Volumetric capnography: the time has come

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Purpose of review
Volumetric capnography (VCap) measures the kinetics of carbon dioxide (CO_2) elimination on a breath-by-breath basis. A volumetric capnogram contains extensive physiological information about metabolic production, circulatory transport and CO_2 elimination within the lungs. VCap is also the best clinical tool to measure dead spaces allowing a detailed analysis of the functional components of each tidal volume, thereby providing clinically useful hints about the lung's efficiency of gas exchange. Difficulties in its bedside measurement, oversimplifications of its interpretation along with prevailing misconceptions regarding dead space analysis have, however, limited its adoption as a routine tool for monitoring mechanically ventilated patients.

Recent findings
Improvements in CO_2 measuring technologies and more advanced algorithms for faster and more accurate analysis of volumetric capnograms have increased our physiological understanding and thus the clinical usefulness of VCap. The recently validated VCap-based method for estimating alveolar partial pressure of CO_2 provided a breakthrough for a fully noninvasive breath-by-breath measurement of physiological dead space.

Summary
Recent advances in VCap and our improved understanding of its clinical implications may help in overcoming the known limitations and reluctances to include expired CO_2 kinetics and dead space analysis in routine bedside monitoring. It is about time to start using this powerful monitoring tool to support decision making in the intensive care environment.

Keywords
dead space, mechanical ventilation, respiratory monitoring, volumetric capnography

INTRODUCTION

Capnography is the measurement and graphical display of CO_2 concentration within the expired gas. Anesthesiologists were the first to adopt it to detect CO_2 problems related to intubation, the use of circular breathing circuits and induction of capnoperitoneum for laparoscopic surgery. Soon it became an essential ISO monitoring requirement for the safe conduct of anesthesia (IEC 60601–2–13:2003 and ISO 80601–2–55:2011). This routine use in anesthesia contrasts with the critical care setting in which paradoxically little attention has been paid to the lung's ability or inability to eliminate CO_2 and capnography is seldom used in respiratory monitoring [1▪▪]. In lieu of lung protective ventilation (LPV) strategies, with tidal volumes as small as 4–6 ml/kg which have become standard of care for most ventilated patients, the continued negligence of CO_2 monitoring is hard to justify especially since increased dead space fractions have repeatedly and consistently been demonstrated to be strongly associated with an increased mortality in patients suffering from acute respiratory distress syndrome (ARDS) [2–5,6▪]. Remarkably, not a single one of the recent multicenter trials on LPV in ARDS has presented data on expired CO_2, let alone on dead space. This lack of clinical data together with the fact that its measurement and interpretation are still considered 'challenging' have once again prevented dead space or other measures of the lung's efficiency of CO_2 elimination from becoming part of the latest definition of ARDS [7]. This reluctance to

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KEY POINTS

- CO_2 elimination is an essential lung function largely neglected in respiratory monitoring.
- VCap is the graphical representation of the CO_2 concentration against the expired volume of one breath and is used to determine dead space.
- The dead spaces of Bohr and Enghoff measure different physiological phenomena; whereas Bohr measures physiological dead space Enghoff provides a global index of gas exchange, which includes shunt effects.
- Mean alveolar PCO_2 can now be measured noninvasively allowing Bohr's dead space to be monitored on a breath-by-breath basis.
- Advances in VCap and our physiological understanding will hopefully contribute to its adoption in critical care monitoring.

monitor expired CO_2 in critically ill patients is in part caused by prevailing misconceptions and a generally poor understanding of how to interpret CO_2 curves and dead spaces [8▪]. It is also in part owed to the intrinsic complexity of the expired CO_2 signal as it aggregates information about CO_2 production at the cellular level, its transport by the systemic circulation and its diffusion into the lungs and finally its elimination by alveolar ventilation. This complexity, however, constitutes the beauty and the curse of capnography as it crunches down in a single graphical representation and in a few numbers a myriad of physiological processes that are by no means static but highly dynamic and thus changing constantly. These dynamics make appropriate assessment and interpretation of capnography highly context and time dependent. In this article, we will briefly review the main characteristics of volume-based capnography and the physiological meaning of the variables derived from it. We will further describe the current understanding and uses of dead space measurements and discuss clinical applications of this powerful and intuitive monitoring tool for patients on mechanical ventilation.

