PaCO₂ and alveolar dead space are more relevant than PaO₂/FiO₂ ratio in monitoring the respiratory response to prone position in ARDS patients: a physiological study

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Abstract

Introduction: Our aims in this study were to report changes in the ratio of alveolar dead space to tidal volume (V\text{Dalv}/V_{T}) in the prone position (PP) and to test whether changes in partial pressure of arterial CO₂ (PaCO₂) may be more relevant than changes in the ratio of partial pressure of arterial O₂ to fraction of inspired O₂ (PaO₂/FiO₂) in defining the respiratory response to PP. We also aimed to validate a recently proposed method of estimation of the physiological dead space (V\text{physiol}/V_{T}) without measurement of expired CO₂.

Methods: Thirteen patients with a PaO₂/FiO₂ ratio < 100 mmHg were included in the study. Plateau pressure (P\text{plat}), positive end-expiratory pressure (PEEP), blood gas analysis and expiratory CO₂ were recorded with patients in the supine position and after 3, 6, 9, 12 and 15 hours in the PP. Responders to PP were defined after 15 hours of PP either by an increase in PaO₂/FiO₂ ratio > 20 mmHg or by a decrease in PaCO₂ > 2 mmHg. Estimated and measured V\text{physiol}/V_{T} ratios were compared.

Results: PP induced a decrease in P\text{plat}, PaCO₂ and V\text{Dalv}/V_{T} ratio and increases in PaO₂/FiO₂ ratios and compliance of the respiratory system (Crs). Maximal changes were observed after six to nine hours. Changes in V\text{Dalv}/V_{T} were correlated with changes in Crs, but not with changes in PaO₂/FiO₂ ratios. When the response was defined by PaO₂/FiO₂ ratio, no significant differences in P\text{plat}, PaCO₂ or V\text{Dalv}/V_{T} alterations between responders (n = 7) and nonresponders (n = 6) were observed. When the response was defined by PaCO₂, four patients were differently classified, and responders (n = 7) had a greater decrease in V\text{Dalv}/V_{T} ratio and in P\text{plat} and a greater increase in PaO₂/FiO₂ ratio and in Crs than nonresponders (n = 6). Estimated V\text{physiol}/V_{T} ratios significantly underestimated measured V\text{physiol}/V_{T} ratios (concordance correlation coefficient 0.19 (interquartile ranges 0.091 to 0.28)), whereas changes during PP were more reliable (concordance correlation coefficient 0.51 (0.32 to 0.66)).

Conclusions: PP induced a decrease in V\text{Dalv}/V_{T} ratio and an improvement in respiratory mechanics. The respiratory response to PP appeared more relevant when PaCO₂ rather than the PaO₂/FiO₂ ratio was used. Estimated V\text{physiol}/V_{T} ratios systematically underestimated measured V\text{physiol}/V_{T} ratios.
Introduction
Since its first description in 1967 [1], it has been accepted that acute respiratory distress syndrome (ARDS) includes a number of lung injuries of various origins whose consequences are decreased lung capacity available for ventilation, leading to the concept of “baby lung” [2]. Considerable progress has been made over the past decade in the ventilatory management of patients with ARDS. In particular, a strict limitation of tidal volume (VT) and plateau pressure (Pplat) below 30 cmH2O reduces mortality [3]. The application of positive end-expiratory pressure (PEEP) is recognized to recruit the lung and to restore functional residual capacity [4], but its optimum level is still widely debated [5].

The prone position (PP) may also be part of the ventilatory strategy. This method was proposed more than 30 years ago, initially in pathophysiological studies [6,7]. Recently, Sud et al. [8] suggested, on the basis of pooled data from randomized, controlled trials, that PP may improve survival in the subgroup of patients with the most severe ARDS, that is, those with a ratio of partial pressure of arterial O2 to fraction of inspired O2 (PaO2/FiO2) < 100 mmHg. Many questions remain unresolved. In particular, response to PP is usually defined according to changes in PaO2, with responders being those in whom the PaO2/FiO2 ratio increases > 20 mmHg after one to six hours in the PP [9-11]. However, we have previously reported that PP allows recruitment of a slow compartment previously excluded from ventilation [12].

