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Dead space analysis at different levels of positive end-expiratory pressure in acute respiratory distress syndrome patients☆

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ABSTRACT

Purpose: To analyze the effects of positive end-expiratory pressure (PEEP) on Bohr's dead space (VD_{Bohr}/VT) in patients with acute respiratory distress syndrome (ARDS).
Material and methods: Fourteen ARDS patients under lung protective ventilation settings were submitted to 4 different levels of PEEP (0, 6, 10, 16 cmH_2O). Respiratory mechanics, hemodynamics and volumetric capnography were recorded at each protocol step.
Results: Two groups of patients responded differently to PEEP when comparing baseline with 16-PEEP: those in which driving pressure increased > 15% ($\Delta P_{>15\%}$, n = 7, p = .016) and those in which the change was ≤15% ($\Delta P_{\le15\%}$, n = 7, p = .700). VD_{Bohr}/VT was higher in $\Delta P_{\le15\%}$ than in $\Delta P_{\le15\%}$ patients at baseline ventilation [0.58 (0.49–0.60) vs 0.46 (0.43–0.46) p = .018], at 0-PEEP [0.50 (0.47–0.54) vs 0.41 (0.40–0.43) p = .012], at 6-PEEP [0.55 (0.49–0.57) vs 0.44 (0.42–0.45) p = .008], at 10-PEEP [0.59 (0.51–0.59) vs 0.45 (0.44–0.46) p = .006] and at 16-PEEP [0.61 (0.56–0.65) vs 0.47 (0.45–0.48) p = .001]. We found a good correlation between ΔP and VD_{Bohr}/VT only in the $\Delta P_{>15\%}$ group (r = 0.74, p < .001).
Conclusions: Increases in PEEP result in higher VD_{Bohr}/VT only when associated with an increase in driving pressure.

1. Introduction

Dead space comprises the *wasted ventilation* represented by all ventilated areas without pulmonary perfusion which do not participates in gas exchange [1]. In patients with acute respiratory distress syndrome (ARDS) dead space increases and dynamically changes during the course of the disease, in response to changes in body position, ventilatory settings and recruitment maneuvers [2-6]. Dead space has also a strong independent prognostic value in the early and late evolution of ARDS [7-9]. Thus, the analysis of dead space provides useful information not only for adjusting lung protective ventilatory settings but also for evaluating responses to treatments and predicting patient's outcomes.

It was recently demonstrated that the mean alveolar partial pressure of CO_2 ($PACO_2$) the one used in the original Bohr equation, can be obtained from the midpoint of phase III of the capnogram [11]. This has provided the unprecedented option to obtain Bohr's dead space (VD_{Bohr}/VT) continuously and fully non-invasively at the bedside by solely using volumetric capnography (VCap) - i.e. the graphical representation of the expired volume of CO_2 (Fig. 1) without the need of an arterial blood sample [1,10]. Thus, clinicians can now make use of the monitoring of VD_{Bohr}/VT to better understand how positive pressure ventilation affects ARDS lungs on a breath-by-breath basis.

There are only a few published studies analyzing the effects of positive end-expiratory pressure (PEEP) on dead space in ARDS [3,12,13]. These studies however, calculate "dead space" using formulas that tend to overestimate this ventilation/perfusion mismatch [14]. The original Bohr's equation is the one measuring the true dead space effect because it eliminates the contamination introduced by shunt when using arterial partial pressure of CO_2 ($PaCO_2$) instead of $PACO_2$ [10,15]. Therefore, VD_{Bohr}/VT theoretically provides more precise

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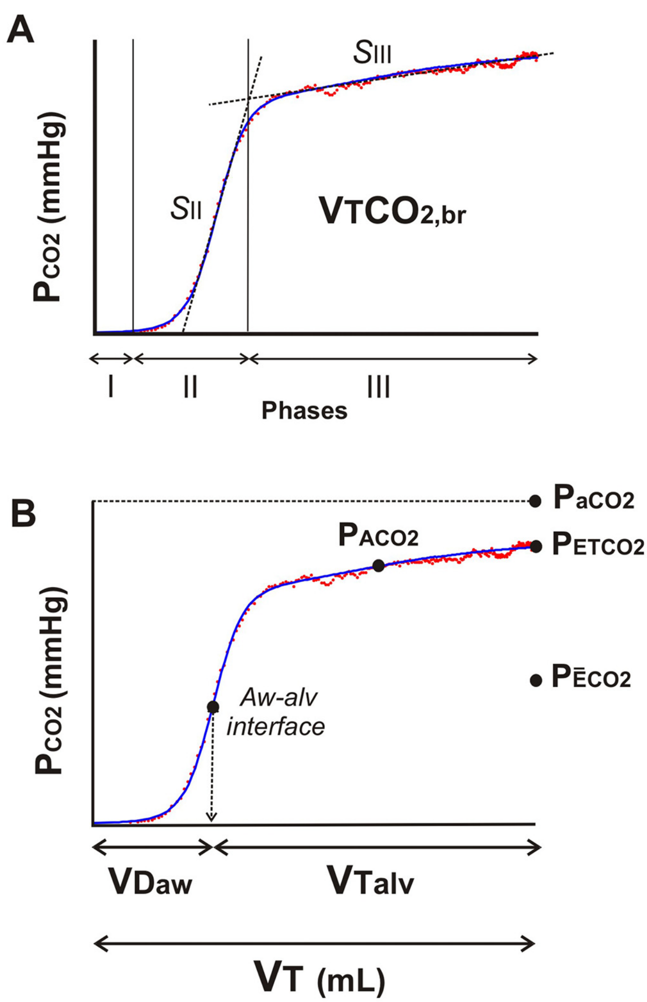