VOLUMETRIC CAPNOGRAPHY

Clinically available modalities of capnography are either time or volume based. Time-based capnography (TCap) plots expired CO_2 against time and constitutes, by far, the most frequently used modality. By integrating the time and volume domains within one graphic, VCap plots the eliminated concentration of CO_2 versus the respective expired tidal volume of a single breath (Fig. 1). Available clinical VCap monitors such as the NM3 (Philips, Wallingford, Connecticut, USA) contain a fast infrared CO_2 sensor and a pneumotachograph within a mainstream airway adapter. This way both CO_2 and flow signals are measured simultaneously and proximally [9]. Although both modalities share

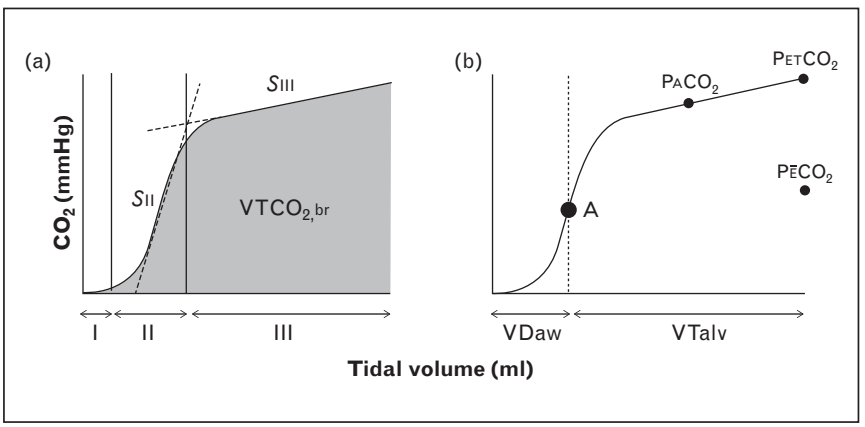

FIGURE 1. Volumetric capnogram derived variables. (a) Phases of the capnogram: Phase I contains the final CO_2-free gas from the previous inspiration that remained within the proximal conducting airways. The steep slope of Phase II (S_{II}) is characterized by the appearance of CO_2-rich gas from the alveolar compartment. The slope of Phase III (S_{III}) is created exclusively by gas from the alveolar compartment. This slope is always positive and reflects the different time constants of emptying alveoli and the continuous influx of CO_2 from the pulmonary capillaries. The shaded area under the curve represents the amount of CO_2 eliminated by one single breath ($VTCO_{2br}$). (b) The midportion of phase II (black dot) marks the mean airway–alveolar (A) interface that separates the airway from the alveolar compartment, which are characterized by convective and diffusive gas transport, respectively. This point also divides the tidal volume into an airway dead space (V_{Daw}) and alveolar tidal volume (V_{Talv}). $PACO_2$, alveolar; $PETCO_2$, end-tidal; $P\bar{E}CO_2$, mixed expired PCO_2. See Table 1 for further explanations of these variables.

many features, VCap offers a more in-depth representation of the kinetics of CO_2 elimination as raw CO_2 concentrations are plotted point-by-point over the expired volume, allowing volume-based variables such as dead space and the amount of CO_2 eliminated per breath to be calculated for each breath.

The volumetric capnogram, also called single breath test of CO_2, is the dynamic representation of the kinetics of CO_2 elimination measured by VCap. Figure 1 and Table 1 [1▪▪,8▪,10–12,13▪,14–17,18▪▪,19▪,20–23] present its main features and variables. Recently, the first-ever reference values for VCap-derived variables for both spontaneously breathing volunteers and corresponding mechanically ventilated patients have been published [24].

The shape of the capnogram and its different components contain relevant physiological information. The slopes of phase II (S_{II}) and III (S_{III}) are determined by the distribution of ventilation within the lungs [16,25]. S_{III} is closely related to the matching of ventilation and perfusion, and can, in the appropriate context, provide a direct visual clue about the heterogeneity of lung ventilation, pulmonary perfusion and the respective matching of ventilation perfusion (V/Q) [10,26].