This was associated with a decrease in partial pressure of arterial CO2 (PaCO2), an indirect risk factor for mortality in patients with ARDS [13]. In a recent study, Siddiki et al. [14] proposed evaluating the physiological dead space fraction (VDphysiol/VT) by using a rearranged alveolar gas equation for PaCO2 without any expired CO2 measurement.

In this context, we conducted a prospective physiological study to evaluate the impact of PP on ventilatory mechanics, gas exchange and VDphysiol. Our main objective was to validate our hypothesis that changes in PaCO2 and VDphysiol might be more relevant than changes in PaO2 in defining the respiratory response to PP. Our second objective was to validate the method of evaluation of the VDphysiol/VT ratio proposed by Siddiki et al. [14].

Materials and methods
In our unit, patients with a PaO2/FiO2 ratio < 100 mmHg after 24 to 48 hours of mechanical ventilation are systematically turned to PP when hemodynamically stable [15]. Our study was approved by the Ethics Committee of the “Société de Réanimation de Langue Française” (SRLF-CE 07-213). After obtaining informed consent from the patients’ relatives, 15 patients were included in the study between January 2008 and March 2010. Inclusion criteria were (1) the presence of ARDS according to the definition of the Acute Respiratory Distress Syndrome Network [3]; (2) persistence of severe hypoxemia after 48 hours of mechanical ventilation, defined as a PaO2/FiO2 ratio < 100 mmHg; and (3) hemodynamic stability, defined as systolic blood pressure > 90 mmHg with norepinephrine infusion at a rate < 0.5 μg/kg/minute. Patients with chronic obstructive pulmonary disease were excluded.

All patients were ventilated in volume-controlled mode (Servo-i; Maquet SA, Ardon, France), sedated and paralyzed by infusion of atracurium. The heat and moisture exchanger was routinely removed and replaced by a heated humidifier to reduce instrumental dead space as previously reported [16]. The ventilator settings included a “moderately restricted” Vt of 6 to 8 mL/kg measured body weight, a respiratory rate allowing us to limit hypercapnia without generating intrinsic PEEP and an inspiration/expiration ratio of 1:2 with an end inspiratory pause of 0.5 seconds. Pplat was strictly limited < 30 cmH2O, and the PEEP selected was that which corrected the intrinsic PEEP, if any [17]. Ventilator settings were kept constant throughout the study. A recruitment maneuver was never used, and suction was not systematically performed. All patients were continuously monitored in terms of blood pressure with an arterial catheter, heart rate and O2 saturation by pulse oximetry.

The study was conducted during the first session of PP. Our sessions routinely last 15 to 18 hours per day. Blood gas analysis, Pplat, total PEEP, end-tidal CO2 (PETCO2) and mixed expired CO2 (PECO2) were recorded with the patient in the supine position, just before turning the patient to the PP, and every 3 hours in the PP until 15 hours had elapsed. Expired CO2 was measured by a sensor positioned between the proximal end of the endotracheal tube and the Y piece of the ventilator circuit (COSMO; Novametrix, Wallingford, CT, USA). The ratio of VD/Vt was calculated using the simplified Bohr equation [18] as follows: (1) \[ \frac{\text{VD}_{\text{alv}}}{\text{VT}} = 1 - \frac{\text{PETCO}_2}{\text{PaCO}_2} \] and (2) \[ \frac{\text{VD}_{\text{physiol}}}{\text{VT}} = 1 - \frac{\text{PECO}_2}{\text{PaCO}_2} \]

The estimated VDphysiol/VT ratio was calculated as \[ 1 - \frac{0.86 \times \text{VCO}_2_{\text{est}}}{(\text{VE} \times \text{PaCO}_2)} \], where VCO2est is the estimated CO2 production calculated using the Harris-Benedict equation [19] and VE is the expired minute ventilation.

