Eur Respir J 2000; 16: 659–664
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European Respiratory Journal
ISSN 0903-1936

Partitioning of dead space - a method and reference values in the awake human

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ABSTRACT: Although dead space is often increased in disease, it is not frequently measured in the clinic. This may reflect that an adequate method as well as reference values are missing.

Healthy males and females, n=38, age 20–61 yrs, were connected to a pneumotachograph and a fast CO_2 analyser after radial artery catheterization. The physiological dead space was partitioned into airway and alveolar dead space using a delineation principle denoted the pre-interface expirate.

Physiological dead space was 201±41 mL in males and 150±34 mL in females. Dead space values were depending upon parameters reflecting lung size (predicted total lung capacity), breathing pattern and age. After multiple correlation the variation decreased and differences between males and females disappeared. The residual SD was then for physiological dead space 18.9 mL.

The clinical use of the new method for determination of dead space can be based upon reference values, with a more narrow range than previous data.

Eur Respir J 2000; 16: 659–664.

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Keywords: Airway, alveolar, carbon dioxide, physiological, respiration

Received: June 25 1999
Accepted after revision April 26 2000

This work was supported by grants from the Swedish Medical Research Council (no. 02872), the Swedish Heart Lung Foundation and the Medical Faculty of Lund.

Dead space is increased in diseases causing uneven ventilation/perfusion, V'/Q' in the lung. A recording of fraction of CO_2 in expired air (F_{E,CO_2}) against expired volume (V_E) the $V_E/F_{E,CO_2}$ curve, and the simultaneous determination of carbon dioxide arterial tension (P_{a,CO_2}) allows determination of physiological dead space ($V_{D,phys}$) and its separation airway dead space ($V_{D,aw}$) and alveolar dead space ($V_{D,alv}$) [1]. The single breath test for CO_2 (SBT-CO_2) allows distinction between mechanisms causing increased respiratory dead space. In lung embolism unequal V'/Q' ratios exists between lung units, which synchronously empty during expiration. This leads to a uniformly low CO_2 content in the expired alveolar gas [2–4]. In obstructive lung disease lung units with different V'/Q' ratios empty at different rates, leading to a CO_2 content which rises during expiration [5, 6]. The test is performed during quiet breathing at rest and requires minimal patient co-operation. However, sparse data on dead space fractions in healthy subjects show wide normal ranges [7–10].

The objectives were to describe a method for SBT-CO_2 and to establish normal values.

Material and methods

Subjects

Twenty females and 18 males, age 20–61 yrs, life long nonsmokers denied cardiac or lung disease, rheumatism, diabetes, high blood pressure or vascular disease. Spirometry total lung capacity (TLC), vital capacity (VC) and forced expiratory volume in one second (FEV_1), electrocardiograph (ECG), blood pressure, and haemoglobin concentration were normal (table 1). The ethical committee approved the study and written consent was obtained from each subject.

Equipment

F_{E,CO_2} was measured with a mainstream analyser, (CO_2 Analyzer 130, Siemens Elema, Solna) [11]. After modification as described in the appendix, the 50% response time of the analyser was 12 ms. Flow rate was measured with a pneumotachograph (Fleisch No. 2; Gould Inc, Cleveland, OH, USA). The frequency response of the flow signal was flat up to 20 Hz. The signals for F_{E,CO_2} and flow are synchronous within ±2 ms. The apparatus dead space (14 mL) was subtracted.

The signals for flow and F_{E,CO_2} were analogue/digital (A/D) converted at 200 Hz in a personal computer. The

Table 1. – Age and spirometry results in per cent of predicted values

	Females	Males
Subjects n	20	18
Age yrs	41 (27–61)	39 (20–58)
VC	117 (87–136)	111 (89–123)
FEV_1	120 (94–143)	115 (86–129)
FEV%	103 (90–116)	104 (82–123)
TLC	111 (95–131)	103 (90–117)

Values presented as median (range). VC: vital capacity; FEV_1: forced expiratory volume in one second; FEV%: FEV_1 in percent of VC; TLC: total lung capacity.

signals were calibrated immediately before each study. Flow and volume are reported at body temperature and ambient pressure, saturated with water vapour (BTPS) conditions. Arterial blood was immediately analysed (ABL 520, Radiometer; Copenhagen, Denmark) after sampling. The calibration of the analysers for P_{a,CO_2} and F_{E,CO_2} were checked with the same calibration gas.

