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Validation of Bohr dead space measured by volumetric capnography

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Abstract *Purpose:* Bohr's dead space (VD_{Bohr}) is commonly calculated using end-tidal CO_2 instead of the true alveolar partial pressure of CO_2 ($PACO_2$). The aim of this work was to validate VD_{Bohr} using $PACO_2$ derived from volumetric capnography (VC) against VD_{Bohr} with $PACO_2$ values obtained from the standard alveolar air formula. *Methods:* Expired gases of seven lung-lavaged pigs were analyzed at different lung conditions using mainstream VC and multiple inert gas elimination technique (MIGET). $PACO_2$ was determined by VC as the midpoint of the slope of phase III of the capnogram, while mean expired partial pressure of CO_2 ($PeCO_2$) was calculated as the mean expired fraction of CO_2 times the barometric minus the water vapor pressure. MIGET estimated expired CO_2 output (VCO_2) and $PeCO_2$ by its V/Q algorithms. Then, $PACO_2$ was obtained applying the alveolar air formula ($PACO_2 = VCO_2$/alveolar ventilation). *Results:* We found close linear correlations between the two methods for calculating both $PACO_2$ ($r = 0.99$) and VD_{Bohr} ($r = 0.96$), respectively (both $p < 0.0001$). Mean $PACO_2$ from VC was very similar to the one obtained by MIGET with a mean bias of −0.10 mmHg and limits of agreement between −2.18 and 1.98 mmHg. Mean VD_{Bohr} from VC was close to the value obtained by MIGET with a mean bias of 0.010 ml and limits of agreement between −0.044 and 0.064 ml. *Conclusions:* VD_{Bohr} can be calculated with accuracy using volumetric capnography.

Keywords Volumetric capnography · $PACO_2$ · Bohr's dead space · Carbon dioxide · Tidal volume · Gas exchange

Introduction

For calculating true dead space, Bohr's formula uses alveolar ($PACO_2$) and mixed expired partial pressures of CO_2 ($PeCO_2$) as:

$$VD_{Bohr} = PACO_2 - PeCO_2/PACO_2$$

[1] assuming that CO_2 in the inspired gases is zero. The measurement of $PACO_2$ is technically difficult and has caused hot debates in the past. Haldane and Priestley [2] believed that representative alveolar CO_2 samples could only be obtained at the end of a forced expiration. Later, Krogh and Lindhard [3] showed that alveolar CO_2 reaches a plateau by the end of expiration once the volume of gas

in the anatomical dead space has been washed out. Fowler [4] confirmed the latter concept by his famous analysis, which to date is considered the reference method for separating alveolar gases from those in the main airways.

Aitken and Clark-Kennedy[5] were the first to suggest that mean $PACO_2$ can be obtained using volumetric capnography (VC). Fletcher et al. [6] confirmed this hypothesis on theoretical grounds describing that mean $PACO_2$ could be measured directly as the midpoint of phase III of VC, a concept that Breen et al. [7] have been supporting over the the last years. To our knowledge, this proposed measurement method for $PACO_2$ has, however, not yet been duly validated. This could be the reason why $PACO_2$ is still erroneously being replaced by $PaCO_2$ or $PETCO_2$ in Bohr's formula. Therefore, the aim of the study was to compare Bohr's dead space using $PACO_2$ values from capnograms with the one in which $PACO_2$ was derived from the standard alveolar air formula:

$$PACO_2 = VCO_2/\mathrm{VA}$$

where VCO_2 is the amount of CO_2 eliminated by the lungs and VA is the alveolar ventilation. VCO_2 was calculated independently applying the mathematical algorithm of the multiple inert gas elimination technique (MIGET) [10, 11].

Methods

We re-analyzed data of seven lung-lavaged pigs in which MIGET was performed, and other data than those presented here have been submitted for publication elsewhere. Anesthetized animals were ventilated using a volume-control mode with fixed settings of tidal volume of 6 ml/kg, 30 breaths/minute, I:E of 1:2 and FiO_2 of 1. Positive end- expiratory pressures (PEEP) from 10 to 22 cmH_2O were randomly assigned to intentionally induce different degrees of lung aeration and V/Q ratios.