Intrinsic PEEP was measured during a four-second end-expiratory occlusion period. Pplat was measured during a 0.5-second end-inspiratory pause. Respiratory system compliance (Crs) was calculated as \[ \text{Crs} = \frac{\text{VT}}{\text{PaCO}_2} \]
(Pplat - PEEP_{total}). Responders to PP were defined in two different ways: (1) an increase in PaO_{2}/FiO_{2} ratio > 20 mmHg after 15 hours of PP or (2) a decrease in PaCO_{2} > 2 mmHg after 15 hours of PP.

**Statistical analysis**

Statistical analysis was performed using StatView 5 software (SAS Institute Inc., Cary, NC, USA). The continuous variables were expressed as medians (1st to 3rd interquartile range). Analysis of variance for repeated measurements was used for each parameter, and \( P < 0.05 \) was considered statistically significant. Measured VD_{physiol}/V_{T} and estimated VD_{physiol}/V_{T} were compared according to Bland-Altman analysis, together with the concordance correlation coefficient in 78 paired data. The same method was used to compare variations of measured and estimated VD_{physiol}/V_{T} every three hours while the patient was in PP.

**Results**

Two patients were excluded from the study because of a history of severe chronic obstructive pulmonary disease, which left a study population of 13 patients. The patients’ median age was 53 years (1st to 3rd interquartile range, 48 to 59 years), their median Simplified Acute Physiology Score II score was 62 (1st to 3rd interquartile range, 35 to 71) and their median Sequential Organ Failure Assessment score was 11 (1st to 3rd interquartile range, 8-13). All patients except one had ARDS of pulmonary origin. Eight patients had pneumonia, with six cases related to streptococcus pneumonia and two due to influenza (H1N1 virus). Two patients had aspiration, one had toxic shock syndrome and two had ARDS due to miscellaneous causes. No patient had abdominal hypertension or traumatic lung injury. Eleven patients required norepinephrine infusion. Respiratory parameters and blood gas analysis at the time of inclusion are reported in Table 1.

A significant increase in PaO_{2}/FiO_{2} ratio occurred after 15 hours of PP, from 70 mmHg (51 to 77) in the supine position to 99 mmHg in the prone (83 to 139) (\( P < 0.0001 \)) (Table 2). A significant decrease in PaCO_{2} was also observed, from 58 mmHg (52 to 60) to 52 mmHg (47 to 56) (\( P = 0.04 \)) (Table 2), with the lowest value occurring after nine hours of PP. As noted in Table 2, Pplat was significantly reduced (\( P = 0.0004 \)) and Crs improved (from 16 mL/cmH_{2}O (13 to 30) to 18 mL/cmH_{2}O (15 to 30); \( P = 0.02 \)). Finally, the VD_{alv}/V_{T} ratio was significantly reduced from 0.42 (0.35 to 0.47) to 0.40 (0.26 to 0.45), with the lowest value occurring after three hours in PP (hour 3) (0.31) (Table 2).

Seven patients were classified as "PaO_{2} responders" and six were classified as "PaO_{2} nonresponders" according to PaO_{2}/FiO_{2} ratio changes. No differences in VD_{alv}/V_{T} ratios or PaCO_{2} or Pplat alterations during PP were observed between groups (Table 3 and Figure 1), whereas Crs increased more in the responders (Table 3). Seven patients were also classified as "PaCO_{2} responders" and six as "PaCO_{2} nonresponders" according to the PaCO_{2} changes. However, when compared with the PaO_{2}/FiO_{2} classification, four patients were classified differently. As shown in Table 4 and Figure 2, VD_{alv}/V_{T}, PaO_{2}/FiO_{2}, PaCO_{2}, Pplat and Crs were significantly more altered in responders than in nonresponders. As shown in Figure 3, we found no correlation between changes in VD_{alv}/V_{T} and changes in PaO_{2}/FiO_{2} (\( P = 0.95 \)), whereas we found a negative correlation between changes in VD_{alv}/V_{T} and changes in Crs (\( r = 0.29, P = 0.03 \)).