Procedure

A spirometry was performed when the subject arrived. An ECG was recorded and a radial catheter was inserted. While calibrations and other preparations were performed the patient remained supine, resting for several minutes in the silent room. Then, the patient was connected to the breathing circuit. The flow and CO_2 signals and end-tidal CO_2 were monitored. No trend of end-tidal CO_2 was allowed. A random variation of end-tidal CO_2 of $\leq$0.2 kPa was awaited. When at least 2 min had passed and a stable breathing pattern and end-tidal CO_2 were observed three consecutive recordings were performed. During each an arterial sample of 2 mL was taken and closed with a heparinized stopper (<500 IU heparin).

Analyses of single breath test for carbon dioxide curves

P_{a,CO_2} and the barometric pressure P_B were used to calculate the fraction of CO_2 in a gas in diffusion equilibrium with arterial blood, F_{a,CO_2}.

$$F_{a,CO_2} = \frac{P_{a,CO_2}}{P_B} \quad (1)$$

From each recording four representative breaths were selected for analysis. The automatic calculation of dead space fractions was based upon segmentation of the tidal volume, V_T, into Phase I (the CO_2 free part of the expired gas), II (mixed airway and alveolar gas) and III (the alveolar plateau) (fig. 1).

The slope of the alveolar plateau (SLOPE), expressed in $\%\cdot L^{-1}$ was calculated as described in *Appendix*.

Airway dead space, $V_{D,aw}$, (or series dead space), was calculated in accordance with the principles by WOLFF and BRUNNER [12]. In patients with obstructive lung disease

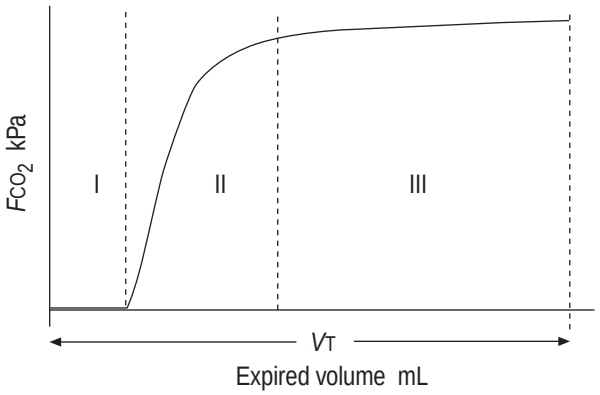

Fig. 1. – The single breath test for carbon dioxide and its partition into phase I, II and III. V_T: tidal volume; F_{CO_2}: fraction of carbon dioxide.

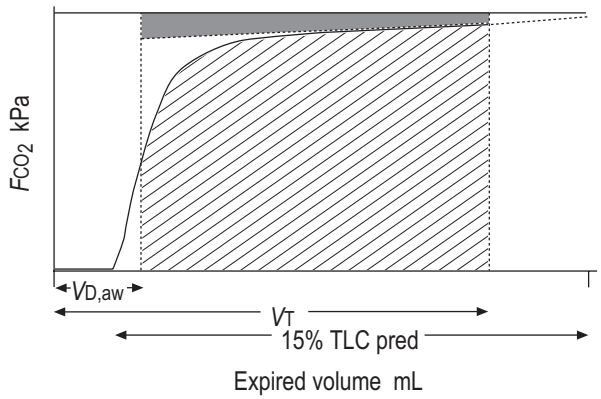

Fig. 2. – Airway dead space ($V_{D,aw}$) was defined as described in the *Appendix*. Physiological dead space ($V_{D,phys}$) was calculated from arterial CO_2 and from the volume of CO_2 expired during the breath (V_{E,CO_2}: ▨). The arterial CO_2 is represented by the fraction of CO_2 in a gas in equilibrium with arterial blood (F_{a,CO_2}; - - -). Alveolar dead space ($V_{D,alv}$) corresponds to the difference between arterial and alveolar CO_2 values (■) between the alveolar plateau and F_{a,CO_2}. Late dead space fraction, $V_{D,late}$ was calculated from the alveolar plateau extrapolated to 15% of the predicted total lung capacity (TLC pred), as further described in text. F_{CO_2}: fraction of CO_2; V_T: tidal volume.

