))$ was compared to the area $A(B)$ (= $\frac{1}{2}V_D\times V_{CO2}(d)+\frac{1}{2}V_A\times (V_{CO2}-V_{CO2}(d))$) with an
error calculated from \[1-(A/B)/(A/A))\times100\] (Results) (fig. 6). 4) In normal subjects, \(P_{a,CO_2}\) did not differ significantly from \(P_{a,CO_2}\) (Results).

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