As shown in Figure 4, estimated VD_{physiol}/V_{T} systematically underestimated measured VD_{physiol}/V_{T}, with a poor concordance correlation coefficient of 0.19 (95% confidence interval (95% CI) 0.091 to 0.28), a bias of 0.16 and an agreement between -0.05 and 0.37. Concerning changes in VD_{physiol}/V_{T} during PP, estimated VD_{physiol}/V_{T} had a concordance correlation coefficient of 0.51 (95% CI 0.32 to 0.66) (Figure 4).

**Discussion**

One of the objectives of our study was to describe alterations in VD_{alv} induced by PP. ARDS is characterized by a heterogeneous lung with the existence of a slow compartment [18,20], defined as areas available for, but partially or totally excluded from, ventilation due in part to a bronchiolar collapse [12,21]. In a previous study, we reported that PP may induce recruitment of this slow compartment, as suggested by its ability to counteract intrinsic PEEP and to decrease the expiratory time constant [12]. In the same study, we also reported

### Table 1 Respiratory parameters and blood gas analysis at inclusion

| Parameters                  | Median     | 1st to 3rd interquartile range |
|-----------------------------|------------|-------------------------------|
| LIS                         | 3.25       | 3 to 3.25                     |
| Tidal volume, mL/kg IDB     | 6.2        | 5.6 to 8.3                    |
| RR, breaths/minute          | 22         | 18 to 26                      |
| PEEP, cmH_{2}O              | 6          | 5 to 7                        |
| FiO_{2}, %                  | 90         | 90 to 100                     |
| Pplat, cmH_{2}O             | 27         | 26 to 28                      |
| PaO_{2}/FiO_{2}, mmHg       | 70         | 51 to 77                      |
| PaCO_{2}, mmHg              | 58         | 52 to 60                      |
| Crs, mL/cmH_{2}O            | 16         | 13 to 30                      |
| VD_{alv}/V_{T}              | 0.42       | 0.35 to 0.47                  |
| VD_{alv}, mL                | 159        | 95 to 236                     |

*Cr(s): compliance of the respiratory system; IDB: ideal body weight; LIS: lung injury score [32]; PaCO_{2}: partial pressure of arterial CO_{2}; PaO_{2}/FiO_{2}: ratio of partial pressure of arterial O_{2} to fraction of inspired O_{2}; PEEP: positive end-expiratory pressure; Pplat: plateau pressure; RR: respiratory rate; VD_{alv}/V_{T}: ratio of alveolar dead space to tidal volume.*
Table 2 Changes in respiratory mechanics, blood gas analysis and VD_{alv} in PP

| Parameters | Supine | PP H3 | PP H6 | PP H9 | PP H12 | PP H15 | P value |
|------------|--------|-------|-------|-------|--------|--------|---------|
| PaO2/FiO2, mmHg | 70 (51 to 77) | 91 (81 to 103) | 87 (73 to 139) | 90 (81 to 111) | 93 (83 to 137) | 99 (83 to 139) | < 0.0001 |
| PaCO2, mmHg | 58 (52 to 60) | 54 (51 to 58) | 54 (45 to 59) | 50 (47 to 59) | 54 (47 to 56) | 52 (47 to 56) | 0.04 |
| Pplat, cmH2O | 27 (26 to 28) | 25 (23 to 27) | 25 (22 to 26) | 25 (23 to 26) | 25 (21 to 26) | 25 (24 to 26) | 0.0004 |
| Crs, mL/cmH2O | 16 (13 to 30) | 18 (14 to 36) | 17 (15 to 40) | 18 (15 to 38) | 19 (15 to 38) | 18 (15 to 30) | 0.02 |
| VD_{alv}/VT | 0.42 (0.35 to 0.47) | 0.31 (0.28 to 0.41) | 0.35 (0.22 to 0.39) | 0.35 (0.26 to 0.39) | 0.39 (0.28 to 0.44) | 0.40 (0.26 to 0.45) | 0.007 |