breathing with large tidal volumes it was found that a highly sloping phase III led to unreasonably high values of $V_{D,aw}$. The slope of the alveolar plateau is also at health influenced by phenomena at the alveolar level [1]. The algorithm was therefore modified (see *Appendix*).

$V_{D,phys}/V_T$ was calculated from the volume of expired CO_2 per breath (V_{E,CO_2}) (fig. 2), V_T, and F_{a,CO_2}.

$$V_{D,phys}/V_T = 1 - (V_{E,CO_2}/V_T)/F_{a,CO_2} \quad (2)$$

Alveolar dead space $V_{D,alv}$ (parallel dead space) was calculated as the difference between $V_{D,phys}$ and $V_{D,aw}$. $V_{D,alv}$ corresponds to the differences between F_{a,CO_2} and the alveolar plateau (fig. 2).

Bohr's dead space ($V_{D,Bohr}$), was calculated according to classical principles, implying that end-tidal fraction of CO_2 replaces F_{a,CO_2} in Equation 2.

$V_{D,Bohr}$ is depending upon the dead space of large airways and of the tidal volume. An alternative focuses on nonsynchronous emptying of alveolar compartments with different V'/Q' ratios leading to smearing of phase II. A dead space fraction calculated in analogy with $V_{D,Bohr}$ over a volume interval starting at the beginning of phase II and ending after a standardized volume equal to 5% of the predicted total lung capacity, TLC pred, is denoted $V_{D,5\%TLC}$ (fig. 3). Predicted TLC represent expected lung size in a subject and is used to standardize for body and lung size. Predicted TLC was calculated from height in m, weight in kg and age in yrs [13]:

TLC pred (males) = -4.73+7.61 Height-0.019 Weight

TLC pred (females) = -6.35-0.016 Age+7.38 Height

The dead space values are expressed in mL and in per cent of V_T.

$V_{D,late}$ used for diagnosis of lung embolism, was determined at a volume of 15% of predicted TLC measured from the beginning of phase II [2–4]. $V_{D,late}$ in percent was calculated from the difference between alveolar and arterial fractions of CO_2 at a volume of 15% of predicted TLC, $\Delta F_{CO_2,late}$, related to F_{a,CO_2} (fig. 2).

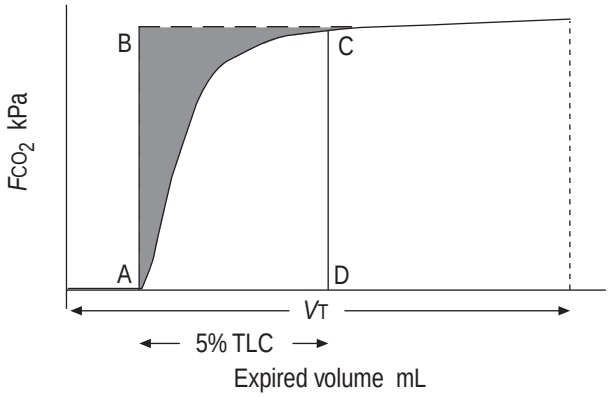

Fig. 3. – Dead space volume equal to 5% of predicted total lung capacity (TLC) ($V_{D,5\%TLC}$) was calculated from the quotient between the shaded area and the rectangle ABCD. The volume range AD starts at the beginning of phase II and covers 5% of the predicted TLC.

$$V_{D,late} = 100(\Delta F_{CO_2,late} / F_{a,CO_2}) \quad (3)$$

An equation was used to extrapolate the alveolar plateau to 15% of predicted TLC.

$$F_{E,CO_2} = a + b \ \ln V_E \quad (4)$$

For calculation of *a* and *b* the initial and last parts of the curve were eliminated. The initial part was defined as (phase I +2.5% of predicted TLC). The last part was 5% of (V_T - phase I).