The volume of CO_2 eliminated can either be expressed per breath ($VTCO_{2br}$) or per minute (VCO_2). $VTCO_{2br}$ is the key VCap variable. Under constant ventilatory conditions, it is a very sensitive indicator of changes in pulmonary blood flow [10,11] and together with the end-tidal partial pressure of CO_2 ($PETCO_2$) can detect changes in cardiac output or predict intravascular volume responsiveness [13▪,14,15]. It is also a fine indicator of the efficiency of ventilation providing a direct measure of a lung's currently functional area for gas exchange. Lung collapse and recruitment cause dynamic changes in this functional alveolar-capillary area, which are witnessed as corresponding decreases or increases in $VTCO_{2br}$ [20,27,28] that can be used to find an appropriate level of PEEP [28]. VCO_2 has traditionally been used to assess metabolic CO_2 production, provided ventilation and perfusion conditions remained unchanged. Furthermore, VCO_2 or $VTCO_{2br}$ defines the ventilatory

Table 1. Volumetric capnography-derived CO_2 volume and tension variables

	Parameter	Calculation	Physiological meaning	Clinical uses
$VTCO_{2br}$	CO_2 elimination per breath	Area under the curve of the capnogram	Breath-by-breath elimination of CO_2	Monitors changes in alveolar ventilation, pulmonary perfusion and in the gas exchange area (i.e., recruitment-collapse and PEEP titration) [10,11]
VCO_2	Minute elimination of CO_2	$VTCO_{2br} \times RR$	In steady-state conditions (constant ventilation and perfusion) it is equal to metabolic CO_2 production	Metabolism, nutrition, adjustment of ventilator settings, monitoring of special conditions such as hypothermia [12]
$PETCO_2$	End-tidal partial pressure of CO_2	Final portion of the capnogram with the highest CO_2 value	Highest final value corresponding to the emptying of alveoli with the longest expiratory time constant	Monitoring of changes in ventilation and perfusion, inappropriately used as a surrogate for $PACO_2$ or $PaCO_2$, assessment of fluid responsiveness [13▪,14,15]
$P\bar{E}CO_2$	Mixed-expired partial pressure of CO_2	$FECO_2 \times (PB - PH_2O)$ or $VTCO_{2br}/VT \times (PB - PH_2O)$	Caused by the dilution of the gas residing within the lung by the CO_2-free inspiratory gas	Essential for calculating physiological dead space [1▪▪,8▪,16,17,18▪▪]
$PACO_2$	Mean alveolar partial pressure of CO_2	Standard PCO_2 equation: $VCO_2 \times K/VA$ or directly from the midportion of phase III of the capnogram	Averaged partial pressure of CO_2 of all ventilated alveoli	Calculation of Bohr's dead space [1▪▪,17,18▪▪,19▪]
$Pa\text{-}ETCO_2$	Arterial to end-tidal gradient of PCO_2	Needs an arterial blood gas sample, normal values 3–5 mmHg	Index of gas exchange reflecting the resistance to diffusion across the alveolar-capillary membrane of CO_2	Reflects changes in the surface area for gas exchange and thus V/Q, diagnosis of pulmonary embolism, it should not be used as a surrogate of alveolar dead space [20–22]
$Pa\text{-}ACO_2$	Arterial to alveolar gradient of PCO_2, normal 4–8 mmHg	Needs an arterial blood gas sample	Better index of gas exchange than $Pa\text{-}ETCO_2$ as it uses an averaged alveolar CO_2 value	Reflects changes in the surface area for gas exchange and thus V/Q more accurately than $Pa\text{-}ETCO_2$. similar to the alveolar-arterial gradient of oxygen but not influenced by the FIO_2 [18▪▪,23]

Numbers refer to corresponding references. $FECO_2$, fraction of expired CO_2; FIO_2, fraction of inspired O_2; K, 0.863 constant to equalize units to express the value in standard temperature and pressure, dry (STPD); PB, barometric pressure; PH_2O, water vapor pressure; RR, respiratory rate; V/Q, ventilation-perfusion ratio; VA, alveolar ventilation (minute ventilation minus dead space ventilation); VT, tidal volume.

requirements and can thus guide ventilator treatment [12].