*Crstitute compliance of the respiratory system; Pp: prone position, Pplat: plateau pressure, VD_{alv}/VT: ratio of alveolar dead space to tidal volume. H3, H6, H9, H12 and H15: 3, 6, 9, 12 and 15 hours of PP, respectively. P value is between supine position and PP. Data are expressed as medians (1st to 3rd interquartile range).

that PP leads to a decrease in PaCO2, suggesting diminution of VD_{alv} (alveolar dead space) [12]. Our present study demonstrates that PP may induce a decrease in VD_{alv}. It occurred from the third hour and was maintained throughout the PP session. VD_{alv} may be the consequence of nonperfused or poorly perfused lung areas in ventilated anterior areas, but also of a slow compartment partially excluded from ventilation. Our results suggest that PP induces functional lung recruitment, especially since decreases in VD_{alv} related to PP were associated with a decrease in Pplat and strongly correlated with improvement in compliance. Interestingly, in a previous study of 16 ARDS patients, Pelosi et al. [22] did not find a decrease in VD_{physiol} after 120 minutes in PP. One of the explanations for this discrepancy could be the different levels of PEEP in the two studies: 12.3 cmH2O in Pelosi et al.’s study and only 6 cmH2O in our study. However, Protti et al. [23], in a study of patients ventilated with a PEEP of 13 cmH2O, demonstrated a strong relation between lung recruitability and decreased PaCO2 related to PP. Pelosi et al. also did not report a decrease in Pplat in PP, as we found, but after returning patients to the supine position [22]. This could be explained by the fact that they used roll under the upper part of the chest wall, leading to a significant impairment in chest wall compliance [22], whereas we did not.

The most beneficial reported effect of PP is oxygenation improvement [24,25]. However, this better oxygenation can be due to (1) lung recruitment related to restoration of functional residual capacity [7] and improvement of the diaphragmatic movement in the posterior part [26-28] or (2) simply to an improvement in the ventilation/perfusion ratio due to a decreased hydrostatic gradient between the anterior and posterior parts of the lung [26,29]. Whereas the first mechanism is crucial, one can say that the second mechanism is less important. This is why the second objective of our study was to test whether the response to PP in terms of PaCO2 was physiologically more relevant than in terms of PaO2/FiO2 ratio.Gattinoni et al. [10] reported that an increase in PaO2/FiO2 ratio > 20 mmHg after six hours of PP is not predictive of the patient’s prognosis, whereas a decline in PaCO2 ≥1 mmHg is. In our present study, 7 of 13 patients were PaO2 responders (increased PaO2/FiO2 ratio > 20 mmHg after 15 hours of PP). However, changes in Pplat, PaCO2 and VD_{alv} did not differ between PaO2 responders and PaO2 nonresponders. On the other hand, 7 of 13 patients were PaCO2 responders (decreased PaCO2 > 2 mmHg after 15 hours of PP). PaCO2 responders had a significant decrease in Pplat and VD_{alv}, as well as a significant increase in oxygenation and compliance, compared with nonresponders. Our results are in accordance with a recent study of 32 ARDS patients [23], in which the investigators reported that PaCO2 variation induced by PP, and not PaO2/FiO2 variation, is associated with lung recruitability. Interestingly, in our study, changes in VD_{alv} were not correlated with changes in oxygenation but were strongly correlated with changes in compliance of the respiratory system.

An unexpected result of our work concerns the change over time of respiratory mechanics, blood gas analysis and VD_{alv}. For many years, our PP protocol has been to turn patients to PP for up to 15 to 18 hours per day. In a recent study, we demonstrated that PP sessions that lasted 18 hours/day were independently associated with survival [31]. In the present study, the maximum effect of PP for VD_{alv}, PaCO2 and Pplat occurred six to nine hours after turning patients to PP. Later the effect seemed to be a decline. How this affects the effect of PP on patient prognosis remains to be elucidated.

