

Reference values for volumetric capnography-derived non-invasive parameters in healthy individuals

Gerardo Tusman · Emiliano Gogniat · Stephan H. Bohm ·
Adriana Scandurra · Fernando Suarez-Sipmann · Agustin Torroba ·
Federico Casella · Sergio Giannasi · Eduardo San Roman

Received: 6 July 2012 / Accepted: 22 January 2013 / Published online: 7 February 2013
© Springer Science+Business Media New York 2013

Abstract The aim of this study was to determine typical values for non-invasive volumetric capnography (VCap) parameters for healthy volunteers and anesthetized individuals. VCap was obtained by a capnograph connected to the airway opening. We prospectively studied 33 healthy volunteers 32 ± 6 years of age weighing 70 ± 13 kg at a height of 171 ± 11 cm in the supine position. Data from these volunteers were compared with a cohort of similar healthy anesthetized patients ventilated with the following settings: tidal volume (VT) of 6–8 mL/kg, respiratory rate 10–15 bpm, PEEP of 5–6 cmH₂O and FiO₂ of 0.5. Volunteers showed better clearance of CO₂ compared to anesthetized patients as indicated by (median and interquartile range): (1) an increased elimination of CO₂ per mL of VT of 0.028 (0.005) in volunteers versus 0.023 (0.003) in anesthetized patients, $p < 0.05$; (2) a lower normalized slope of phase III of 0.26 (0.17) in volunteers versus 0.39 (0.38) in anesthetized patients, $p < 0.05$; and (3) a lower Bohr dead space ratio of 0.23 (0.05) in volunteers versus

0.28 (0.05) in anesthetized patients, $p < 0.05$. This study presents reference values for non-invasive volumetric capnography-derived parameters in healthy individuals. Mechanical ventilation and anesthesia altered these values significantly.

Keywords Volumetric capnography · CO₂ · Dead space · Slope of phase III · Mechanical ventilation

1 Introduction

The ideal respiratory monitoring for mechanically ventilated patients should provide clinically relevant information at the bedside in real-time and, most importantly, in an entirely non-invasive way. Volumetric capnography (VCap), the plot of expired CO₂ over the volume of one tidal breath, has the potential to fulfill these requirements (Fig. 1) [1–3]. Thus, VCap delivers breath-by-breath physiologically meaningful information on the lung's function such as the tidal elimination of CO₂ (VTCO_{2,br}), the slope of phase III (S_{III}) and Bohr's dead space ratio (VD_{Bohr}/VT) [4–7].

Despite its obvious clinical advantages VCap has not reached popularity as a non-invasive means of respiratory

This work was performed at Hospital Privado de Comunidad, Mar del Plata, Argentina and Hospital Italiano, Buenos Aires, Argentina.

Electronic supplementary material The online version of this article (doi:10.1007/s10877-013-9433-x) contains supplementary material, which is available to authorized users.

G. Tusman (✉) · A. Torroba · F. Casella
Department of Anesthesiology, Hospital Privado de Comunidad,
Mar del Plata, Argentina
e-mail: gtusman@hotmail.com

E. Gogniat · S. Giannasi · E. S. Roman
Department of Critical Care Medicine, Hospital Italiano,
Buenos Aires, Argentina

S. H. Bohm
Swisstom AG, Landquart, Switzerland

A. Scandurra
Bioengineering Laboratory, Electronic Department, School of
Engineering, Mar del Plata University, Mar del Plata, Argentina

