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

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Keywords:
ARDS
Volumetric capnography
PEEP
$PACO_2$
Dead space
Carbon dioxide

A B S T R A C T

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% ($\Delta P_{\leq 15\%}$, n = 7, p = .700). VD_{Bohr}/VT was higher in $\Delta P_{\leq 15\%}$ than in $\Delta P_{\leq 15\%}$ 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

☆ This study was performed at the Hospital Italiano de Buenos Aires, Buenos Aires, Argentina.The study was supported by local resources of the Hospital Universitario Italiano, Buenos Aires, Argentina.This study was presented in October 2015 at the National Meeting of Intensive Care Medicine in Mar del Plata, Buenos Aires, Argentina.
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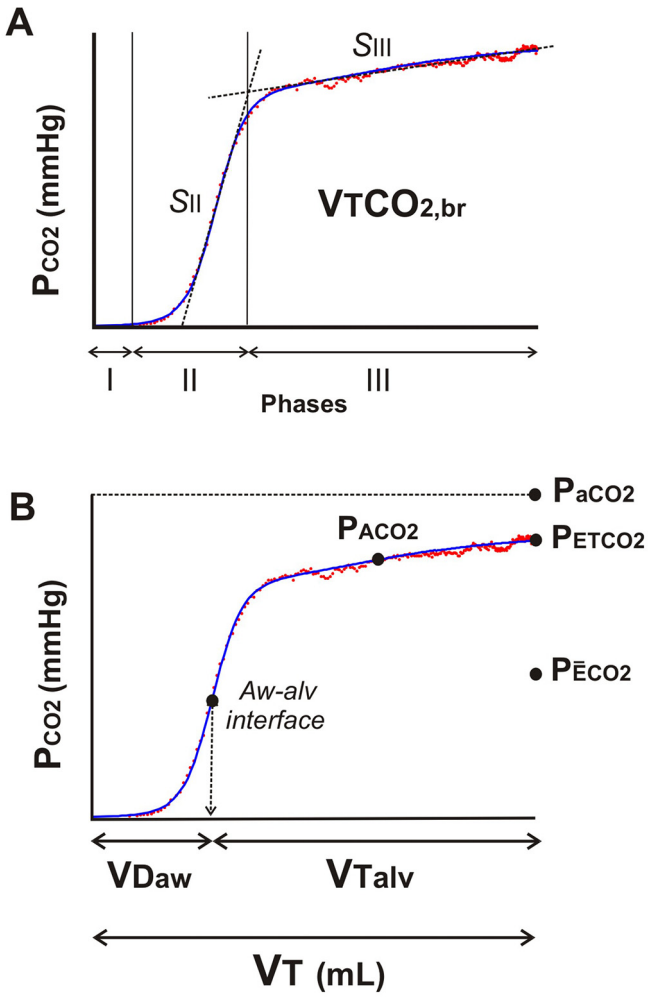

Fig. 1. Volumetric capnography. Panel A: The volumetric capnogram plots the expired CO_2 in one expired tidal volume (VT). The curve has three phases: Phase I represents the last inspired gas free of CO_2, phase II constitutes the increasing expired CO_2 that comes from lung units with different expiratory 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 midpoint 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

inflection point of the capnogram (Fig. 1B) [19]. This airway dead space includes an additional instrumental dead space caused by the use of the HME (40 mL) placed between the CO_2 mainstream sensor and the endotracheal tube. 2) The alveolar dead space was obtained by subtracting VD_{aw} from VD_{Bohr}. This component was presented as a ratio to the alveolar tidal volume (VD_{alv}/VT_{alv}). All VCap-derived variables were calculated on a breath-by-breath basis and averaged to obtain one single value per protocol step.

- The Enghoff's index of gas exchange was calculated using $PaCO_2$ obtained by arterial blood sampling as [14]:

$$\text{Enghoff}'\text{s index} = (PaCO_2 - P\bar{E}CO_2)/PaCO_2$$

Plateau pressure (Pplat) and intrinsic PEEP were measured during 3 s inspiratory and expiratory holds, respectively. Driving pressure (ΔP) was then calculated as Pplat minus total PEEP (intrinsic + extrinsic PEEP), static respiratory compliance as Crs = VT/(Pplat – total PEEP) and airway resistance as Raw = (peak pressure - Pplat) /peak inspiratory flow.

2.3. Study protocol

First FIO_2 was increased to 1 to avoid potential hypoxemia at low levels of PEEP. We recorded the data at baseline ventilation, as described above, during 15 min. Thereafter, we studied four levels of PEEP - 0, 6, 10 and 16 cmH_2O - applied in a random order using a randomization table. Each PEEP step was maintained for 10 min and was preceded by 5 min of baseline ventilation. In case of arterial hypoxemia ($SpO_2 < 90\%$) during lower PEEP ventilation the protocol was interrupted and patients submitted to a rescue lung recruitment maneuver. Infusion rates of fluids and vasoactive drugs were kept constant throughout the study and adjusted according to the attending physician's criterion following routine clinical practice.