The second objective of our study was to validate a recently proposed method to evaluate the VD_{physiol}/VT ratio [14]. The method is based on CO2 production calculated from the Harris-Benedict equation [19] and on the expired minute ventilation. Siddiki et al. [14] reported that it was associated with mortality in acute lung injury patients in a dose-response manner and proposed its routine use to estimate VD_{physiol}/VT. However, they did not report any comparison with measured VD_{physiol}/VT. In the present study, we have demonstrated that this method significantly
Table 3 Changes in respiratory mechanics, blood gas analysis and \( V_{\text{Dalv}} \) in PaO\(_2\) responders (n = 7) and PaO\(_2\) nonresponders (n = 6)\(^a\)

| Parameters          | Supine | PP H3       | PP H6       | PP H9       | PP H12      | PP H15       | \( P \) value |
|---------------------|--------|-------------|-------------|-------------|-------------|-------------|--------------|
| \( \text{PaO}_2/\text{FiO}_2, \text{mmHg} \) | R   | 51 (48 to 69) | 91 (86 to 112) | 94 (83 to 142) | 97 (86 to 126) | 98 (93 to 142) | 108 (99 to 142) | 0.0003       |
|                     | NR    | 77 (76 to 81) | 91 (82 to 99) | 79 (73 to 88) | 84 (82 to 99) | 84 (82 to 87) | 89 (82 to 97) |              |
| \( V_{\text{Dalv}}/V_T \) | R   | 0.43 (0.41 to 0.47) | 0.35 (0.31 to 0.46) | 0.35 (0.29 to 0.41) | 0.38 (0.23 to 0.42) | 0.40 (0.31 to 0.40) | 0.41 (0.32 to 0.45) | 0.31          |
|                     | NR    | 0.42 (0.36 to 0.50) | 0.35 (0.28 to 0.47) | 0.31 (0.22 to 0.43) | 0.32 (0.27 to 0.44) | 0.36 (0.28 to 0.51) | 0.35 (0.27 to 0.53) |              |
| \( \text{PaCO}_2, \text{mmHg} \) | R   | 58 (54 to 60) | 52 (51 to 58) | 51 (47 to 57) | 49 (48 to 53) | 54 (48 to 55) | 51 (47 to 55) | 0.14          |
|                     | NR    | 55 (52 to 60) | 56 (51 to 62) | 57 (48 to 62) | 55 (48 to 60) | 54 (48 to 63) | 53 (48 to 58) |              |
| \( \text{Pplat}, \text{cmH}_2\text{O} \) | R   | 27 (27 to 30) | 25 (22 to 26) | 24 (23 to 26) | 24 (23 to 26) | 24 (22 to 26) | 24 (22 to 26) | 0.27          |
|                     | NR    | 27 (24 to 28) | 25 (24 to 28) | 25 (22 to 26) | 25 (23 to 27) | 26 (22 to 26) | 26 (25 to 26) |              |
| \( \text{Crs}, \text{mL/cmH}_2\text{O} \) | R   | 16 (13 to 28) | 19 (16 to 37) | 18 (16 to 38) | 18 (16 to 35) | 20 (17 to 35) | 19 (17 to 33) | 0.023         |
|                     | NR    | 19 (14 to 31) | 21 (14 to 33) | 21 (14 to 36) | 21 (14 to 34) | 19 (15 to 34) | 19 (15 to 34) |              |