Statistical analysis

Paired and unpaired t-test was used for comparison within and between groups, respectively. Single and multiple linear orthogonal regression based upon the least square method was used to define the normal range for a parameter. The LINEST function of Excel, 5.0 was used for this purpose. For analyses of SLOPE nonlinear regression based upon a power equation was used.

Results

P_{a,CO_2} was on average 5.10 kPa before connecting the patient to the mouthpiece. It increased to 5.19 kPa at the first dead space measurement and to 5.30 kPa during the second one ($p<0.001$). At the third recording, the value remained stable at 5.30 kPa. As steady state is important, results representing the average of the second and third measurements were further analysed. The breathing pattern was stable during the recordings (table 2). P_{a,CO_2} did not depend upon age. P_{a,O_2}, however, fell with age: P_{a,O_2}= 15.4-0.0754 Age (kPa) ($r=0.58$, RSD=1.15 kPa, $p<0.01$).

The nonlinear relationship between SLOPE and V_T was significant ($p<0.001$) and could be described by as:

$$\text{SLOPE} = 31324 \times V_T^{-1.535} \quad (5)$$

Observed deviations from the regression decreased with increasing tidal volume. The standard deviation $266/V_T$ yielded the normal range depicted in figure 4.

Table 2. – Arterial blood gases and breathing pattern observed in the three recordings

Parameters	Recording I	Recording II	Recording III
P_{a,CO_2} kPa	5.19±0.43 (4.41–5.77)	5.30±0.45 (4.41–5.84)	5.30±0.46 (4.41–5.85)
P_{a,O_2} kPa	12.5±1.9 (10.0–15.2)	12.2±1.5 (9.8–14.6)	12.5±1.5 (10.2–14.8)
V_T mL	647±206 (401–1040)	643±198 (397–1017)	648±176 (389–906)
f_R breaths·min^{-1}	11.9±2.6 (8.2–16.5)	12.0±2.6 (8.6–16.5)	12.2±2.7 (8.5–16.3)
V'_E L·min^{-1}	7.5±2.3 (5.2–12.5)	7.5±2.1 (5.3–12.2)	7.7±2.1 (4.8–12.5)

Values presented as mean±SD (5th-95th percentile intervals). P_{a,CO_2}: arterial carbon dioxide tension; P_{a,O_2}: arterial oxygen tension; V_T: tidal volume; f_R: respiratory frequency; V'_E: minute ventilation.

$V_{D,aw}$ was higher in males than in females (table 3). $V_{D,aw}$ in per cent of V_T was on average 19±4% and as per cent of predicted TLC 1.8±0.3%. $V_{D,aw}$ was, to a significant degree, depending upon predicted TLC and V_T (table 4).

$V_{D,phys}$ was higher in males than in females (table 3). After correlation to predicted TLC, V_T and age the residual standard deviation (RSD) of $V_{D,phys}$ for the whole group fell to ~50% of the SD observed in males or females (tables 3 and 4). When the same correlation was made for females and males separately the RSD increased slightly in females and decreased in males, both to a nonsignificant degree. Also $V_{D,phys}$% was significantly correlated to predicted TLC, V_T and age in the whole material (table 4). No significant benefits were obtained by separating males and females.

$V_{D,alv}$ did not differ significantly between sexes (table 3). A large variability in $V_{D,alv}$ reflected a strong correlation to V_T and age (table 4).

$V_{D,Bohr}$ was smaller in females than in males (table 3), and correlated to predicted TLC, V_T and age, while $V_{D,Bohr}$ in per cent of V_T ($V_{D,Bohr}$%) correlated to predicted TLC and V_T (table 4). $V_{D,5\%TLC}$ was 25.5±4.3% and correlated to predicted TLC and V_T (table 4). On average 5% of predicted TLC was 318 mL.