We recorded respiratory, hemodynamic, and VCap derived parameters. We analyzed the VCap parameters of the last 2 min of each protocol steps, including >30 breaths or data-points. Arterial blood gases were obtained at the end of each PEEP level period.

2.4. Statistical analysis

Statistical analysis was performed using R software (R version 3.2.3). Normality was assessed by the Shapiro-Wilk test. For comparisons between different PEEP steps - the Kruskal-Wallis non-parametric test was used. To study the intra-subject variation of the studied parameters, each parameter was analyzed by a linear regression with patient fixed effects. The linear model used the different levels of PEEP as dummy variables to allow different functional forms of the effect. Intra-subject variations are referenced to baseline PEEP level. Data is presented as *n* (%) for proportions and median and 1st–3rd interquartile for continuous variables. Spearman correlation was used to study the correlation with the ΔP. A p-value < .05 was considered statistically significant.

3. Results

We included 14 consecutive patients whose characteristics are detailed in Table 1. Seven patients presented mild, 4 moderate and 3 severe ARDS with 36% global hospital mortality at day 28. All patients completed the protocol uneventfully and none required a rescue lung recruitment maneuver during the low PEEP steps.

Tables 2 and 3 present the median values of studied parameters of all patients pooled together. At constant hemodynamic and ventilatory conditions, the changes in Pplat compared to baseline were significant at 0-PEEP (−35%, p < .001), 6-PEEP (−18%, p < .002) and 16-PEEP (43%, p < .001) (Table 2). There were no significant differences during the protocol in any of the VCap derived-variables (Table 3).

Table 1
Baseline characteristics of the patients.

	All n = 14	ΔP > 15% n = 7	ΔP ≤ 15% n = 7
Age, years	62 (36–73)	66 (53–76)	53 (22–73)
Gender			
Female	5 [36]	3 [42]	2 [28]
Male	9 [64]	4 [58]	5 [72]
Weight, kg	79 (64–100)	77 (68–87)	85 (50–109)
Height, cm	170 (159–174)	170 (164–174)	162 (157–178)
LIS	2.2 (1.7–3.0)	1.7 (1.7–2.7)	2.7 (2.0–3.0)
Apache II	19 (15–26)	20 (13–24)	18 (16–31)
VT, ml/kg PBW	6.8 (6.2–7.7)	6.5 (6.1–7.8)	6.8 (6.2–7.5)
PEEP, cmH_2O	11 (10–11)	11 (10–11)	10 (10–11)
PaO_2/FiO_2, mmHg	192 (108–246)	226 (92–279)	169 (114–232)
Diagnosis			
Pneumonia	11 [79]	6 [85]	5 [71]
Lung contusion	1 [7]	0	1 [14.5]
Sepsis	2 [14]	1 [15]	1 [14.5]
Duration of mechanical ventilation, days	19 (12–30)	21 (16–32)	17 (9–30)
ICU stay, days	26 (17–42)	24 (16–37)	26 (17–61)
Outcome at day 28			
Death	5 [36]	4 [57]	1 [14]

Data are presented as median and 1st–3rd quartiles)or absolute values and proportions [%].

The global response to PEEP (Tables 2 and 3) was very different from the individual response of each patient. According to changes in ΔP we analyzed a posteriori two types of response to PEEP: patients in which ΔP increased >15% when comparing baseline with 16-PEEP ($\Delta P_{>15\%}$, n = 7) and those in which ΔP changed ≤15% ($\Delta P_{\leq 15\%}$, n = 7). In $\Delta P_{>15\%}$ patients, ΔP increased from 13.6 (11.7–13.9) cmH_2O at baseline to 19.3 (16.8–21.9) cmH_2O at 16-PEEP (p = .016). In $\Delta P_{\leq 15\%}$ patients, ΔP at baseline was similar than at 16-PEEP [11.6 (10–14.2) vs 12.6 (11.8–14.2) cmH_2O, respectively (p = .700)].

Fig. 2 displays the individual behavior of dead spaces according to changes in ΔP. $\Delta P_{>15\%}$ patients presented higher absolute dead space values when compared with $\Delta P_{\leq 15\%}$ patients. The inter-group analysis is presented in Table 4. Both, VD_{Bohr}/VT and the Enghoff's index were higher in $\Delta P_{>15\%}$ group than in $\Delta P_{\leq 15\%}$ group at all PEEP levels. Airway and alveolar sub-components of dead space followed the same trend showing significance at different PEEP steps.