\(^a\)Crs: compliance of the respiratory system; NR: nonresponders; PP: prone position; Pplat: plateau pressure; R: responders; \( V_{\text{Dalv}}/V_T \): ratio of alveolar dead space to tidal volume. \( P \) values represent comparison of changes between responders and nonresponders. H3, H6, H9 and H15: 3, 6, 9, 12 and 15 hours of PP, respectively. Responders are defined as patients whose \( \text{PaO}_2/\text{FiO}_2 \) increased > 20 mmHg after 15 hours of PP.
Table 4 Changes in respiratory mechanics, blood gas analysis and VD_{alv} in PaCO$_2$ responders ($n=7$) and PaCO$_2$ nonresponders ($n=6$)$^a$

| Parameters                  | Median | 1st to 3rd interquartile range | Median | 1st to 3rd interquartile range | Median | 1st to 3rd interquartile range | Median | 1st to 3rd interquartile range | Median | 1st to 3rd interquartile range | Median | 1st to 3rd interquartile range | Median | 1st to 3rd interquartile range | $P$ values |
|-----------------------------|--------|--------------------------------|--------|--------------------------------|--------|--------------------------------|--------|--------------------------------|--------|--------------------------------|--------|--------------------------------|--------|--------------------------------|------------|
| PaCO$_2$, mmHg              | R 58   | (55 to 59)                     | 57     | (51 to 57)                     | 54     | (44 to 57)                     | 50     | (46 to 53)                     | 50     | (46 to 55)                     | 50     | (47 to 52)                     | 0.005   |                                |
|                            | NR 56  | (49 to 60)                     | 52     | (49 to 60)                     | 54     | (49 to 62)                     | 54     | (49 to 60)                     | 56     | (51 to 62)                     | 57     | (49 to 59)                     |         |                                |
| VD$_{alv}$/VT               | R 0.40 | (0.37 to 0.45)                 | 0.31   | (0.29 to 0.46)                 | 0.23   | (0.31 to 0.40)                 | 0.26   | (0.26 to 0.42)                 | 0.28   | (0.24 to 0.44)                 | 0.28   | (0.23 to 0.43)                 | 0.005   |                                |
|                            | NR 0.45| (0.42 to 0.51)                 | 0.38   | (0.32 to 0.47)                 | 0.38   | (0.35 to 0.43)                 | 0.37   | (0.33 to 0.45)                 | 0.42   | (0.39 to 0.51)                 | 0.44   | (0.39 to 0.54)                 |         |                                |
| PaO$_2$/FiO$_2$, mmHg       | R 70   | (59 to 78)                     | 103    | (96 to 136)                    | 138    | (83 to 146)                    | 111    | (91 to 156)                    | 136    | (95 to 142)                    | 139    | (103 to 148)                   | 0.0001  |                                |
|                            | NR 63  | (44 to 76)                     | 83     | (80 to 89)                     | 79     | (73 to 88)                     | 83     | (74 to 88)                     | 84     | (62 to 87)                     | 89     | (70 to 97)                     |         |                                |
| Pplat, cmH$_2$O             | R 27   | (24 to 27)                     | 23     | (22 to 25)                     | 23     | (20 to 25)                     | 23     | (22 to 25)                     | 21     | (21 to 25)                     | 23     | (21 to 25)                     | 0.002   |                                |
|                            | NR 28  | (26 to 28)                     | 26     | (24 to 28)                     | 26     | (25 to 28)                     | 26     | (25 to 28)                     | 26     | (25 to 26)                     | 26     | (25 to 26)                     |         |                                |
| Crs, mL/cmH$_2$O            | R 28   | (15 to 30)                     | 30     | (18 to 36)                     | 34     | (17 to 41)                     | 32     | (18 to 38)                     | 32     | (19 to 39)                     | 31     | (18 to 39)                     | 0.002   |                                |
|                            | NR 15  | (12 to 20)                     | 15     | (13 to 24)                     | 15     | (13 to 23)                     | 15     | (13 to 23)                     | 15     | (14 to 22)                     | 15     | (14 to 22)                     |         |                                |

$^a$Crs: compliance of the respiratory system; NR: nonresponders; PP: prone position; Pplat: plateau pressure; R: responders; VD$_{alv}$/VT: ratio of alveolar dead space to tidal volume. $P$ value represents comparison of changes between responders and nonresponders. H$_3$, H$_6$, H$_9$, H$_12$ and H$_15$: 3, 6, 9, 12 and 15 hours of PP, respectively. Responders are defined as patients whose PaCO$_2$ decreased > 2 mmHg after 15 hours of PP.