The end-tidal CO_2 ($PETCO_2$) can easily be obtained from both time- and volume-based capnograms. Due to its noninvasiveness and availability in both time- and volume-based capnography, it is often – but unduly – used as a surrogate for arterial CO_2 ($PaCO_2$). Along the same lines of simplification $PETCO_2$ has also been used as a substitute for alveolar PCO_2 ($PACO_2$) when calculating dead space. However, under most clinical conditions, and especially in severely diseased lungs, the physiologically unjustified misuse of $PETCO_2$ introduces significant errors caused by venous admixture and the positive sloping of S_{III}. The shallower S_{III} seen in TCap as compared with VCap (where the exponential nature of expiratory flow results in a more real and steeper S_{III}) has led to the false assumption that $PETCO_2$ and $PACO_2$ are equal. The arterial to end-tidal gradient of CO_2 or parameters derived from it such as the so-called alveolar dead space fraction ($Pa\text{-}ETCO_2/PaCO_2$) have shown diagnostic value in detecting pulmonary embolisms, especially when combined with the measurement of D-dimer [21,22].

DEAD SPACE

Dead space refers to the inefficient or wasted portion of ventilation, that is, the fraction of the tidal volume not participating in gas exchange. This inefficiency is caused by both 'dead volume' from the conducting airways and those alveolar compartments that do not receive capillary blood flow and are thus characterized by an infinite V/Q. VCap is the principal clinical tool to measure dead space and as it is based on the analysis of expired CO_2 and volumes, several considerations need to be taken into account [17]: First, the inspired gas must be free of CO_2 as it dilutes the gas coming from gas-exchanging units into which CO_2 is continuously delivered by pulmonary perfusion. It is this dilution that is taken into account when calculating dead space assuming that a temporary equilibration has been reached at least for the period of the breath currently analyzed. Second, as CO_2 is a moderately soluble gas and as each one of the millions of alveoli has its own singular V/Q value and individual alveolar CO_2 level, any dead space value includes not only true dead space conditions with a V/Q approaching infinity but also all compartments with high and low V/Q ratios.

Physiological dead space

Christian Bohr was the first to describe dead space in 1891. He applied the principle of mass conservation for CO_2 to estimate the dilution of the expired gas by the inspiratory gas filling the conductive airways and proposed the following now famous Bohr equation:

$$VD_{Bohr}/VT = (PACO_2 - P\bar{E}CO_2)/PACO_2$$

where $PACO_2$ is the mean alveolar and $P\bar{E}CO_2$ the mixed-expired partial pressure of CO_2.

In the past, clinical measurement of VD_{Bohr} had been always difficult and prone to errors as it required a mixing chamber (i.e., a Douglas bag) to measure $PACO_2$. Therefore, based on the assumption that in an ideal lung with a normal V/Q distribution capillary equals alveolar CO_2, Enghoff proposed a modification of Bohr's original formula replacing $PACO_2$ with arterial PCO_2 ($PaCO_2$):

$$VD_{Enghoff}/VT = PaCO_2 - P\bar{E}CO_2/PaCO_2$$

Enghoff's brilliant and practical simplification soon became the standard bedside method to obtain physiological dead space (VD_{Phys}), in the literature often referred to as VD/VT. Nevertheless, its measurement is still 'invasive' as it requires an arterial blood gas sample to be collected simultaneously with the corresponding $P\bar{E}CO_2$ value. The introduction of VCap by Fletcher *et al.* [16] further simplified the clinical measurement of dead space. Once the direct estimate of $P\bar{E}CO_2$ from the capnogram (Table 1) had been solidly validated against different reference methods [19▪,29,30], VCap became the clinical standard for determining dead space. The measurement of real $PACO_2$, however, remained the major unresolved problem that triggered the search for potential solutions. It had been known from previous physiological studies that alveolar CO_2 changes along the respiratory cycle [31] and the mean value is best represented by an alveolar gas sample taken around midexpiration [32]. This made Fletcher *et al.* [16] suggest that $PACO_2$ could theoretically be obtained from the midportion of phase III of the volumetric capnogram, an idea that was later confirmed by Breen *et al.* [33]. Fortunately, the concept of obtaining $PACO_2$ from the midportion of phase III has recently been validated against the multiple inert gas elimination technique (MIGET) [19▪]. Now that this major limitation has been overcome, reliable measurements of true VD_{Phys} from VCap can be obtained noninvasively on a breath-by-breath basis, thereby opening unprecedented new monitoring possibilities for mechanically ventilated patients.