Fig. 3 shows the intra-group analysis of the main studied volumetric capnography derived-parameters comparing the differences between baseline with each PEEP step. In $\Delta P_{>15\%}$ patients, VD_{Bohr}/VT significantly decreased at 0-PEEP (p = .001) but increased at 16-PEEP (p = .001) mainly due to changes in the airway sub-component. At 16-PEEP both, VD_{aw}/VT and VD_{alv}/VT_{alv} increased but reaching significance only in the airways sub-component. In $\Delta P_{\leq 15\%}$ patients, VD_{Bohr}/VT decreased at 0-PEEP (p = .013) but did not significantly change at higher PEEP levels. VD_{aw}/VT increased significantly at 10-PEEP and 16-PEEP while VD_{alv}/VT_{alv} maintained stable along the protocol steps. We found good correlations between driving pressure and VD_{Bohr}/VT (r = 0.74, p < .001), VD_{aw}/VT (r = 0.72, p < .001) and Enghoff index (r = 0.73, p < .001) in patients belonging to $\Delta P_{>15\%}$ but this correlation was absent in $\Delta P_{\leq 15\%}$ (r = −0.007, −0.34 and −0.25, respectively).

$VTCO_{2,br}$ presented the opposite response compared to dead space: more elimination of CO_2 was related with low dead space and vice versa (Table 4). The $\Delta P_{\leq 15\%}$ group presented higher values than the $\Delta P_{>15\%}$ at all PEEP steps but reaching statistical significance only at 16-PEEP (p = .025). The intra-group analysis showed that $VTCO_{2,br}$ significantly decreased in the $\Delta P_{>15\%}$ group at 16-PEEP (Fig. 3). In the $\Delta P_{\leq 15\%}$ group, $VTCO_{2,br}$ values were lower than baseline at all protocol steps, although their absolute values kept higher than the

Table 2
Hemodynamics and respiratory data in all patients.

Parameter	Baseline	PEEP (cmH_2O)			
		0	6	10	16
MAP (mmHg)	78 (71–86)	75 (68–82)	79 (73–87)	77 (68–84)	79 (67–81)
HR (bpm)	84 (63–91)	79 (65–93)	77 (61–95)	79 (64–92)	80 (64–92)
CO (L/min)	6.2 (5.4–7.5)	6.9 (5.8–7.7)	6.4 (5.3–8.4)	6.4 (5.7–7.6)	6.1 (4.6–7.4)
VT (mL)	428 (371–512)	460 (386–511)	435 (368–496)	438 (376–493)	422 (380–485)
RR (bpm)	20 (20–23)	20 (20–23)	20 (20–23)	20 (20–23)	20 (20–23)
Pplat (cmH_2O)	23 (22–25)	15 (14–17)	19 (18–21)	24 (22–26)	33 (29–37)
		$p \leq .001$	$p \leq .002$		$p \leq .001$
ΔP (cmH_2O)	12.7 (10.8–14.0)	12.9 (10.3–15.2)	12.0 (9.4–14.7)	12.5 (11.2–15.6)	16.3 (12.4–20.4)
Crs (mL/cmH_2O)	38 (29–42)	36 (26–43)	39 (27–41)	35 (29–39)	26 (23–34)
Raw ($cmH_2O/L/s$)	17 (16–21)	20 (15–24)	17 (14–22)	18 (14–20)	18 (15–21)
PaO_2/FIO_2 (mmHg)	192 (118–236)	133 (106–207)	193 (108–242)	231 (131–261)	243 (137–277)

MAP = mean arterial pressure, HR = heart rate, CO = cardiac output, VT = tidal volume, RR = respiratory rate, Pplat = plateau pressure, ΔP = driving pressure, Crs = static respiratory system compliance, Raw = airway resistance and PaO_2/FIO_2 = arterial partial pressure of oxygen-to-inspired fraction of oxygen ratio. Data is presented as median and 1st–3rd quartiles. Kruskal-Wallis non-parametric test for comparison with baseline.

absolute values found in the $\Delta P_{>15\%}$ group at all PEEP steps as observed in Table 4.

Finally, Sn_{III} was higher in $\Delta P_{>15\%}$ than in $\Delta P_{\leq 15\%}$ patients at 16-PEEP ($p = .035$, Table 4).

4. Discussion

This study illustrates that incremental levels of PEEP have an unpredictable physiological response in patients with ARDS. Taken all patients together, higher levels of PEEP resulted in an increase in arterial oxygenation but an impaired respiratory compliance, driving pressure and physiological dead space. The increase in dead space was mainly related to changes in the airway dead space whereas the alveolar subcomponent remained largely unchanged. Contrarily, when patients were divided according to their response in driving pressure, Bohr's dead space was higher in those in which driving pressure increased more than 15% when compared with those in which it did not. In the group with higher ΔP both, the airway and alveolar subcomponents of dead space increased in most of the analyzed PEEP steps (Table 4).

The comparison of dead space values among studies is difficult because its calculation is affected by many factors. These include etiology and severity of ARDS, formula applied (Bohr vs Enghoff), methodological aspects of the analysis, ventilatory settings, population's age and comorbidities, site of mainstream CO_2/flow sensor placement and size of instrumental dead space among others. In our study, most of the patients had mild ARDS of pulmonary origin with a slightly higher dead space than those with ARDS of extra-pulmonary causes [20]. In addition, the use of an HME increased the measured VD_{aw}/VT, which resulted in higher VD_{Bohr}/VT and Enghoff's index values but an underestimation of VD_{alv}/VT_{alv}.