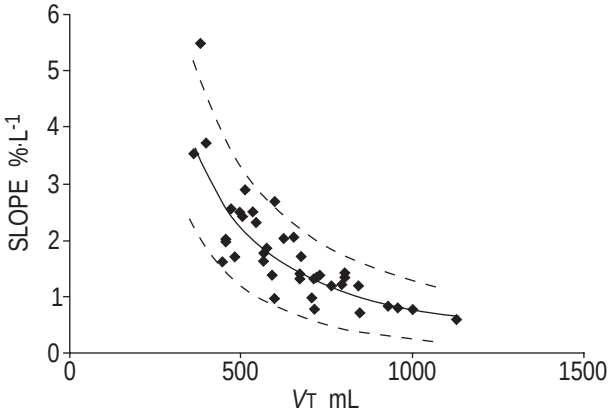

Fig. 4. – The slope of the alveolar plateau (SLOPE) was related to tidal volume (V_T) drawn line, SLOPE=$31324 \times V_T^{-1.536}$. The 95% confidence interval, interrupted lines, was based upon the SD $266/V_T$.

Table 3. – Partitioning of dead space

	Female mL	Male mL	All subjects % of V_T
$V_{D,aw}$	100±14	136±23***	18.8±4.2
	(83–122)	(100–167)	(12.9–25.8)
$V_{D,phys}$	150±34	201±41***	27.5±4.6
	(114–216)	(137–255)	(20.9–35.8)
$V_{D,alv}$	51±26	66±26	8.8±2.6
	(24–105)	(30–101)	(5.3–13.4)
$V_{D,Bohr}$	130±21	170±30***	23.7±3.8
	(103–164)	(133–207)	(18.4–29.6)

Data presented as mean±SD (5th-95th percentile interval). $V_{D,aw}$: airway dead space; $V_{D,phys}$: physiological dead space; $V_{D,alv}$: alveolar dead space; $V_{D,Bohr}$: Bohr′s dead space; ***: p<0.001.

$V_{D,late}$ was -1.0±4.2%. V_T and age had a significant influence on $V_{D,late}$. TLC pred had a slight, but significant, influence. After correlation to V_T, age and predicted TLC the RSD of $V_{D,late}$ decreased to 3.1% (table 4).

To ease the interpretation of an SBT-CO_2 the computer may report the predicted values as shown in table 5.

Discussion

The SBT-CO_2 allows determination of airway and physiological dead space. The diagnosis of embolism may be based upon $V_{D,late}$ [2–4], while diagnostics of emphysema and asthma may be based upon features related to phase II [5, 6]. The SBT-CO_2 has not become widely used. Reasons for this may be that adequate methods and reference values have not been available.

Even small phase shifts between flow and CO_2 signals lead to significant errors [14]. The mainstream CO_2 Analyzer 930, however fast, can be further speeded up by changing one of its internal amplifiers (see *Appendix*). After this modification there is no significant phase shift between the two signals. As the difference between arterial and expired CO_2 conveys important information cross calibration between the blood gas analyser and the gas analyser is essential. P_{a,CO_2} should be immediately measured and reported with two decimals (in kPa).

As varying alveolar ventilation leads to nonequilibrium between expired and arterial CO_2 [15], determination of physiological, alveolar and late dead space relies upon steady state. Although measurements started when end tidal CO_2 was stable P_{a,CO_2} was not stable until after the second measurement (table 2). At least 3 min should be allowed after connection to the mouthpiece.

Advantages with a spontaneous breathing pattern are that steady state can be reached and that the results represent physiological conditions. A drawback may be large differences in V_T. The influence of V_T on various measures of dead space makes it necessary to use reference values, specific for the actual V_T. Still some data may be of little use in subjects breathing at low V_T. This appears particularly be the case for SLOPE, the variability of which increases at low V_T. The finding that $V_{D,late}$ correlates to V_T and is negative at low V_T is probably a sign of that the alveolar plateau as defined in the *Appendix* is influenced by airway gas, particularly at low V_T.

A high SLOPE obscures the transition between phase II and III and may lead to overestimation of $V_{D,aw}$ determined according to FOWLER [7] and LANGLEY et al. [16]. The algorithm of WOLFF and BRUNNER [12] partially solves this problem. However, in obstructive disease, when SLOPE is high and V_T large it is regularly found that $V_{D,aw}$ is unduly large when determined according to WOLFF and BRUNNER [12]. When their principle is applied in two steps, as discussed in the *Appendix*, the influence of SLOPE on $V_{D,aw}$ is eliminated.