F. Suarez-Sipmann
Department of Surgical Sciences, Clinical Physiology University
Hospital, Uppsala, Sweden

F. Suarez-Sipmann
Instituto de investigación Sanitaria. Fundación Jiménez Díaz.
IIS-FJD, CIBERES, Madrid, Spain

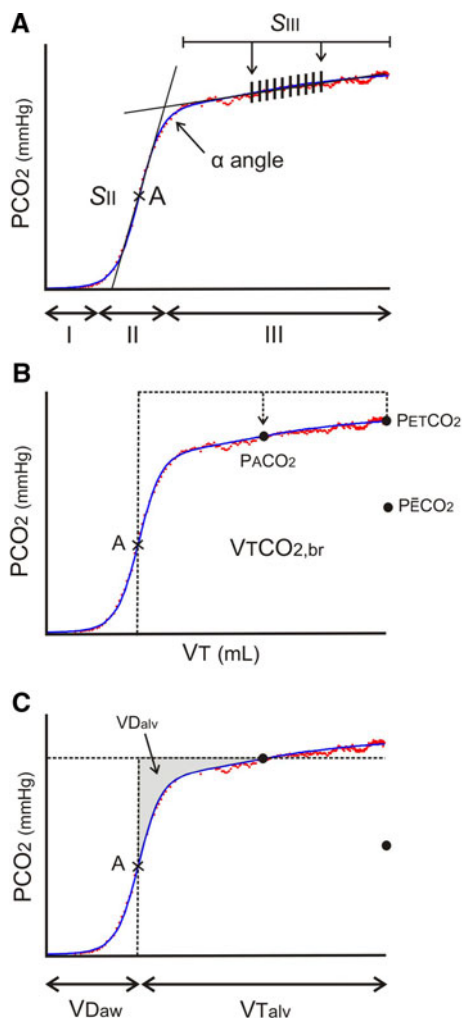


Fig. 1 Volumetric capnography-derived non-invasive parameters. **a** The volumetric capnogram (VCap) is divided into three phases I, II and III, which are indexed by VT. The slope of phase II is calculated at the inflection point of VCap (Point A). The slope of phase III is calculated as the mean value of the 10 individual slopes at the corresponding points along the middle third of alveolar plateau. **b** The respective location of the end-tidal (PETCO₂), the mean alveolar (PACO₂) and the mixed expired (PĒCO₂) partial pressures of CO₂ are shown in the graphic. The area under the curve corresponds to the amount of CO₂ eliminated per tidal breath (VTCO_{2,br}). **c** At the inflection point A, the tidal volume is partitioned into the airway dead space (VD_{aw}) and the alveolar tidal volume (VT_{alv}). The alveolar dead space (VD_{alv}, grey area) is calculated by subtracting VD_{aw} from the physiological dead space as determined by Bohr's equation. For more details see text

monitoring for mechanically ventilated patients for the following main reasons: (1) the calculation of dead space according to Enghoff requires invasive and intermittent measurements of blood gases [8, 9], (2) the clinical meaning of many of the VCap-derived parameters is not well known, and (3) normal values for most of the non-invasive parameters have not yet been established.

This study is intended to provide supporting data to the above point 3. We strongly believe that the knowledge of

reference values for the non-invasive VCap parameters in healthy individuals is essential to interpret results from clinical patients. Almost all published reference values were obtained using both, Enghoff's and Fowler's methods. It is known, however, that Enghoff's approach is invasive and overestimates dead space due to the inclusion of shunt effects [2, 5, 8–10] and that Fowler's method induces errors in the calculation of VCap-parameters if capnograms are deformed such as in patients with pulmonary diseases [11–13].

We have recently described a mathematical method to accurately calculate VCap-derived non-invasive parameters like S_{III} and dead space [13, 14]. The objective of this observational study was to present reference values for these parameters for healthy individuals.

2 Methods

After approval by the local ethics committee, we studied two populations of healthy individuals:

1. **Volunteers** Thirty three healthy volunteers were prospectively analyzed after signing an informed consent form. All volunteers fulfilled the following inclusion criteria: age between 25 and 50 years, body mass index between 21 and 30 kg/m², non-smoker, regular age-adjusted physical exercise and absence of known cardiac, metabolic, neuromuscular or respiratory diseases with normal spirometry.
2. **Patients** To compare the above reference data with those of anesthetized patients, we retrospectively reviewed our database and selected a cohort of 33 individuals that best matched the demographic characteristics of the healthy volunteers. Eligible patients were non-smokers free of cardiac, respiratory or neuromuscular diseases who underwent elective non-complex and neither laparoscopic nor thoracic surgeries in supine position.

2.1 Volumetric capnography

Volumetric capnograms and respiratory mechanics were recorded on-line using the NICO respiratory monitor (Respironics, Wallingford, Conn., USA). NICO's disposable mainstream flow, pressure and CO₂ sensors adapter was placed at the airways opening. CO₂ was measured by an infrared sensor (response time <60 ms and accuracy of ± 2 mmHg) and airway flow was determined across a fixed orifice using differential pressure sensors (range 2–180 L and accuracy of ± 3 %). Volumes were automatically compensated for body temperature and water vapor pressure (BTPS). The CO₂ sensor was zeroed

according to manufacturer guides before examining each subject. Data were stored in a laptop using the Datacoll software (Respironics, Wallingford, Conn., USA) and later analyzed off-line.

Volumetric capnograms were constructed from raw CO₂ and flow data, which were then processed according to a method previously published by our group [13]. In essence this method uses a Levenberg–Marquardt algorithm to optimize parameters of a function defined ad-hoc to fit the original VCap raw data. This procedure was performed in Matlab® (Mathworks, Natick, MA, USA). From this mathematical representation of all data points comprising the VCap the following set of non-invasive parameters was derived as shown in Fig. 1:

2.2 Variables related to the shape of VCap (Fig. 1a)

- Volume of phase I is the portion of the tidal volume free of CO₂ which is formed by the apparatus and part of the airway dead space. It was calculated from the end of inspiration (detected by the flow signal) until the start of CO₂ elimination coinciding with the point of the left maximum of the 3rd derivative (maximum rate of change of the 2nd derivative). This volume was normalized by VT (VI/VT).
 - Volume of phase II constitutes the portion of the tidal volume where increasing amounts of CO₂ are leaving the lungs at different rates of ventilation and perfusion. This phase extends from the point of maximum rate of change of the 2nd derivative until the intersection of the lines running along the slopes of phase II and III. This volume was normalized by VT (VII/VT).
 - Phase III represents pure alveolar gas coming from the end of phase II until the gas at end of expiration, at the end-tidal partial pressure of CO₂ (PETCO₂). This volume was also normalized by VT (VIII/VT).
 - The slope of phase II (S_{II}) was determined as the value of the 1st derivative at the inflection point (point A) of the mathematical function.
 - The slope of phase III (S_{III}) was calculated using only data from the right hand maximum of the 3rd derivative of the mathematical function until the end of VT. This portion of the capnogram was then separated into three thirds and the middle third was divided into ten equidistant points. The slope of the curve on each point was computed as the value of their 1st derivative in each one of these points. The mean value of such 10 slope values constituted S_{III} . This slope, normalized (S_{nIII}) as the quotient between S_{III} and the mixed expired CO₂ fraction ($F\bar{E}CO_2 = VTCO_{2,br}/VT$), facilitates comparisons of slopes coming from tidal volumes of different sizes [15].
- The angle alpha (α) is the angle formed by the intersection between the regression lines of phase II and III.