We found 3 studies testing the effects of PEEP on dead space in ARDS [3,12,13]. Suter et al. reported lower VD/VT values (0.36–0.42) than ours (0.44–0.51) using the Kuwabaras' correction for the shunt effect when using the Enghoff's formula [3]. The high VT used (13–15 mL/kg) and the measurement of VD_{aw}/VT by the N_2 single-breath test could explain their low physiological and airway dead space and high alveolar dead space values [21]. Blanch et al. calculated dead space substituting $PACO_2$ by $PETCO_2$ in 17 ARDS patients [12]. This approach, however, overestimates dead space due to the positive sloping of phase III that can explain why their VD_{Bohr}/VT values were 0.1 to 0.2 higher than ours (Table 3).

Finally, Beydon et al. analyzed the changes in Enghoff's modification of Bohr's formula in 10 ARDS patients [13]. They reported Enghoff's index (0.53–0.56) and VD_{aw}/VT (0.29–0.33) values lower than the ones we have found (Table 3). Such lower dead space values can be explained again by the higher absolute mean VT (623 mL) used in their study as the dead space fraction is inversely related to the size of VT [21] and by the additional instrumental dead space caused by the HME in our patients.

More recently Doorduin et al. measured Bohr's dead space and the Enghoff index in 15 ARDS patients ventilated with lung protective settings and 12 cmH_2O of PEEP [22]. They found mean VD_{Bohr}/VT values of 0.45 ± 0.07 and mean Enghoff index of 0.68 ± 0.09, which were similar to the values we have obtained at 10 cmH_2O in our study when analyzing all patients together (Table 3).

Blanch et al. and Beydon et al. studies report only modest increases in physiological and airway dead space with increasing PEEP levels [12,13]. Verscheure et al. reasoned that the small changes in dead space seen in these studies could be related to the fact that results were analyzed as group data; which may have masked larger changes in individual patients who presented lung overdistension or those

Table 3
Volumetric capnography-derived parameters and partial pressures of CO_2 of all patients pooled together.

Parameters	Baseline	PEEP (cmH_2O)			
		0	6	10	16
VD_{Bohr}/VT	0.46 (0.44–0.56)	0.44 (0.41–0.48)	0.45 (0.43–0.52)	0.47 (0.45–0.56)	0.51 (0.46–0.60)
VD_{aw}/VT	0.34 (0.30–0.45)	0.33 (0.29–0.36)	0.34 (0.30–0.40)	0.37 (0.31–0.45)	0.39 (0.34–0.47)
VD_{alv}/VT_{alv}	0.20 (0.18–0.21)	0.18 (0.15–0.22)	0.19 (0.17–0.23)	0.19 (0.15–0.23)	0.22 (0.17–0.24)
Enghoff index	0.67 (0.63–0.74)	0.71 (0.60–0.73)	0.71 (0.58–0.74)	0.70 (0.63–0.75)	0.69 (0.59–0.77)
$VTCO_{2,br}$ (mL)	8.64 (7.13–9.12)	8.12 (6.51–9.67)	7.89 (6.26–9.26)	7.85 (5.92–9.1)	7.57 (5.63–9)
Sn_{III} (L^{-1})	1.16 (1.07–2.3)	1.67 (1.48–2.16)	1.41 (1.17–2.15)	1.37 (1.16–2.09)	1.49 (1.24–1.83)
$PaCO_2$ (mmHg)	43 (39–48)	42 (37–53)	41 (36–54)	42 (39–52)	40 (38–51)
$PETCO_2$ (mmHg)	32 (29–34)	31 (28–35)	30 (28–34)	31 (29–35)	32 (29–35)
$PACO_2$ (mmHg)	29 (26–33)	27 (23–30)	28 (24–31)	28 (25–32)	29 (25–32)

VD_{Bohr}/VT = Bohr's dead space to tidal volume ratio, VD_{aw}/VT = airway dead space to tidal volume ratio, VD_{alv}/VT_{alv} = alveolar dead space to alveolar tidal volume ratio, $VTCO_{2,br}$ = tidal elimination of carbon dioxide, Sn_{III} = normalized slope of phase III, $PaCO_2$ = arterial partial pressure of CO_2, $PETCO_2$ = end-tidal partial pressure of CO_2 and $PACO_2$ = mean alveolar partial pressure of CO_2. Kruskal-Wallis non-parametric test for comparison with baseline. Data is presented as median and 1st–3rd quartiles.