The classical $V_{D,Bohr}$ is still merited as a noninvasive measure of nonsynchronous emptying of alveolar compartments with different V'/Q'. $V_{D,Bohr}$ is, however, depending upon $V_{D,aw}$ and the V_T. $V_{D,5\%TLC}$ is an alternative, independent upon $V_{D,aw}$ and V_T. FLETCHER *et al.* [14] suggested the use of "efficiency" which represents the reciprocal of dead space [1, 17].

Body and lung size is a factor that obviously influences dead space. In the present study predicted TLC was used as an indicator of size. After correlation to TLC pred otherwise important differences between males and females were eliminated. Sex independent reference values may reflect that differences between males and females reflect size and not quality of lungs. V_T shows a large variation that is independent of body size. V_T was therefore used as a parameter reflecting the individual breathing pattern. It was natural to consider that age might influence dead space.

Although the observations showed wide ranges of dead space values, still wider ranges have been reported [7–10]. When TLC pred, V_T and age were taken into account the normal range decreased to such an extent that the

Table 4. – The results of multiple correlation

Parameter Y	Constant	k1 TLC pred	k2 V_T	k3 Age	RSD	R
$V_{D,aw}$ mL	4.9	0.0113**	0.062**	–	15.2	0.81
$V_{D,phys}$ mL	-65.2	0.0116**	0.173**	1.33**	18.9	0.91
$V_{D,phys}$% %	19.0	0.00182**	-0.0155**	0.168**	3.3	0.70
$V_{D,alv}$ mL	-57.9	–	0.112**	1.07**	14.5	0.88
$V_{D,Bohr}$ mL	-20.7	0.0100**	0.122**	0.662**	13.8	0.91
$V_{D,Bohr}$% %	25.4	0.00139**	-0.0164**	–	2.6	0.73
$V_{D,5\%TLC}$ %	34.3	-0.00214**	0.0075*	–	3.5	0.57
$V_{D,late}$ %	-11.7	-0.00084*	0.0171**	0.123**	2.8	0.76

The parameter Y was expressed as: Y=constant+k1 TLC pred+k2 V_T+k3 Age. The significance of k1–k3 is denoted **: p≤0.01; *: p≤0.05. RSD: residual standard deviation; R: correlation coefficient; $V_{D,aw}$: airway dead space; $V_{D,phys}$: physiological dead space; $V_{D,phys}$%: $V_{D,phys}$ in percent of tidal volume (V_T); $V_{D,alv}$: alveolar dead space; $V_{D,Bohr}$: Bohr′s dead space; $V_{D,Bohr}$%: $V_{D,Bohr}$ in per cent of tidal volume; $V_{D,5\%TLC}$: dead space volume equal to 5% total lung capacity; $V_{D,late}$: late alveolar dead space.

Table 5. – Parameter reference values*

	$V_{D,aw}$ mL	$V_{D,phys}$ mL	$V_{D,phys}$% %	$V_{D,alv}$ mL	$V_{D,Bohr}$ mL	$V_{D,Bohr}$% %	$V_{D,5\%TLC}$ %	$V_{D,late}$ %
Expected	93	132	29	39	116	25	26	-3.07
RSD	15.2	18.9	3.3	14.5	13.8	2.6	3.5	2.8
Upper limit$^+$	63	96	22	11	89	20	19	-9
Lower limit$^+$	123	169	35	67	143	30	33	2

*: obtained after entering a predicted total lung capacity (TLC) of 5,300 mL, a tidal volume of 456 mL and an age of 43 yrs into an Excel spreadsheet (Excel; Microsoft Corporation, Seattle, WA, USA); $^+$: expected value ±1.95 residual standard deviations (RSD). $V_{D,aw}$: airway dead space; $V_{D,phys}$: physiological dead space; $V_{D,phys}$%: $V_{D,phys}$ in percent of tidal volume (V_T); $V_{D,alv}$: alveolar dead space; $V_{D,Bohr}$: Bohr's dead space; $V_{D,Bohr}$%: $V_{D,Bohr}$ in per cent of tidal volume; $V_{D,5\%TLC}$: dead space volume equal to 5% total lung capacity; $V_{D,late}$: late alveolar dead space.

diagnostic value of dead space determinations must be considerably enhanced (table 4). It appears possible that promising results in the diagnostics of embolism based on $V_{D,late}$ reached without such considerations may be further enhanced [2–4]. The SBT-CO_2 has also been of value in other diseases with vascular engagement [18].