2.3 CO₂ tension-based values and elimination of CO₂ (Fig. 1b)

- PETCO₂ was calculated as the last expiratory CO₂ value just prior to the start of the next inspiration.
- PACO₂ is the mean alveolar PCO₂ value located on S_{III} at the midpoint between the mathematical inflection point of VCap (point A) and PETCO₂ [5, 14].
- $P\bar{E}CO_2$ is the mixed partial pressure of CO₂ calculated multiplying $F\bar{E}CO_2$ by the difference between barometric and water vapor pressures [16].
- VTCO_{2,br}, the tidal elimination of CO₂ was obtained by integrating the flow and CO₂ signals over the entire breath [3]. This volume of expired CO₂ was indexed by tidal volume (VTCO_{2,br}/VT).

2.4 Dead space variables (Fig. 1c)

- The ratio of dead space to tidal volume was calculated in a non-invasive fashion using Bohr's formula [4, 14]:

$$V_{DBohr}/V_T \text{ OR } V_D/V_T = (P_{ACO_2} - P\bar{E}CO_2)/P_{ACO_2}$$

- V_{Dphys} is the physiological dead space obtained as:

$$V_{Dphys} = V_{DBohr}/V_T * V_T$$

- V_{Daw} is the airway dead space measured as the volume found at point A. V_{Daw} was normalized by VT (V_{Daw}/VT) [13, 17].
- V_{Dalv} is the alveolar dead space calculated by subtracting V_{Daw} from V_{Dphys} . The alveolar dead space was then normalized by VT (V_{Dalv}/VT) and also by the alveolar portion of the tidal volume ($V_{Dalv}/V_{T_{alv}}$).

2.5 Study protocol in volunteers

During the study volunteers embraced the end of the mainstream CO₂-flow sensor with their lips while their nose was occluded by a clamp. Subjects were examined in both, the supine and in the recumbent position (data on the latter condition are presented in the on-line supplement, only). They were asked to relax and to adjust their normal breathing until they found a comfortable ventilator pattern that allowed them to keep VT relatively constant. In order

to make up for the high variability of VT normally found during spontaneous breathing [18, 19], three runs in both, the supine and the sitting body position were allocated in random order using sealed envelopes. Each run lasted 4 min. After 2 min of stable breathing, data belonging to the subsequent 2 min were analyzed whereby breaths from the three runs in each position were pooled. We excluded from the analysis: (1) any deformed breaths either due to artifacts or errors in the acquisition system that would cause the algorithms to fail and (2) any breaths outside the $\pm 50\%$ range of the median VT value of each run in order to avoid the inclusion of sighs or very low VT.

2.6 Anesthesia and CO₂ recording in patients

Anesthesia was induced with propofol 1.5–2 mg kg⁻¹, vecuronium 0.08–1 mg kg⁻¹ and fentanyl 3–4 μ g kg⁻¹ and maintained with isoflourane 0.5–0.7 MAC plus remifentanyl 0.5–1 μ g kg⁻¹ h⁻¹. A multiparametric monitor Cardiocap/5 (GE Healthcare, Datex-Ohmeda, Helsinki, Finland) recorded vital signs. The above data was recorded in a laptop using the software Datex Collect (GE Healthcare, Datex-Ohmeda, Helsinki, Finland). Volumetric capnography was recorded by the NICO monitor (Respironics, Wallingford, Conn., USA).

Lungs were ventilated in volume controlled mode through a cuffed endotracheal tube using the Advance workstation (GE Healthcare, Madison, WI, US) with the following ventilator settings: VT between 6 and 8 ml kg⁻¹ of lean body weight, respiratory rate between 10 and 15 breaths min⁻¹, PEEP between 5–6 cmH₂O, I:E ratio of 1:2 without inspiratory pause and FiO₂ of 0.5. Ventilation was adjusted to maintain PETCO₂ at 33 ± 3 mmHg by changing the respiratory rate.

For data retrieval we selected a period of 15 min of stable anesthesia and hemodynamic defined as: esophageal temperature 36.5 ± 0.5 C°, SpO₂ between 97 and 100 %, mean arterial pressure between 55 and 80 mmHg, heart rate between 55 and 90 bpm and PETCO₂ varying no more than ± 1 mmHg during the recording time. Depending on the respiratory rate set on the ventilator we selected 20–30 breaths from the last 2 min of such 15-minutes steady-state periods for VCap analysis.

2.7 Data analysis

Statistical analysis was performed using Matlab® (Mathworks, Natick, MA, USA). A non-normal distribution of all parameters studied except for VI/VT was determined by the Lilliefors' test. Therefore, Wilcoxon's rank sum test was used to compare data between supine volunteers and patients and between sitting and recumbent volunteers. Values are presented as median and interquartile

range. A p value <0.05 was considered statistically significant. Functional relationship between capnographic parameters (VTCO_{2,br}, S_{III} and dead space) versus height and size of VT were computed by regression analysis to fit data with a two-term power model. The coefficient of determination (r^2) was computed to test the goodness of fit of the model.