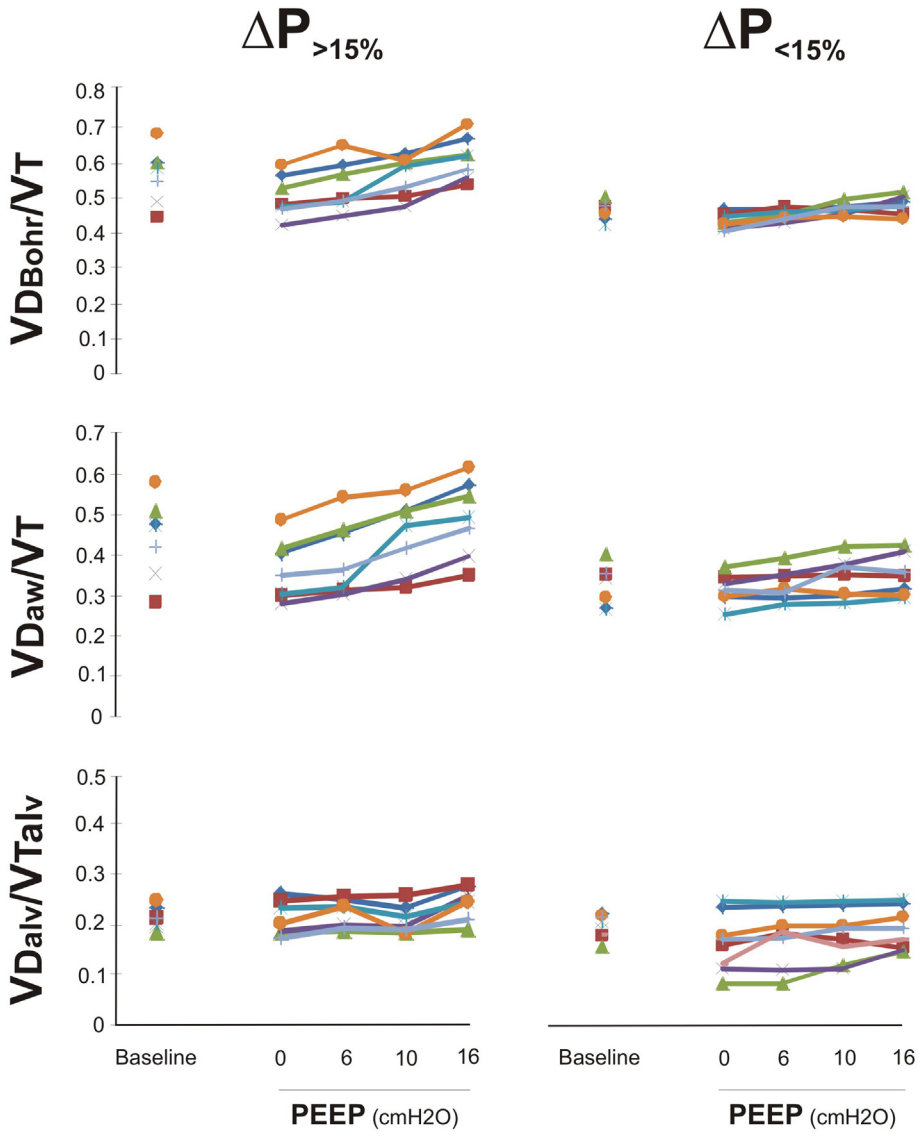

Fig. 2. Dead spaces according to changes in driving pressure in response to PEEP. VD_{Bohr}/VT = Bohr's dead space, VD_{aw}/VT = airway dead space; VD_{alv}/VT_{alv} = alveolar dead space to alveolar tidal volume ratio; $\Delta P_{>15\%}$ patients ($n = 7$) in which driving pressure increased >15% with an increase of PEEP from baseline to 16 of cmH_2O. $\Delta P_{\leq 15\%}$ represents patients ($n = 7$) in which driving pressure changed ≤ 15% from baseline to 16 of PEEP.

with some lung recruitment effect in response to PEEP [15]. Thus, we decided to analyze our data also according to individualized patterns of response to PEEP. We found that in half of the patients, PEEP potentially induced overdistension detected by an increment in ΔP and dead space. In the other half, PEEP had a minimal effect on these parameters (Figs. 2 and 3, Table 4). In the $\Delta P_{\leq 15\%}$ group, patients seemed to respond predominantly with a recruitment effect leading to more favorable lung mechanics and lower dead space, which resulted in a higher elimination of CO_2 and a lower $PaCO_2$ when compared to $\Delta P_{>15\%}$ patients. Despite the absolute values of VD_{alv}/VT_{alv} were clearly underestimated by the use of HME, this parameter significantly increased only in the $\Delta P_{>15\%}$ group, suggesting a potential alveolar overdistension at high PEEP levels in those patients (Table 4). The higher Sn_{III} values found in patients with ΔP >15%, was likely related to more ventilation/perfusion inhomogeneities when compared with the $\Delta P_{\leq 15\%}$ group [23].

An interesting aspect derived from the changes observed in Fig. 3 is that these capnographic derived parameters are useful in detecting the variable response to PEEP in ARDS patients. For example, in the $\Delta P_{>15\%}$ group, VD_{alv}/VT_{alv} decreased when increasing PEEP from 6 to 10 cmH_2O of PEEP suggesting a lung recruitment effect. However, after a further increase from 10 to 16 cmH_2O this dead space fraction augmented as a probable indication of alveolar overdistension.