Standard ECG, transcutaneous O_2 saturation by pulse oximetry and invasive blood pressure via a femoral catheter were monitored. Volumetric capnography (the dynamic measurement of expired CO_2 vs. expired volume; called VC in the following text) was recorded by a NICO capnograph (Respironics, Wallingford, CT). CO_2 was measured by an infrared mainstream sensor Capnostat 3 (response time <60 ms and resolution 2 mmHg) placed at the airway opening.

Volumetric capnography was fitted by Levenberg-Marquardt curves using a custom-made MatLab program (Mathworks, Natick, MA) [8], and parameters were mathematically derived from them (for details, see on-line suplement). Briefly, the first step was to determine the limit between airway dead space and alveolar tidal volume, which according to Fowler's [4] concept is represented by the midpoint of phase II. This *midpoint* of phase II is the inflection point of the whole capnogram where its curvature changes sign. Our algorithm determines this inflection point as the maximum of the first derivative of the mathematical function fitted to the set of data points comprising the capnogram of each breath. Then, $PACO_2$ was determined from VC as the midpoint of the line of the slope of phase III, starting at the inflection point of the capnogram and terminating at $PETCO_2$.

Alveolar tidal volume multiplied by the respiratory rate determines alveolar ventilation (VA). The elimination of CO_2 (VCO_2) was calculated as the area under the curve of VC multiplied by the respiratory rate. $PETCO_2$ is the partial pressure of CO_2 found at the end of expiration. Mean $PeCO_2$ was determined by multiplying the fractional expired CO_2 concentration by the barometric pressure minus the water vapor pressure [9].

VCO_2 and $PeCO_2$ were also calculated independently from MIGET's V/Q analysis in the way described by West [10] and applied by Wagner et al. [11]. We used the VCO_2 to calculate $PACO_2$ by the alveolar gas formula.

Expired gases for MIGET analysis were sampled via a heated mixing box connected to the ventilator's exhaust valve. Arterial blood samples were obtained simultaneously and analyzed immediately by an ABL 300 (Radiometer, Copenhagen, Denmark). Thirty capnograms belonging to this sampling period were analyzed, and a representative mean cycle was calculated.

Pearson's linear correlation coefficients were calculated. The degree of agreement between the two techniques was calculated as outlined by Bland-Altman.

Results

A total of 49 sets of measurements were analyzed. The table shows the variables studied and the value of VD_{Bohr} calculated from the $PACO_2$ and $PeCO_2$ values obtained by the two methods (Table 1).

We found close correlations between the parameters $PACO_2$ and VD_{Bohr} (Fig. 1) and between $PeCO_2$ and VCO_2 (Fig. 2 on-line supplement) measured by VC and mathematically derived from MIGET.

Mean $PACO_2$ from VC was very similar to the value obtained by MIGET with a mean bias of −0.10 mmHg and limits of agreement between −2.18 and 1.98 mmHg. $PeCO_2$ for VC and MIGET showed a mean bias of −0.49 mmHg and limits of agreement between −2.45 and 1.47 mmHg. The VCO_2 measured by VC was higher than the corresponding value calculated by MIGET with a mean bias of −4.2 mL/min and limits of agreement between −19.2 and 10.8 ml/min. Mean VD_{Bohr} from VC was very similar to the value obtained by MIGET with a

Table 1 Study variables

	PaCo$_2$ (mmHg)	PetCO$_2$ (mmHg)	PACO$_2$ (mmHg)	PeCO$_2$ (mmHg)	VCO$_2$ (mmHg)	VD_{Bohr}
VC		55 ± 13	51.6 ± 11	21.9 ± 4	129 ± 26	0.56 ± .04
MIGET	72 ± 15		51.4 ± 12	22.3 ± 4	125 ± 27	0.54 ±. 05

Data presented as mean and SD. Note that the high PaCO$_2$ has been caused by large atelectasis and ventilation/perfusion mismatch that was intentionally produced by repeated lung lavages
PaCO$_2$ Arterial partial pressue of CO$_2$ obtained by arterial blood gas analysis, *PetCO$_2$* end-tidal partial pressue of CO$_2$, *PACO$_2$* mean alveolar partial pressue of CO$_2$, *PeCO$_2$* mixed expired partial pressue of CO$_2$, *VCO$_2$* amount of CO$_2$ eliminated by the lungs per minute, *VD$_{Bohr}$* dead space calculated by Bohr's formula (PACO$_2$−PeCO$_2$/PACO$_2$), *VC* volumetric capnography, *MIGET* multiple inert gas elimination technique