Components of physiological dead space: airway and alveolar dead space

To fully exploit the potential of dead space analysis its two major components, airway dead space (VD_{aw}) and alveolar dead space (VD_{alv}) must be

differentiated. VD_{aw} is the quantitatively larger component filling the conducting airways and any segment of the breathing circuit located beyond the Y-piece. Its noninvasive measurement using expired gas was established by Fowler [34] many decades ago. He proposed a geometrical method to identify the airway-alveolar gas interface located at the midportion of phase II (Fig. 1). Although most current methods are based on Fowler's geometrical approach, the shape of the capnogram can greatly affect its accuracy. Therefore, new mathematical approaches have been proposed to improve the robustness of V_{Daw} determination [35]. Once VD_{phys} and VD_{aw} are known VD_{alv} is easily calculated by simply subtracting VD_{aw} from VD_{phys}.

The essential difference between Bohr's and Enghoff's approaches

The use of $PaCO_2$ as a surrogate for $PACO_2$ introduced a flaw in the concept of dead space. Pathologic lungs, but also healthy lungs under mechanical ventilation, are never ideal but always suffer from shunt and dead space. Whenever CO_2-rich venous blood passes through poorly or nonventilated areas, $PaCO_2$ increases. Therefore, progressive increase in shunt makes $PaCO_2$ values systematically depart from those of $PACO_2$ [17,36], which leads to an overestimation of the true VD_{Phys} if Enghoff's approach is used. This 'contamination' of alveolar dead space by venous admixture, also called shunt-related [37], apparent or fictitious [16] dead space, is well known [36] but has in fact nothing to do with the original concept of dead space [17]. Although large shunt fractions (>20–30%) are needed to significantly affect calculated dead space values [23], the contamination can yet have important clinical implications once it is acknowledged that VD_{Bohr} and $VD_{Enghoff}$ represent different physiological phenomena [18▪▪] (Fig. 2).

By using measured $PACO_2$ instead of $PaCO_2$, Bohr's formula provides values of true VD_{Phys}, characterized exclusively by compartments with a high and/or infinite V/Q without being affected by venous admixture. In contrast, $VD_{Enghoff}$ cannot be considered a dead space in the strict sense of its definition as it includes all causes of V/Q inhomogeneity (Fig. 2). However, $VD_{Enghoff}$ is an excellent global index of a lung's efficiency of gas exchange. Very likely this is why it is such a good and consistent early predictor of mortality in ARDS patients, which performs better than any known oxygenation index [2–5,6▪]. Thus, the combined analysis of VD_{Bohr} and $VD_{Enghoff}$ provides complementary descriptions of the causes of any given inefficiency of gas exchange due to either high or low V/Q ratios. Based exclusively on CO_2-related variables clinicians can now make a differential diagnosis and monitor specifically the responses to changing ventilator settings. All that is needed is an arterial blood gas sample and a simultaneous advanced analysis of expired CO_2.