4.1. Clinical implications of the results

Bohr's dead space describes the inefficiency of the lung to eliminate CO_2 and is related to potential overdistension during positive-pressure mechanical ventilation [1,3,10,15]. This important physiological concept has gained renewed attention since now VD_{Bohr}/VT can be measured breath by breath by the non-invasive estimation of $PACO_2$ with VCap [11].

This study provides novel information about the changes in Bohr's dead space and its sub-components induced by PEEP in ARDS patients. Both Bohr's and Enghoff's equations are clinically relevant but provide different information in mechanically ventilated patients [1,10,14]. Using the original Bohr formula the "contamination" effect of low VQ and shunt areas on its calculation, present in the Enghoff's approach, is minimized [11,22,24]. This allows evaluating the effects of PEEP on gas exchange exclusively from the perspective of its impact on the

Table 4
Comparison of main variables between groups.

Parameters	ΔP	Baseline	PEEP (cmH_2O)			
			0	6	10	16
VDBohr/VT	ΔP > 15%	0.58 (0.49–0.60)	0.50 (0.47–0.54)	0.55 (0.49–0.57)	0.59 (0.51–0.59)	0.61 (0.56–0.65)
	ΔP ≤ 15%	0.46 (0.43–0.46)	0.41 (0.40–0.43)	0.44 (0.42–0.45)	0.45 (0.44–0.46)	0.47 (0.45–0.48)
		P = .018	P = .012	P = .008	P = .006	P = .001
VDaw/VT	ΔP > 15%	0.47 (0.37–0.48)	0.38 (0.31–0.40)	0.43 (0.33–0.45)	0.48 (0.36–0.50)	0.51 (0.41–0.55)
	ΔP ≤ 15%	0.34 (0.27–0.34)	0.31 (0.29–0.33)	0.31 (0.29–0.34)	0.35 (0.29–0.37)	0.34 (0.30–0.38)
		P = .035			P = .047	P = .018
VDalv/VTalv	ΔP > 15%	0.22 (0.20–0.23)	0.20 (0.19–0.23)	0.22 (0.20–0.24)	0.21 (0.18–0.23)	0.25 (0.24–0.27)
	ΔP ≤ 15%	0.19 (0.17–0.20)	0.16 (0.15–0.24)	0.17 (0.17–0.24)	0.16 (0.13–0.21)	0.16 (0.14–0.21)
		P = .025		P = .047		P = .008
Enghoff index	ΔP > 15%	0.74 (0.74–0.75)	0.74 (0.73–0.74)	0.76 (0.74–0.77)	0.76 (0.75–0.76)	0.78 (0.77–0.79)
	ΔP ≤ 15%	0.63 (0.58–0.65)	0.59 (0.56–0.70)	0.58 (0.55–0.69)	0.63 (0.54–0.69)	0.58 (0.53–0.63)
		P = .001	P = .025	P = .008	P = .006	P = .002
$VTCO_{2,br}$ (mL)	ΔP > 15%	6.5 (5.7–8.4)	6.6 (5.9–7.6)	6.3 (5.7–7.3)	5.8 (5.3–7.1)	5.2 (5.1–6.4)
	ΔP ≤ 15%	9.0 (8.4–11.8)	8.3 (7.9–10.7)	8.2 (7.8–10.5)	8.3 (7.6–10.6)	9.0 (7.5–10.9)
						P = .025
Sn_{III} (L^{-1})	ΔP > 15%	2.6 (1.5–2.8)	2.1 (1.8–2.2)	2.3 (1.6–2.4)	2.5 (1.5–3.0)	2.5 (1.5–3.4)
	ΔP ≤ 15%	1.1 (1.1–1.3)	1.5 (1.5–1.8)	1.4 (1.2–1.7)	1.3 (1.0–1.5)	1.4 (1.0–1.6)
						P = .035
$PaCO_2$ (mmHg)	ΔP > 15%	47 (42–54)	47 (38–54)	48 (36–56)	46 (39–55)	48 (42–56)
	ΔP ≤ 15%	41 (39–46)	43 (39–49)	43 (38–49)	43 (41–45)	40 (37–40)
pH	ΔP > 15%	7.32 (7.27–7.33)	7.31 (7.27–7.34)	7.3 (7.27–7.34)	7.31 (7.28–7.33)	7.29 (7.25–7.32)
	ΔP ≤ 15%	7.36 (7.34–7.42)	7.37 (7.32–7.45)	7.36 (7.32–7.45)	7.37 (7.33–7.46)	7.36 (7.34–7.42)
Crs (mL/cmH_2O)	ΔP > 15%	37 (31–39)	36 (35–37)	39 (36–40)	36 (31–37)	24 (22–25)
	ΔP ≤ 15%	38 (27–44)	36 (23–46)	38 (24–42)	34 (28–42)	33 (26–40)
ΔP (cmH_2O)	ΔP > 15%	13.6 (11.7–13.9)	12.9 (11.6–13.8)	12 (10.2–13.7)	13.2 (12–16.7)	19.3 (16.8–21.9)
	ΔP ≤ 15%	11.6 (10.0–14.2)	13.8 (9.8–16.1)	12.3 (9.1–15)	12.5 (10.7–14.5)	12.6 (11.8–14.2)
						P = .05