$V_{D,aw}$ was independent of age. The present data on $V_{D,aw}$ in males are similar to those of FOWLER [7], who found that sex and V_T were of importance. KARS *et al*. [10], who did not distinguish between males and females, found slightly higher values for $V_{D,aw}$.

V'/Q' inequality increases [19] and P_{a,O_2} decreases with age [8]. The present findings, that parameters reflecting alveolar gas exchange, $V_{D,alv}$, $V_{D,phys}$, $V_{D,Bohr}$ and $V_{D,late}$ increase with age, could accordingly be expected.

The magnitude of $V_{D,phys}$ and the dependence upon V_T agree with data from ASMUSSEN and NIELSEN [9]. In patients with essentially normal lung function ERIKSSON *et al*. [2] found that $V_{D,late}$ was slightly negative which was confirmed.

In conclusion, a method for dead space measurement based upon a fast carbon dioxide analyser was described. Steady state is only achieved after a period on mouthpiece of 3 min. The variability of dead space values observed in healthy males and females was large. After correlation for age, lung size and breathing pattern modest variability remained. This correction should be regarded as a prerequisite for clinical use.

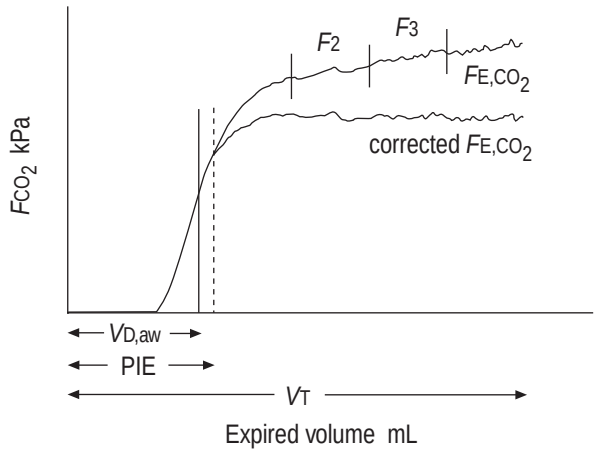

Fig. 5. – Example of how correction of alveolar slope affects the determination of $V_{D,aw}$. F_{CO_2}: fraction of carbon dioxide; F_{E,CO_2}: fraction of CO_2 in expired air; $V_{D,aw}$: airway dead space.

Appendix

Calculation of $V_{D,aw}$

The pre-interface expirate (PIE), which according to WOLFF and BRUNNER [12] represents "the smallest possible of determinable values of $V_{D,aw}$" was determined. In spite of truncation performed according to this reference it was observed that PIE was unduly influenced by a sloping alveolar plateau in subjects with large V_T. This influence was eliminated by correction for the alveolar slope. The volume range between PIE and the full V_T was divided into four equal parts. The mean value of F_{E,CO_2} was calculated for the second and third part, F_2 and F_3, respectively:

$$\text{SLOPE} = (F_3 - F_2) \times 4/(V_T - \text{PIE})$$

The curve was corrected for the slope over the segment from PIE to V_T (fig. 5). From the corrected new curve, $V_{D,aw}$ was calculated according to the algorithm of WOLFF and BRUNNER [12].

Modification of the carbon dioxide analyser

The CO_2 Analyzer 130 has on a board an amplifier of type LM 308 situated immediately after the CO_2 transducer and feeding the capacitors of the demodulator. The limited power of this amplifier limits the response rate of the analyser. The amplifier was exchanged for one of type LF 355 to decrease the rise time of the analyser.

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