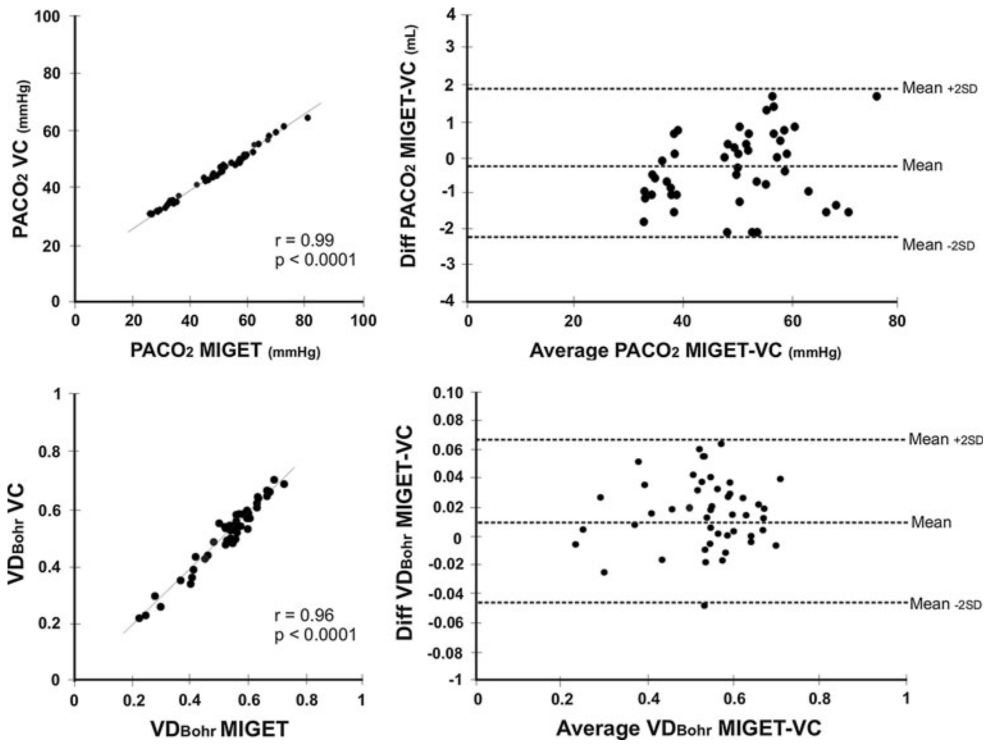

Fig. 1 Linear correlation and Bland-Altman plots of key study variables. Pearson's correlations (*left plots*) and Bland-Altman analysis (*right plots*) for PACO$_2$ (*upper*) and VD$_{Bohr}$ (*lower*) values obtained by volumetric capnography (VC) versus the ones calculated from MIGET

mean bias of 0.010 ml and limits of agreement between −0.044 and 0.064 ml.

Discussion

These results show that VD$_{Bohr}$ can be measured directly and with accuracy using VC. The mean PACO$_2$ found at the midpoint of the slope of the phase III of the capnograms was well correlated with the one obtained by the alveolar air equation using VCO$_2$ values provided by MIGET.

The normal variations in the alveolar CO$_2$ tension during the respiratory cycle (decrease in inspiration and increase in expiration) make it difficult to obtain physical gas samples truly representative of alveolar CO$_2$. Therefore, mean or average PACO$_2$ is the value to be used in any physiological calculations where alveolar air comes into play, hoping that this will make dead space calculations more reliable and reproducible. Since capnographs placed at the airway opening usually do not sample CO$_2$ values during inspiration, the measurement of mean PACO$_2$ is performed during the expiratory time only. Already as early as 1951, Dubois et al. [12] pointed out that mean PACO$_2$ is best represented by an alveolar sample taken shortly after mid-expiratory time.