VD_{Bohr}/VT = Bohr's dead space to tidal volume ratio, VD_{aw}/VT = airway dead space to tidal volume ratio, VD_{alv}/VT_{alv} = alveolar dead space to alveolar tidal volume ratio, $VTCO_{2,br}$ = tidal elimination of carbon, Sn_{III} = normalized slope of phase III, $PaCO_2$ = arterial partial pressure of carbon dioxide, Crs = static respiratory system compliance and ΔP = driving pressure. Krustal-Wallis non-parametric test for inter-group comparison. Data is presented as median and 1st–3rd quartiles.

high V/Q behavior of the overall V/Q mismatch spectrum. This is an important, but often neglected, pathophysiological aspect in the ventilated ARDS patient. First, because tolerance and adequacy to permissive hypercapnia, a negative consequence of protective ventilation, must be carefully assessed. Second, because more than its mere effect on oxygenation, the setting of PEEP and tidal volume should prioritize minimizing any potential overdistension in the airway and alveolar compartments. The Enghoff index informs about the global efficiency of gas exchange including the entire spectrum of V/Q inequalities. Therefore, if the Enghoff index decreases in response to an increase in PEEP it does not necessarily mean an improvement in lung mechanics as the reduction in shunt may predominate [3,5,24]. On the contrary if Bohr's dead space remains unchanged (or decreases) it indicates that the increase in PEEP did not result in more overdistension.

VCap derived-parameters were able to discriminate patients with opposing responses to PEEP. Those presenting minimal changes in ΔP in response to PEEP had a lower dead space, Enghoff index, Sn_{III} and $PaCO_2$ and a higher elimination of CO_2 at baseline conditions (Table 4). Published data confirm that such positive effect of PEEP on VCap derived variables can be explained by an improvement in lung mechanics and a reduction of shunt, more homogeneous distribution of ventilation and a larger surface area for gas exchange [24]. Thus, not only dead space but also $VTCO_{2,br}$ and Sn_{III}, seem useful parameters to predict the response to PEEP and possibly lung recruitment in a given patient.

4.2. Limitations

The time spent at each PEEP level for its evaluation was only 10 min which may have been insufficient to allow adequate CO_2 kinetics equilibration. The same is true for baseline ventilation between protocol steps. We chose this period to minimize the time on less favorable PEEP levels such as 0 or 16 cmH_2O, which have potential negative effects on arterial oxygenation and possible lung overdistension, respectively. Furthermore, previous data from an experimental model of ARDS demonstrated that 5 min was enough time to reach the maximum effect in CO_2 kinetics after a step change in PEEP [25].

Most of our patients had a mild ARDS of pulmonary origin and the extrapolation of our results to severe ARDS of extra-pulmonary causes is difficult. In our patients $PaCO_2$ could be controlled using a mean RR of 20 bpm despite using low VTs. This expiratory time ≥2.0 s resulted in phase III slopes of sufficient duration to allow an accurate calculation of $PACO_2$ and dead space. In Severe ARDS patients the frequently used higher RR and shorter expiratory times could, however, affect dead space calculation by a truncated slope of phase III complicating the estimation of $PACO_2$ within the volumetric capnogram. Recently, Doorduin et al. did not report any technical limitations for measuring $PACO_2$ and VD_{Bohr}/VT in ARDS patients ventilated with the ARDSnet strategy [22]. Nevertheless, whether the estimation of VD_{Bohr}/VT is compromised in situations with higher respiratory rates and higher levels of PEEP is yet to be established.

VT changed slightly among PEEP steps despite the fixed set 6 mL/kg predicted body weight (Tables 1 and 2). These small differences between set and measured expiratory VT are commonly observed in ventilated patients and, provided compressive volume is compensated for, are related to modifications in respiratory mechanics, changes in end-expiratory volume induced by PEEP or the effect of cardiogenic oscillations among other factors. However, these small variations in VT between studied moments were ≤2%, without statistical significance and had no influence on dead space results.