2.8 Results

All volunteers complete the protocol successfully. Their characteristics and respiratory function data are presented in Table 1.

The tension-based values and the elimination of CO₂ per breath are presented in Table 2. These values were higher in volunteers than in patients despite both groups breathing at similar tidal volumes. The absolute amount of CO₂ eliminated per breath was 15.3 (8.4) mL in volunteers and 11.9 (2.9) mL in anesthetized patients. When relating this parameter to the size of the tidal breaths (VTCO_{2,br}/VT), such value was 18 % higher in volunteers than in patients (Table 2). We found that the elimination of CO₂ per breath was primarily dependent on the size of VT_{alv} ($r^2 = 0.83$, $p < 0.0001$) (Fig. 2).

The absolute value of S_{III} was 0.009 (0.005) in volunteers and 0.012 (0.009) in patients. The volunteers showed relatively higher S_{II} (10 %) and lower S_{nIII} (−67 %) and angle alpha (−1.3 %) than the patients (Table 2). S_{nIII} was dependent on both, the size of VT_{alv} ($r^2 = 0.64$, $p < 0.0001$) and VTCO_{2,br} ($r^2 = 0.55$, $p < 0.0001$) (Fig. 2).

Dead space data are presented in Table 3. All volunteers had a VD_{phys} of less than 1/4th of VT, with VD_{aw} contributing approximately 80 % and VD_{alv} the remaining 20 % to the total inefficiency of gas exchange. We neither found a relationship between dead space and body weight nor body mass index. However, VD_{aw} ($r^2 = 0.63$, $p < 0.0001$) and VD_{phys} ($r^2 = 0.53$, $p < 0.0001$) both showed a dependency on height while VD_{phys} ($r^2 = 0.50$, $p < 0.0001$) was dependent on VT (Fig. 3).

When compared to volunteers patients showed a significantly increased VD_{Bohr}/VT (+18 %) which was mainly due to an increased alveolar dead space (Table 3).

For interested readers additional data on volunteers in the sitting position as well as an analysis of all data for gender differences are presented in the on-line supplement.

3 Discussion

This study in healthy adults provides typical values for volumetric capnography-derived parameters. The novelty

Table 1 Demographic and lung function data of healthy volunteers and patients

	Age (years)	Gender (M/F)	Weight (kg)	Height (cm)	BMI (kg/cm ²)	FVC (L) (pred. [%])	FEV ₁ (L) (pred. [%])	FEV ₁ /FVC (pred. [%])
Healthy volunteers (n = 33)	32 ± 6	15 M/18F	70 ± 13	171 ± 11	24 ± 2	4.60 ± 1.2 (102 %)	3.73 ± 0.9 (101 %)	82 ± 5 (98 %)
Healthy patients (n = 33)	37 ± 7	14 M/19F	73 ± 13	168 ± 10	26 ± 3	n.a.	n.a.	n.a.

Data presented as mean ± standard deviation

BMI body mass index calculated as weight/height², FVC functional vital capacity as absolute volume and in brackets as % of predicted value, FEV₁ forced expired volume within one second as absolute volume and in brackets as % of predicted value and ratio of FEV₁/FVC in brackets as % of predicted value, n.a. not available

Table 2 Volumetric capnography-derived parameters in volunteers and in anesthetized patients

VCap parameters		Healthy awake volunteers (n = 33)	Healthy anesthetized patients (n = 33)
CO ₂ tension-based values and the elimination of CO ₂	PETCO ₂ (mmHg)	36 (7)	32 (5)*
	PACO ₂ (mmHg)	34 (6)	29 (3)*
	PECO ₂ (mmHg)	26 (5)	21 (4)*
	VT _{CO₂,br} /VT	0.028 (0.005)	0.023 (0.003)*
Shape-related VCap parameters	VI/VT	0.08 (0.05)	0.11 (0.04)*
	VII/VT	0.17 (0.06)	0.15 (0.04)*
	VIII/VT	0.75 (0.09)	0.75 (0.05)
	S _{II} (mmHg/mL)	0.43 (0.20)	0.39 (0.11)*
	S _{nIII} (L ⁻¹)	0.26 (0.17)	0.39 (0.38)*
Angle (°)	157 (9)	159 (6)*	

Values presented as median and interquartile range. Wilcoxon’s test compared supine volunteers with supine patients (*) a *p* < 0.05 indicating significant differences

VCap volumetric capnography, PETCO₂, PACO₂ and PECO₂ end-tidal, mean alveolar and mixed expired partial pressures of CO₂, respectively. VT_{CO₂,br}/VT amount of expired CO₂ within one breath normalized by tidal volume. S_{II} slope of phase II and S_{nIII} normalized slope of phase III. Angle *alpha* = the one formed by the intersection between the regression lines of phase II and III

of our findings is that such reference values for VCap parameters were measured in a completely non-invasive fashion and with an improved methodology [5, 13, 14]. These typical values can be used as a reference to determine the lung function in patients undergoing mechanical ventilation. Thus, VCap parameters will help clinicians to adjust the ventilatory settings and/or to detect a pathological condition like a pulmonary embolism.