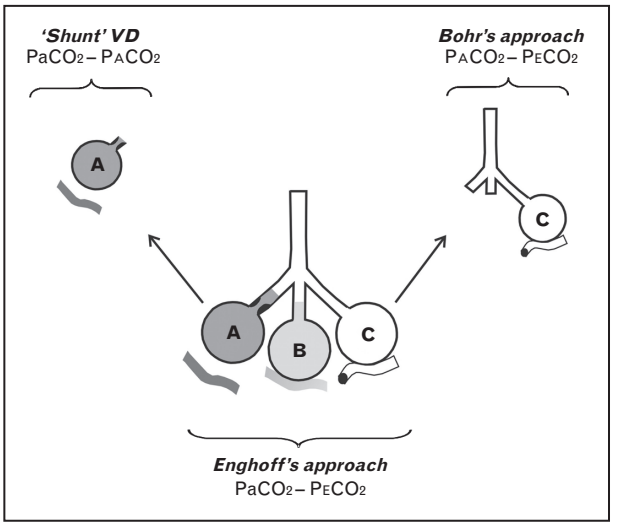

FIGURE 2. Schematic representation of Riley's three-compartment lung model explaining the differences between Bohr's and Enghoff's approaches of measuring dead space and further depicting the meaning of the arterial to alveolar gradient of CO_2. A: Nonventilated but perfused alveolus ($V/Q = 0 =$ shunt). B: Normally ventilated and perfused alveolus. C: Ventilated but not perfused alveolus ($V/Q = \infty$). Note that a full range of alveoli with low to high V/Q exist within B – A and B – C, respectively, which are not represented here. VD_{Bohr} measures true physiologic dead space as it only includes alveoli with a high and/or infinite V/Q. $VD_{Enghoff}$, by using $PaCO_2$, measures the full range of V/Q abnormalities and is, therefore, a global index of the efficiency of gas exchange but not a dead space in the classical sense of the word. Shunt effects, which 'contaminate' Enghoff's approach are represented by the difference between arterial and alveolar CO_2 levels.

Making use of the information obtained by volumetric capnography-based dead space monitoring

Strictly speaking dead space is a volume not a space. Therefore, one unique feature of VCap is that it contains the information about all anatomical-functional volumes comprising any tidal volume. These relative volumes are of clinical interest as a tidal volume is not only related to gas exchange but also to the mechanical stress inflicted upon the lung by each breath delivered. Figure 3 presents the distribution of the different components of a delivered tidal volume measured in an ARDS patient undergoing LPV.