Fig. 1. Volumetric capnography. Panel A: The volumetric capnogram plots the expired CO_2 in one expired tidal volume (VT). The curve has three phases: Phase I represents the last inspired gas free of CO_2, phase II constitutes the increasing expired CO_2 that comes from lung units with different expiratory time-constants and phase III is the pure alveolar gas. The Levenberg-Marquat method finds a mathematical function (blue line) that fits the raw CO_2 and volume data (red dots) from which the phases, slope of phase II (S_{II}), slope of phase III (S_{III}) and the area under the curve ($VTCO_{2,br}$) are calculated (Panel A). Panel B: The airway-alveolar interface (*Aw-alv*), or the limit between the conducting airways and the alveolar compartment, separate the tidal volume into two components: airway dead space (VD_{aw}) and alveolar tidal volume (VT_{alv}). The end-tidal, alveolar and mixed-expired partial pressures of CO_2 ($PETCO_2$, $PACO_2$ and $P\bar{E}CO_2$, respectively) can be derived from the capnogram. The dotted line represents the theoretical position of the arterial partial pressure of CO_2 ($PaCO_2$) but is not a part of the capnogram. More information is found in reference # 19.

information about the pulmonary elimination of CO_2 than other alternative formulas.

The aim of this experimental and interventional study was to describe the effect of PEEP on VD_{Bohr}/VT and its sub-components in mechanically ventilated patients with ARDS.

2. Materials and methods

The study was performed in the Intensive Care Unit of the Hospital Italiano de Buenos Aires, Buenos Aires, Argentina (NCT02889770). The protocol was approved by the local Ethical Committee and the signed Informed Consent was obtained from the patient's next of kin.

2.1. Selection of patients and monitoring

We included patients ≥18 years old with ARDS, according to the Berlin definition [16] who had been submitted to at least 12 h of mechanical ventilation [17]. Patients with hemodynamic instability, heart failure, chest wall abnormalities and with a previous chronic respiratory disease were excluded.

Baseline ventilation was performed in a volume controlled ventilation mode (Servoi, Maquet, Solna, Sweden) with a tidal volume (VT) of 6 mL/kg of predicted body weight, respiratory rate adjusted to ensure a pH ≥ 7.30 without creating intrinsic PEEP, I:E 1:2 with 15% inspiratory pause and inspired oxygen fraction (FIO_2) of 0.5 (or higher whenever SaO_2 was <90%). PEEP of 10 cmH_2O was selected during baseline ventilation in accordance to the ARDSNet low tidal volume study in which average values when using the PEEP/FiO_2 table were around 9–10 cmH_2O [18] and following the standardized ventilation proposed by Villar et al. to identify severe persistent ARDS [17].

All patients were studied in the supine position and sedated with propofol at 60–80 $\mu g \cdot kg^{-1}$ min^{-1} and remifentanyl at 0.3–0.5 $\mu g \cdot kg^{-1}.min^{-1}$. ECG, heart rate and pulse oximetry monitoring were continuously monitored (IntelliVue MP 20, Philips Medizin Systeme, Germany). A 20G catheter was placed in the radial artery for invasive mean arterial pressure (MAP) and cardiac index monitoring (Vigileo, Edwards Lifesciences, Irvine, CA, USA) and for arterial blood sampling. Fluid therapy and vasoactive drugs were adjusted to maintain a MAP ≥60 mmHg, CI ≥2.5 L/min/m^2 and urine output ≥30 mL/h.

2.2. Respiratory mechanics and volumetric capnography

Expired CO_2 and lung mechanics were measured by the NICO monitor (Philips Respironics, Philadelphia, PA). This device combines an infrared mainstream CO_2 sensor with a fixed-orifice differential pressure and flow sensor placed at the airway opening. Data were recorded continuously and downloaded by the software Flowtool Viewer (Philips Respironics, Philadelphia, PA). Volumetric capnograms were reconstructed for analysis using customized software programmed in MatLab ® (Mathworks, Natick, MA, USA). The Levenberg-Marquardt algorithm adjusts a mathematical function to the expired CO_2 volume obtained from the NICO raw data from which the following breath-by-breath capnographic derived-parameters were calculated (Fig. 1) [19]:

- $VTCO_{2,br}$ is the amount of expired CO_2 in one breath obtained by integrating the flow and CO_2 signal over the entire breath (Fig. 1A).
- The volumetric capnogram was divided in 3 phases: volume of phase I, is the portion of the VT free of CO_2 constituted by the instrumental and part of the airway dead space. Volume of phase II, constitutes the portion of VT where increasing amounts of CO_2 are leaving lung units with different ventilation/perfusion rates qualitatively defined by its slope (S_{II}). The volume of phase III contains pure alveolar gas with its corresponding slope (S_{III}) (Fig. 1A).
- Sn_{III} is the normalized slope of phase III. It was calculated selecting 10 data-points belonging to the middle portion of phase III, where the slope of each point was computed as the 1st derivative. Then, the mean value of those 10 points determined the slope of phase III, which was normalized by dividing it by the mixed expired fraction of CO_2.
- $PACO_2$ is the mean alveolar partial pressure of CO_2 found at the mid-point of the slope of phase III (Fig. 1B).
- $P\bar{E}CO_2$ is the mixed expired partial pressure of CO_2 determined by the following equation:

$$P\bar{E}CO_2 = (VTCO_{2,br}/VT) * (\text{barometric pressure} - \text{water vapor})$$

- Physiological dead space was calculated by the Bohr's equation [1] as:

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

Bohr's dead space was further divided in its sub-components [10]: 1) airway dead space-to-VT ratio (VD_{aw}/VT), where VD_{aw} is determined at the airway-alveolar interface corresponding to the mathematical