3.1 The elimination of CO₂ per breath

VT_{CO₂,br} is the main VCap parameter that, surprisingly, is not presented in most of publications related to VCap in humans. We reported in this paper its typical values for

healthy individuals in both, awake and anesthetized conditions. As VT_{CO₂,br} is dependent on the size of a breath, it was normalized by tidal volume to allow comparisons among individuals.

VT_{CO₂,br}/VT depends on the balance between the factors that determine the body’s CO₂ kinetics: efficiency of ventilation, distribution of lung perfusion, global V/Q ratio, area of gas exchange and metabolism [7, 20]. Therefore, the differences in VT_{CO₂,br}/VT observed between spontaneously breathing volunteers and anesthetized subjects can be explained by changes in such CO₂ kinetics.

As demographics of patients and volunteers were similar, we assumed that differences in VT_{CO₂,br}/VT between the groups were mainly originating from the effect that anesthesia and positive-pressure ventilation had on the matching of V/Q. It is well known that anesthesia decreases end-expiratory lung volumes and causes lung collapse in dependent lung areas [21–23]. Ventilatory inefficiencies are a multi-factorial problem in which the respiratory muscle dysfunction induced by anesthetic drugs plays a major role. Mechanical ventilation, on the other hand, can affect lung function in many ways depending on the ventilatory settings applied. Mechanical ventilation not only supports normal ventilation in some lung areas but can also induce collapse and/or overdistension in others [21–24].

Due to the strict non-invasiveness of our study we were unable to analyze the role of lung perfusion and gas exchange on the clearance of CO₂. However, we can assert that anesthesia and mechanical ventilation decreased VT_{CO₂,br}/VT by a more heterogeneous distribution of ventilation and perfusion which find their expression in both, a steeper S_{nIII} and an increased dead space [2, 5, 6, 15, 25] (see below).

3.2 The slope of phase III

Many theories had been postulated to explain the positive sloping of phase III. Consensus exists that S_{III} represents ventilation inhomogeneities generated by convection and diffusion transport of a particular gas within lungs. As the

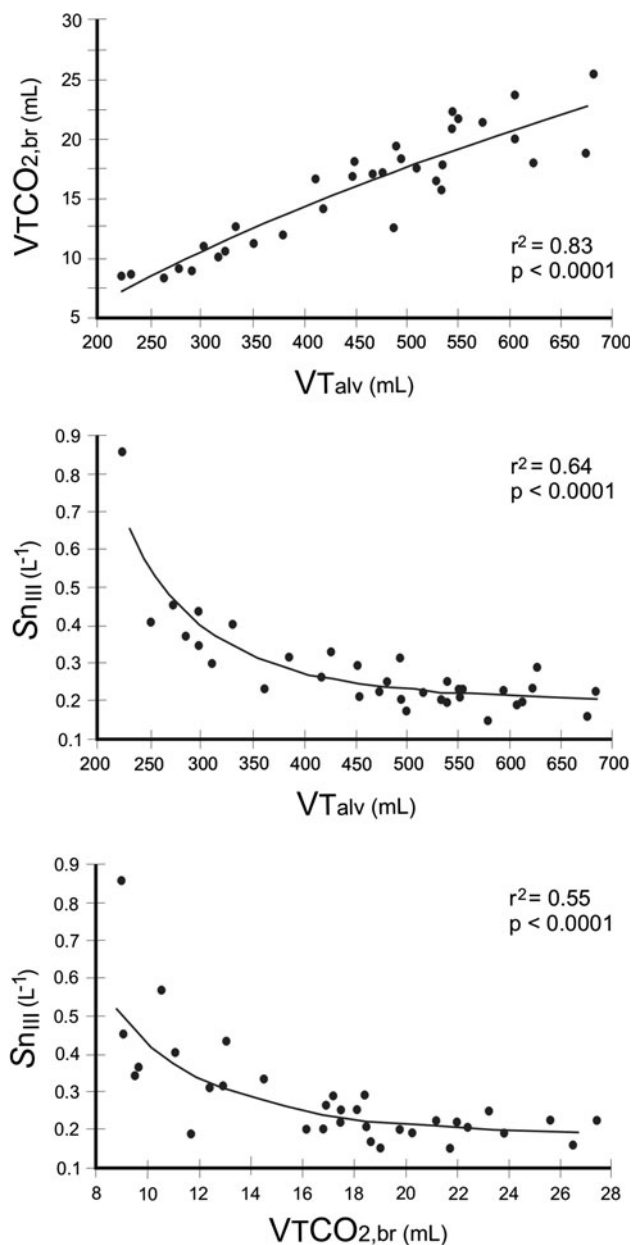


Fig. 2 Functional relations between VT_{alv} , $VTCO_{2,br}$ and Sn_{III} . $VTCO_{2,br}$ = the amount of CO_2 eliminated per tidal breath, VT_{alv} = the alveolar tidal volume and Sn_{III} = normalized slope of phase III. The functional relationship between the above parameters was determined by regression analysis. Data were fitted with a two-term power model according to the following equation: $y = a x^b + c$. The coefficient of determination (r^2) was computed to test the goodness of fit of such model. Each dot represents a median value for each volunteer

alveolar CO_2 sloping depends also on heterogeneities in pulmonary perfusion, S_{III} of VCap can be considered a good qualitative estimate of the global V/Q ratio [6, 15, 25]. Higher S_{III} indicate disturbances in the matching of V and Q whereas lower slope values a better matching [6]. Thus, S_{III} is typically increased in COPD, asthmatic crisis

or anesthesia-induced atelectasis while it decreases with the inhalation of beta-2 adrenergic drugs or with lung recruitments [26–29].