The pragmatic decision of classifying patients according to a ΔP > or ≤ 15% may sound arbitrary but helped us to group patients that followed a clearly defined pattern and allowed us to present our findings in a clearer way. These findings are in line with Verscheure et al. that highlighted the shortcomings of analyzing data only as a single group,

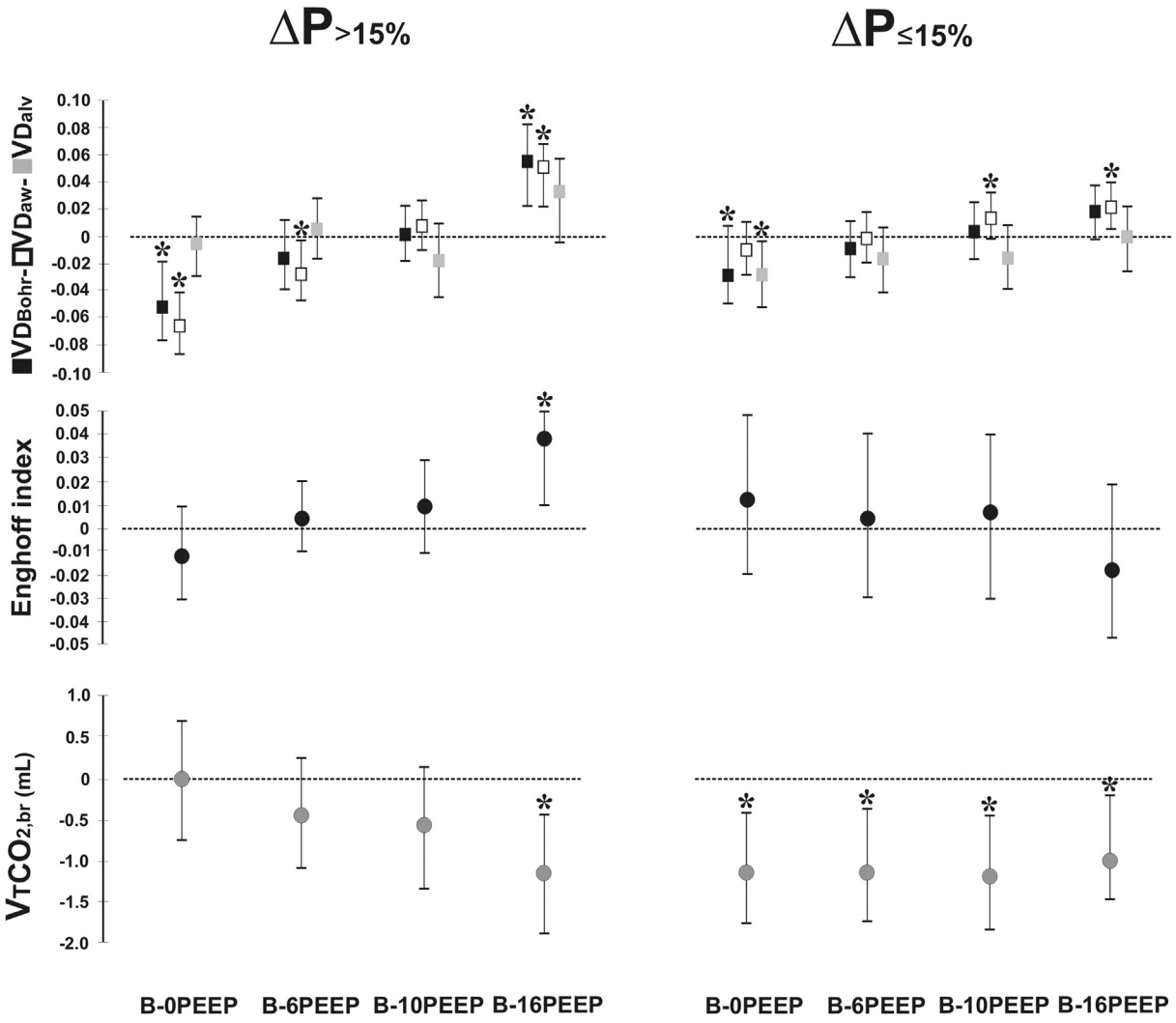

Fig. 3. Intra-group differences of the main studied volumetric capnography derived-parameters. VD_{Bohr}/VT = Bohr's dead space, VD_{aw}/VT = airway dead space, VD_{alv}/VT_{alv} = alveolar dead space to alveolar tidal volume ratio, and $VTCO_{2,br}$ = elimination of CO_2 per breath. Data is presented as mean and 95% confidence intervals. Comparisons were made between baseline values and each PEEP step, *p ˂ .05.

without taking into account individual responses [15]. This cut-off was not created to clinically classify patients because neither the number of patients nor the study protocol was designed for these purposes.

The low number of patients and the physiologic-exploratory nature of our study do not allow us to draw any conclusion or further interpretation about the results observed in patients' outcome between ΔP-groups.

4.3. Conclusion

In ARDS patients, increases in PEEP resulted in higher dead space only when associated with a parallel increase in driving pressure. Volumetric capnography could complement lung mechanics in discriminating the different responses to PEEP identifying those at higher risk for overdistension. This information could help clinicians to better individualize protective ventilatory settings at the bedside.

Contributions

EG, MD, JD, NR, AM, SG performed literature search and data collection. EG, MM, JR, AM, SG, ESR, FSS and GT performed study design, analysis of data, manuscript preparation and final review.

Conflict of interest

No potential conflicts of interest exist except for GT and FSS who perform consultating activities for Maquet regarding volumetric capnography. Matías Madorno is partner and manager of MBMed S.A.

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