Aitken and Clack-Kennedy [5] originally described a method to obtain alveolar gas using volumetric capnograms during excercise. Fletcher et al. [6] took this principle a step further and suggested the calculus of alveolar dead space using the mean value of PACO$_2$ measured directly from VC. They reasoned that the mean PACO$_2$ is represented by the midpoint of the slope of phase III of the alveolar compartment. This idea was applied by Breen et al. [7] using the $P\text{AECO}_2$, another acronym for mean $P\text{ACO}_2$. Breen et al. [7] highlighted the differences between the $P\text{ACO}_2$ measured by time-based and by volume-based capnography pointing out that only if CO_2 were weighted by the exhaled volume, $P\text{ACO}_2$ could be found in the midpoint of phase III. For this reason, methods estimating $P\text{ACO}_2$ on a time basis are not accurate enough to accomplish this task [13].

To our knowledge much of the above reasoning is based on theoretical concepts, assumptions and measurements using old technologies, but has never been adequately validated. Therefore, we used the alveolar air formula as reference, which is based on the mathematical principle that $P\text{ACO}_2$ depends on the ratio between the amount of CO_2 eliminated by the lungs and the alveolar ventilation.

Our results support the following concepts of VD_{Bohr}:

First, Enghoff's modification of Bohr's formula using the concept of *ideal* $P\text{ACO}_2$ ($P\text{ACO}_2 = P\text{aCO}_2$) described by Riley is still an approximation because, even in healthy lungs, anatomical dead space is always present, and anatomical shunt increases the difference between $P\text{aCO}_2$ and $P\text{ACO}_2$ [14, 15]. Therefore, the Bohr-Enghoff formula includes the effect of any venous admixture within the lungs, giving a higher value than VD_{Bohr}. This overestimated dead space has been called *shunt dead space* by Suter et al. [16], although it has little to do with the classical concept of dead space in the sense of a ventilated but not perfused lung unit [17].

Our experimental data support the above statement. At all times $P\text{aCO}_2$ was higher than $P\text{ACO}_2$ because of the V/Q mismatch induced by the different degrees of lung overdistension and collapse. Thus, in real lungs the value of $P\text{aCO}_2$ and $P\text{ACO}_2$ cannot be assumed to be equal.

Second, an error in VD_{Bohr} is also observed when in Bohr's formula $P\text{ETCO}_2$ is used instead of $P\text{ACO}_2$ as the slope of phase III is positive in almost all patients. $P\text{ETCO}_2$ will overstimate the real VD_{Bohr} value because $P\text{ETCO}_2 > P\text{ACO}_2$. For example, our data show that VD_{Bohr} based on $P\text{ETCO}_2$ was 0.61 ± 0.05, a value that was 9 and 13% higher than VD_{Bohr} obtained using $P\text{ACO}_2$ from VC and from MIGET, respectively.

Third, considering the previous point, the popular index Pa-ETCO$_2$ should become more reliable and physiologically more correct if it were re-written as Pa-ACO$_2$ since both $P\text{aCO}_2$ and $P\text{ACO}_2$ are representing *mean* CO_2 values in the blood and the alveolar compartment, respectively. $P\text{ETCO}_2$, on the other hand, represents only a group of alveoli with low V/Q ratios and/or low expiratory time constants, which contribute high concentrations of CO_2 at the end of expiration.

Fourth, our data confirm the results of previous validations of VC-derived $P\text{eCO}_2$, such as the one published by Kallet et al. [9].

We conclude that the original Bohr formula can be applied on a breath-by-breath basis and with accuracy if PACO_2 is determined from the midpoint of the slope of phase III of the volumetric capnogram. $P\text{ACO}_2$ should neither be replaced by $P\text{ETCO}_2$ nor by the invasive $P\text{aCO}_2$. The proposed measurements of $P\text{ACO}_2$ are highly dependent on a robust determination of the slope of phase III. As long as such breath-by-breath features are not available for bedside use, clinicians are left with the manual calculation of $P\text{ACO}_2$. However, using the alveolar air formula with $V\text{CO}_2$ and VA coming from volumetric capnography, determination of dead space becomes easy and entirely non-invasive.

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