Following the above reasoning, it is imperative to know reference values for S_{III} in order to turn this easy-to-obtain parameter, which reflects global V/Q matching, into one of particular clinical usefulness (Table 2). Like other VCap variables S_{III} is highly dependent and inversely proportional to the size of VT as demonstrated in the awake volunteers [30] and in the anesthetized patients alike [31, 32]. Our results fit with the above findings (Fig. 2). Therefore, to allow comparisons between patients of different body sizes breathing at different VT, S_{III} should be normalized by VT or by mixed expired CO_2 concentration as suggested by Scherer et al. [15].

The higher Sn_{III} observed in patients compared to the awake volunteers can be interpreted as a sign of V/Q mismatching. In other words, general anesthesia and mechanical ventilation in our patients seem to have impaired gas mixing and diffusional transport of CO_2 within their lungs.

3.3 Dead space

We have recently validated a VCap-based non-invasive method to determine mean $PACO_2$ [14] (Fig. 1b). This method may turn out to become clinically relevant since it allows Bohr's dead space to be determined without the need for arterial blood. Enghoff's modification of Bohr's original formula which replaces $PACO_2$ by $PaCO_2$ has long been used to overcome the lack of reliable $PACO_2$ [8]. The problem with Enghoff's approach is that it systematically overestimates dead spaces as it includes all causes of V/Q mismatching, from real dead space to shunt, the latter being witnessed by increased $Pa-ACO_2$ gradients [5, 9, 10]. Thus, we have recently proposed the following clinical approach to assessing the efficiency of gas exchange in mechanically ventilated patients [5, 14]: (1) Use of Enghoff's formula as an index of global V/Q mismatching. This index is calculated intermittently as soon as arterial blood gas values become available. (2) Use of mean $PACO_2$ and Bohr's original formula to determine breath-by-breath real dead spaces.

In our study dead space was proportional to the size of VT (Fig. 3 and on-line supplement). Our results match well with the findings of Åström et al. [30] who observed that differences in lung size explained differences in dead spaces between genders. Therefore, normalizing absolute dead space values by VT seems an appropriate way to compare patients of different body sizes.

Most of the published data on dead space were determined according to Enghoff's method. In healthy awake individuals, Enghoff's and Bohr's formulas should provide rather similar results because $Pa-ACO_2$ gradients are

Table 3 Dead space volumes and fractions in healthy volunteers and in anesthetized patients

VT and dead spaces	Healthy awake volunteers (n = 33)	Healthy anesthetized patients (n = 33)
VT (mL)	546 (203)	513 (128)
VD _{phys} (mL)	123 (44)	149 (27)*
VD _{aw} (mL)	92 (39)	100 (24)*
VD _{alv} (mL)	26 (25)	47 (19)*
VD _{Bohr} /VT	0.23 (0.05)	0.28 (0.05)*
VD _{aw} /VT	0.17 (0.07)	0.18 (0.04)*
VD _{alv} /VT	0.05 (0.05)	0.09 (0.03)*
VD _{alv} /VT _{alv}	0.07 (0.05)	0.11 (0.04)*

Values expressed as median and interquartile range. Wilcoxon’s test compared supine volunteers with patients (*) with a $p < 0.05$ indicating significant differences

VT tidal volume, VD_{phys} physiological, VD_{aw} airway and VD_{alv} alveolar dead spaces and their normalizations either by tidal volume or by VT_{alv} alveolar tidal volume, respectively

minimal. Using Enghoff’s formula, Åström et al. [30]

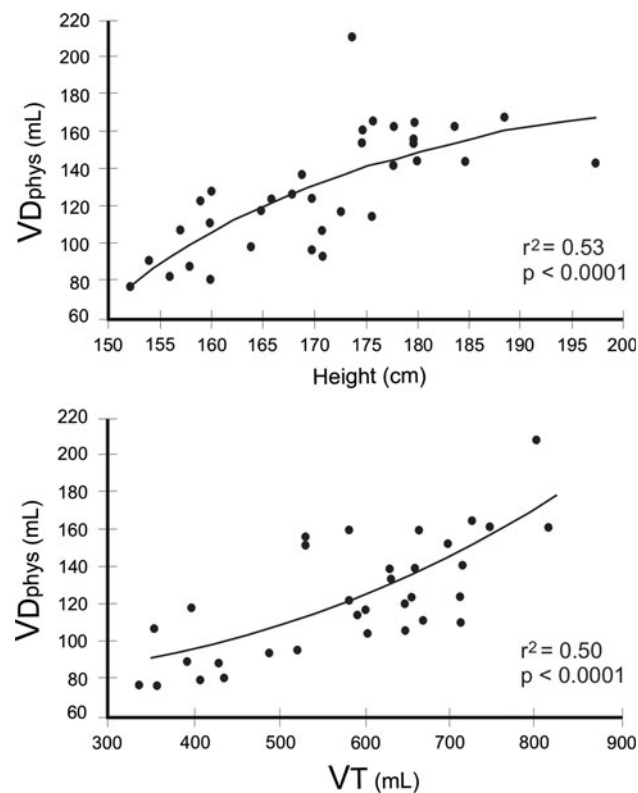


Fig. 3 Functional relations between VD_{phys} with VT and body height. VD_{phys} = physiological dead space and VT = tidal volume. The functional relationship between the above parameters was determined by regression analysis. Data were fitted with a two-term power model according to the following equation: $y = ax^b + c$. The coefficient of determination (r^2) was computed to test the goodness of fit of such model. Each dot represents a median value for each volunteer

showed a VD/VT of 0.24 ± 0.04 and a VD_{alv}/VT of 0.09 ± 0.03 . Larson et al. [33] on the other hand showed VD/VT of 0.25 ± 0.04 and a VD_{alv}/VT_{alv} of 0.10 ± 0.07 . Although clinically insignificant these values are slightly higher than the ones we obtained using Bohr’s formula (Table 3).