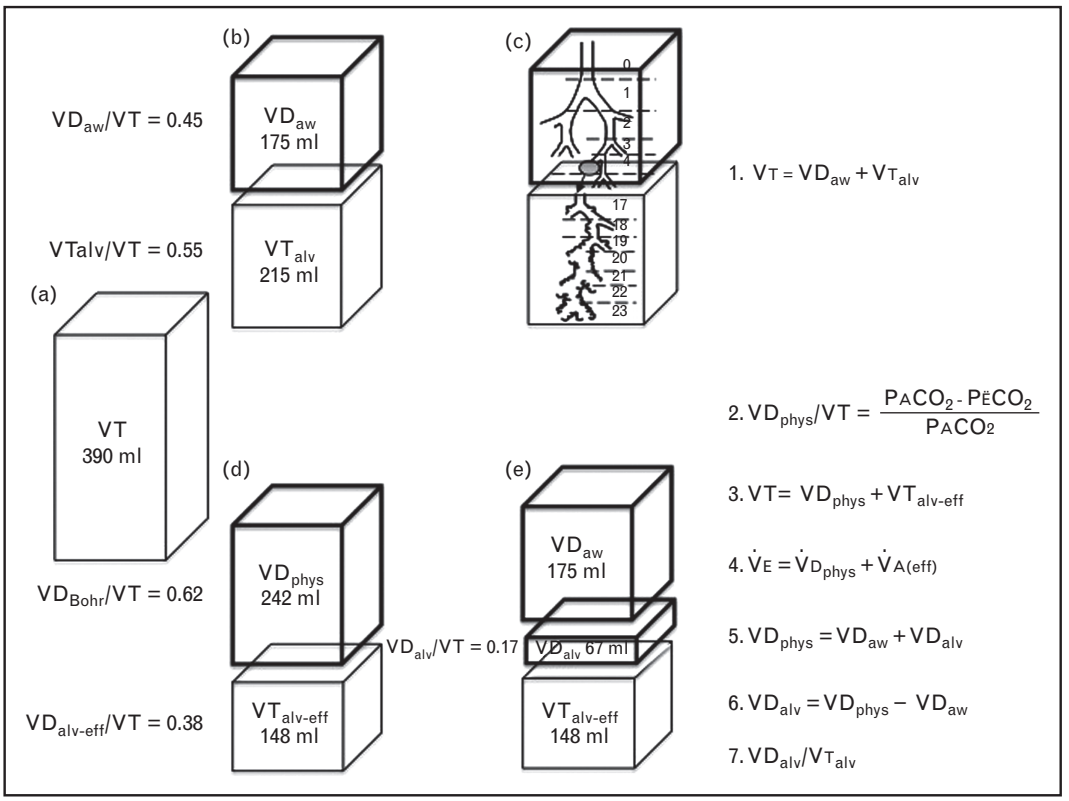

FIGURE 3. Components of the tidal volume as defined by volumetric capnography. Data from an ARDS patient ventilated with 6 ml/kg and PEEP of 16 cmH_2O. Numbers in the boxes represent absolute volumes obtained by multiplying the different fractions by tidal volume. Boxes with thicker lines reflect inefficient and boxes with thinner lines efficient portions of tidal volume. Noninvasively volumetric capnography-based $VD_{Bohr}/VT = 0.62$. Measured $VD_{Enghoff}$ (not shown) = 0.66. (a) Tidal volume delivered. (b) After calculating airway dead space fraction (VD_{aw}/VT) by Fowler's method the alveolar fraction (VT_{alv}/VT) of the VT is obtained. The VT can simply be divided into its airway dead space volume (VD_{aw}) and its alveolar tidal volume (VT_{alv}), which can be referred to an anatomic correspondence (c) by the classic branching of the respiratory system into conductive and gas-exchanging compartments. Note that whenever alveolar ventilation is calculated from VT_{alv} (Eq. 1), it will also include an inefficient portion corresponding to alveolar dead space (VD_{alv}). (d) Division of VT into its inefficient (VT_{Bohr}/VT) and efficient ($VT_{alv\text{-}eff}$) components (see also Eq. 3), which can also be expressed on the basis of minute ventilation (Eq. 4). (e) Subtracting VD_{aw}/VT from VD_{Bohr}/VT identifies alveolar dead space fraction (VD_{alv}/VT) according to Eqs. 4 and 5. Equation 7 provides an index of the lung's efficiency at its alveolar level as it reflects the efficient fraction of alveolar tidal volume (b).

Apart from providing an instant characterization of the ventilated lung, the effects of changes in tidal volume or PEEP on this distribution can easily be visualized. This visualization eases the detection of unbalanced ventilator settings, which cause either excessive hyperventilation or ineffective and inefficient alveolar ventilation. Under constant ventilator settings VCap monitoring can help detect deficits in lung perfusion due to central hypovolemia or embolic events [11]. It can also unveil inadequate LPV settings as VD_{Bohr} should theoretically be more sensitive and specific in detecting lung overdistension than $VD_{Enghoff}$. For example, in an atelectatic lung an increase in PEEP may not affect or even decrease $VD_{Enghoff}$, provided it improves the 'fictitious' component of dead space, i.e. venous admixture or shunt. A concomitant increase in VD_{Bohr} will, however, unmask the overdistension brought about by too high PEEP. Taking also the V_{Daw} component into account may help discriminate airway from alveolar overdistension (Fig. 2).

CONCLUSION

Volumetric capnography is a powerful monitoring tool that provides real-time information about the efficiency of a lung's ventilation and perfusion. Technical advances in its measurement and signal analysis have boosted our understanding of CO_2 kinetics. The novel possibility to measure VD_{Phys} entirely noninvasively in every breath may be an important step toward routine use of dead space monitoring in ventilated patients. The time has come to introduce VCap in routine critical care practice.

Acknowledgements

None.

Conflicts of interest

F.S-S. received a grant from the Fondo de Investigacién Sanitaria'' Instituto de salud Carlos III, Spain, FIS_PI070136 and performs consultant activities for Maquet Critical Care. S.H.B. is owner of a patent on volumetric capnography. G.T. performs consultant activities for Maquet Critical Care and is owner of a patent on volumetric capnography.

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