Charron et al. Critical Care 2011, 15:R175
http://ccforum.com/content/15/4/R175
Page 6 of 10
underestimates $VD_{physiol}/VT$, rendering it not accurate enough to assess the degree of lung injury. Interestingly, changes in estimated $VD_{physiol}/VT$ during PP appeared better correlated with changes in measured $VD_{physiol}/VT$ and could be proposed in the future in this field. Siddiki et al. [14] proposed the method in the context of a much larger series than ours and in patients with less severe ARDS, rendering it difficult to draw any definitive conclusions.

Our work is limited by the small number of patients included. This is a consequence of our routine protocol, which strictly restricts PP to patients with the most severe ARDS, that is, those with a $PaO_2/FiO_2$ ratio $< 100$ mmHg after 48 hours of ventilation. This also explains why it is not possible to link our results to outcomes. However, despite this limitation, we consider our results relevant from a physiological point of view.

Conclusions

In conclusion, our study demonstrates that PP induces a decrease in $PaCO_2$ and $VD_{alv}$. This is related to an improvement in respiratory mechanics, with a decrease in $Pplat$ and an increase in compliance. Testing the response to PP appeared to be physiologically more relevant when using $PaCO_2$ changes rather than $PaO_2/FiO_2$ changes. How this may affect management at the bedside remains to be studied. Estimated $VD_{physiol}/VT$ ratios systematically underestimated measured $VD_{physiol}/VT$ ratios.

Key messages

- PP induced a decrease in $VD_{alv}/VT$, which was correlated with an improvement in respiratory mechanics.
- Defining the respiratory response to PP appeared more relevant when using $PaCO_2$ changes rather than $PaO_2/FiO_2$ changes.
Figure 2 Alterations during PP in PaO₂/FiO₂, PaCO₂, plateau pressure (Pplat) and alveolar dead space (VDalv/VT) in responders (solid lines) and nonresponders (dotted lines) according to PaCO₂ changes. "PaCO₂ responders" were defined by a decrease in PaCO₂ > 2 mmHg after 15 hours of PP (PP H15). Shown are box and whisker plots. Median = horizontal line inside the box; upper and lower quartiles = whisker plot. Boxes and triangles represent values higher or lower than the upper or lower quartiles. *P < 0.05 for comparison of changes in responders versus nonresponders. PP: prone position.

Figure 3 Correlation between changes in alveolar dead space (ΔVDalv/VT) and changes in compliance of the respiratory system (ΔCrs, left) or in PaO₂/FiO₂ (ΔPaO₂/FiO₂, right) at each time of the study when compared with the supine position.
Estimated $V_{D\text{physiol}}/V_T$ using the Harris-Benedict equation systematically underestimated measured $V_{D\text{physiol}}/V_T$.

**Abbreviations**

ARDS: acute respiratory distress syndrome; $P_{\text{PECO2}}$: mixed expired $PCO_2$; PEEP: positive end-expiratory pressure; $P_{\text{ETCO2}}$: end-tidal $PCO_2$; PP: prone position; $P_{\text{PLat}}$: plateau pressure; $VD_{\text{alv}}$: alveolar dead space; $V_{D\text{physiol}}$: physiological dead space.

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**Authors’ contributions**

CC contributed to the acquisition of data, performed the data analysis, participated in the design of the study and the interpretation of the data, and wrote the manuscript. XR contributed to the acquisition of data, performed the data analysis and participated in the design of the study and the interpretation of the data. AVB performed the data analysis, participated in the design of the study and the interpretation of the data, and wrote the manuscript. FJ participated in the design of the study and the interpretation of the data. All authors read and approved the final manuscript.

**Competing interests**

The authors declare that they have no competing interests, except that of receiving funds from Maquet SA (Ardon, France) to support the cost of publication.

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