Our results on airways dead spaces are quite different. While Fowler, in his pioneer paper [17], found VD_{aw}/VT as high as 0.26 ± 7.6 , Åström et al. [30] showed VD_{aw}/VT to be around 0.19 ± 0.04 , a value similar to the one we present in Table 3. We reason that such differences depend on the method used to determine VD_{aw}. The accuracy of VD_{aw} varies considerably with the method used as was previously demonstrated by Wolff et al. [11], Tang et al. [12] and by our own group [13].

The changes observed in VD are more complex in anesthetized than in awake individuals. Anesthesia and mechanical ventilation can lead to: (1) decreases in VD_{aw} and increases in VD_{alv} due to lower end-expiratory lung volumes [34, 35]; (2) increases in both, VD_{aw} [36] and VD_{alv} due to positive-pressure ventilation [29, 31] and (3) increases in Enghoff’s *apparent* VD_{alv} due to anesthesia-induced atelectasis with high shunt and low V/Q areas [5, 8–10].

Compared to volunteers at similar VT, patients showed higher dead spaces caused by increases in its constituents, airway and alveolar. Furthermore, the dead spaces of patients we present were slightly lower than those previously published. Nunn and Hill calculated in supine anesthetized humans a VD/VT of $0.32 (\pm 0.06)$ using Enghoff’s formula [37], which is higher than the $0.28 (0.05)$ we determined for our patients using Bohr’s original equation thereby excluding any potential contribution that shunt might have had.

4 Limitations

The present study design deviates from what might be considered ideal. However, the options for a practical protocol in routine clinical patients are limited. Patients undergoing anesthesia are either sedated or nervous and therefore suffer from conditions known to have profound effects on alveolar ventilation and thus partial pressures of CO₂. Both, hypo- and hyperventilation would have prevented the acquisition of normal values for volumetric capnography-derived parameters. While comparative VCap data documenting lung function before and after induction of anesthesia might be of clinical interest, the assumed lack of patient cooperation made us work with cooperative volunteers with documented perfectly healthy lungs (Table 1) to obtain in the most direct way the desired reference values and rather choose an appropriate healthy patient cohort to indirectly document the effects of anesthesia.

5 Conclusions

In this paper we present a set of normal reference values for VCap-derived non-invasive parameters obtained in healthy individuals. Compared to these values we found clinically significant changes in the anesthetized supine individuals breathing at similar tidal volumes. These changes are indicative of the known negative effects of anesthesia and positive-pressure mechanical ventilation on ventilatory efficiency.

References

- Bartels J, Severinghaus JW, Forster RE, Briscoe WA, Bates DV. The respiratory dead space measured by single breath analysis of oxygen, carbon dioxide, nitrogen or helium. *J Clin Invest.* 1954;33:41–8.
- Fletcher R, Jonson B. The concept of deadspace with special reference to the single breath test for carbon dioxide. *Br J Anaesth.* 1981;53:77–88.
- Breen PH, Isserles SA, Harrison BA, Roizen MF. Simple computer measurement of pulmonary VCO₂ per breath. *J Appl Physiol.* 1992;72:2029–35.
- Bohr C. Über die Lungeatmung. *Skand Arch Physiol.* 1891;2: 236–8.
- Tusman G, Suarez Sipmann F, Bohm SH. Rationale of dead space measurement by volumetric capnography. *Anesth Analg.* 2012;114:866–74.
- Tusman G, Suarez Sipmann F, Bohm SH, Borges JB, Hedenstierna G. Capnography reflects ventilation/perfusion distribution in a model of acute lung injury. *Acta Anaesthesiol Scand.* 2011; 55:597–606.
- Tusman G, Bohm SH, Suarez Sipmann F, Scandurra A, Hedenstierna G. Lung recruitment and positive end-expiratory pressure have different effects on CO₂ elimination in healthy and sick lungs. *Anesth Analg.* 2010;111:968–77.
- Enghoff H. Volumen inefficax. Bemerkungen zur Frage des schädlichen Raumes. *Uppsala Läkareforen Forhandl.* 1938;44:191–218.
- Fletcher R. Deadspace, invasive and non-invasive. *Br J Anaesth.* 1985;57:245–9.
- Wagner P. Causes of high physiological dead space in critically ill patients. *Crit Care.* 2008;12:148–9.
- Wolff G, Brunner JX, Weibel W, Bowes CL, Muchenberger R, Bertschmann W. Anatomical and series dead space volume: concept and measurement in clinical praxis. *ACP Applied Cardiopulmonary Pathophysiology.* 1989;2:299–307.
- Tang Y, Turner MJ, Baker AB. Systematic errors and susceptibility to noise of four methods for calculating anatomical dead space from the CO₂ expirogram. *Br J Anaesth.* 2007;98:828–34.
- Tusman G, Scandurra A, Bohm SH, Suarez Sipmann F, Clara F. Model fitting of volumetric capnograms improves calculations of airway dead space and slope of phase III. *J Clin Monitor Computing.* 2009;23:197–206.
- Tusman G, Suarez Sipmann F, Borges JB, Hedenstierna G, Bohm SH. Validation of Bohr dead space measured by volumetric capnography. *Intensive Care Med.* 2011;37:870–4.
- Scherer PW, Gobran SJ, Baumgardner JE, Bartkowski R, Neufeld GR. Numerical and experimental study of steady-state CO₂ and inert gas washout. *J Appl Physiol.* 1988;64:1022–9.
- Kallet RH, Daniel BM, Garcia O, Matthey MA. Accuracy of physiological dead space measurements in patients with ARDS using volumetric capnography: comparison with the metabolic monitor method. *Respir Care.* 2005;50:462–7.
- Fowler WS. Lung function studies II. The respiratory dead space. *Am J Physiol.* 1948;154:405–16.
- Hlastala MP, Wranne B, Lenfant CJ. Cyclical variations in FRC and other respiratory variables in resting man. *J Appl Physiol.* 1973;34:670–6.
- Verschuren F, Heinonen E, Clause D, Zech F, Reynaert MS, Liistro G. Volumetric capnography: reliability and reproducibility in spontaneously breathing patients. *Clin Physiol Funct Imaging.* 2005;25:275–80.
- Breen PH, Isserles SA, Taitelman UZ. Non-steady state monitoring by respiratory gas exchange. *J Clin Monit.* 2000;16:351–60.
- Hedenstierna G, Strandberg Å, Brismar B, Lundquist H, Svensson L, Tokics L. Functional Residual Capacity, Thoracoabdominal Dimensions, and Central Blood Volume during General Anesthesia with Muscle Paralysis and Mechanical Ventilation. *Anesthesiology.* 1985;62:247–54.
- Hedenstierna G. Ventilation-perfusion relationships during anaesthesia. *Thorax.* 1995;50:85–91.
- Brismar B, Hedenstierna G, Lundquist H, Strandberg Å, Svensson L, Tokics L. Pulmonary densities during anaesthesia with muscular relaxation - A proposal of atelectasis. *Anesthesiology.* 1985;62:422–8.
- Terragni PP, Rosboch G, Tealdi A, Corno E, Menaldo E, Davini O. Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2007;175:160–6.
- Hofbrand BI. The expiratory capnogram: a measure of ventilation-perfusion inequalities. *Thorax.* 1966;21:518–24.
- Blanch LL, Fernandez R, Saura P, Baigorri F, Artigas A. Relationship between expired capnogram and respiratory system resistance in critically ill patients during total ventilatory support. *Eur Respir J.* 1999;13:1048–54.
- Schwardt JF, Gobran SR, Neufeld GR, Auk burg SJ, Scherer PW. Sensitivity of CO₂ washout to changes in acinar structure in a single-path model of lung airways. *Ann Biomed Eng.* 1991;19:679–97.
- Downie SR, Salome CM, Verbank S, Thompson B, Berend N, King GG. Ventilation heterogeneity is a major determinant of airway hyperresponsiveness in asthma, independent of airway inflammation. *Thorax.* 2007;62:684–9.
- Tusman G, Böhm SH, Suárez Sipmann F, Turchetto E. Alveolar recruitment improves ventilatory efficiency of the lungs during anesthesia. *Can J Anesth.* 2004;51:723–7.
- Åström E, Niklason L, Drefeldt B, Bajc M, Jonson B. Partitioning of dead space – a method and reference values in the awake human. *Eur Respir J.* 2000;16:659–64.
- Fletcher R, Jonson B. Deadspace and the single breath test for carbon dioxide during anaesthesia and artificial ventilation. Effects of tidal volume and frequency of respiration. *Br J Anaesth.* 1984;56:109–19.
- Ream RS, Schreiner MS, Neff JD, McRae KM, Jawad AF, Scherer PW, Neufeld GR. Volumetric capnography in children. Influence of growth on alveolar plateau slope. *Anesthesiology.* 1985;82:64–73.
- Larson CP, Severinghaus JW. Postural variations in dead space and CO₂ gradients breathing air and O₂. *J Appl Physiol.* 1962;17:417–20.
- Severinghaus JW, Stupfel M. Alveolar deadspace as an index of distribution of blood flow in pulmonary capillaries. *J Appl Physiol.* 1957;10:335–48.
- Schulz A, Schlz H, Heilmann P, Brand P, Heyder J. Pulmonary dead space and airway dimensions in dogs at different levels of lung inflation. *J Appl Physiol.* 1994;76:1896–902.
- Hedenstierna G, McCarthy G. The effect of anaesthesia and intermittent positive pressure ventilation with different frequencies on the anatomical and alveolar deadspace. *Br J Anaesth.* 1975;47:847–52.
- Nunn JF, Hill DW. Respiratory dead space and arterial to end-tidal CO₂ difference in anesthetized man. *J Appl Physiol.* 1960;15:383–9.