End-tidal to arterial PCO₂ ratio: a bedside meter of the overall gas exchanger performance

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Abstract

Background: The physiological dead space is a strong indicator of severity and outcome of acute respiratory distress syndrome (ARDS). The “ideal” alveolar PCO₂, in equilibrium with pulmonary capillary PCO₂, is a central concept in the physiological dead space measurement. As it cannot be measured, it is surrogated by arterial PCO₂ which, unfortunately, may be far higher than ideal alveolar PCO₂, when the right-to-left venous admixture is present. The “ideal” alveolar PCO₂ equals the end-tidal PCO₂ (PETCO₂) only in absence of alveolar dead space. Therefore, in the perfect gas exchanger (alveolar dead space = 0, venous admixture = 0), the PETCO₂/PaCO₂ is 1, as PETCO₂, PaCO₂ and PaCO₂ are equal. Our aim is to investigate if and at which extent the PETCO₂/PaCO₂, a comprehensive meter of the “gas exchanger” performance, is related to the anatomo physiological characteristics in ARDS.

Results: We retrospectively studied 200 patients with ARDS. The source was a database in which we collected since 2003 all the patients enrolled in different CT scan studies. The PETCO₂/PaCO₂, measured at 5 cmH₂O airway pressure, significantly decreased from mild to mild–moderate moderate–severe and severe ARDS. The overall populations was divided into four groups (~ 50 patients each) according to the quartiles of the PETCO₂/PaCO₂ (lowest ratio, the worst = group 1, highest ratio, the best = group 4). The progressive increase PETCO₂/PaCO₂ from quartile 1 to 4 (i.e., the progressive approach to the “perfect” gas exchanger value of 1.0) was associated with a significant decrease of non-aerated tissue, inohomogeneity index and increase of well-aerated tissue. The respiratory system elastance significantly improved from quartile 1 to 4, as well as the PaO₂/FiO₂ and PaCO₂. The improvement of PETCO₂/PaCO₂ was also associated with a significant decrease of physiological dead space and venous admixture. When PEEP was increased from 5 to 15 cmH₂O, the greatest improvement of non-aerated tissue, PaO₂ and venous admixture were observed in quartile 1 of PETCO₂/PaCO₂ and the worst deterioration of dead space in quartile 4.

Conclusion: The ratio PETCO₂/PaCO₂ is highly correlated with CT scan, physiological and clinical variables. It appears as an excellent measure of the overall “gas exchanger” status.

Keywords: PETCO₂, Acute respiratory distress syndrome, Severity, Monitoring

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Introduction

The physiological dead space, which includes both the anatomical and alveolar dead space, is a strong indicator of severity and outcome of acute respiratory distress syndrome (ARDS) [1, 2]. The computation of the physiological dead space is based on the dilution of the ideal alveolar PCO₂ (PACO₂). This ideal PCO₂, introduced by Riley, cannot be measured directly and it is assumed to be equal to the capillary PCO₂ (PcCO₂) [3] which leaves the ventilated/perfused pulmonary units [4]. As the PcCO₂ cannot be measured directly, the arterial PCO₂ (PaCO₂) is assumed to be its surrogate. Therefore, the assumption on which the physiological dead space is computed is that PACO₂, PcCO₂ and PaCO₂ have identical values. While this is nearly correct in the normal lung, in the diseased lung, as in ARDS, the PaCO₂ is higher than PcCO₂ and PACO₂ due to the presence of venous admixture (in Riley’s model, the fraction of blood which flows through “non-aerated lung regions” maintaining the same PO₂ and PCO₂ of the mixed venous blood). Consequently, PaCO₂ is the result of the weighted average of blood coming from the ideal compartment (PcCO₂) and of mixed venous PCO₂ (PvCO₂) [5]. It is therefore easy to understand why the venous admixture, i.e., a variable which measures the oxygenation impairment, has an effect on variables which describe the wasted ventilation. To compute the alveolar dead space, we may assume that the end-tidal CO₂ (PETCO₂) is representative of the actual alveolar gases. In this case, the PETCO₂ is lower than the PACO₂ depending on the amount of alveolar dead space.

The measurement of the PETCO₂ is easily performed in intensive care. Therefore, the alveolar dead space may be derived as follows:

\[
\text{Alveolar dead space} = 1 - \frac{\text{EtCO}_2}{\text{PaCO}_2}.
\]

As the alveolar dead space, as measured by the equation above, depends both on the “true” alveolar dead space and on the extent of the venous admixture, the PETCO₂/PaCO₂ ratio may be seen as a direct overall meter of the gas exchanger performance in a scale from 0 to 1. Indeed, a PETCO₂/PaCO₂ ratio equal to 1 represents the perfect gas exchanger, being, in this condition, the alveolar dead space and the venous admixture equal to 0. The presence of alveolar dead space and/or venous admixture at different extent would progressively decrease this ratio from the unity, reflecting the progressive deterioration of the gas exchanger in its two components, oxygenation and CO₂ removal.

The aim of this study is to investigate whether the PETCO₂/PaCO₂, easily measurable at the bedside, can be an adequate tool to assess the physio-anatomical condition of the gas exchanger.

Materials and methods

Study population

This study population consisted of 200 patients, studied from 2003 and 2016 in two university hospitals (Policlinico Milano, Milan, Italy and University Medical Center Göttingen, Göttingen, Germany). All patients suffered from ARDS according to the Berlin criteria [6]. The ethics committee was notified and permission to use the data was granted (Göttingen Antragsnummer 14/12/12).
Recorded variables
For each patient, the CT scans were acquired at 5, 15 and 45 cmH2O of airway pressure. We reported the anatomical variables derived from the CT quantitative analysis: namely, hyperinflated (−1000/−900 HU), well aerated (−900/−500 HU), poorly inflated (−500/−200 HU) and non-aerated (−100/+100 HU) tissues [7, 8]. Recruitability was computed as the fraction of non-aerated tissue at 5 cmH2O minus the fraction of non-aerated tissue at 45 cmH2O [9]. Lung inhomogeneity was computed on a voxel-by-voxel basis, as the ratio of gas content between acinar size lung units and surrounding lung units [10]. A ratio equal to 1 would indicate perfect homogeneity, a ratio of 2 would indicate an inflation of the central lung unit double than the surrounding units. At 5 and 15 cmH2O of airway pressure, we collected the mechanical ventilation settings and respiratory mechanics variables (tidal volume, respiratory rate, alveolar ventilation, and respiratory system elastance), hemodynamics (systolic and diastolic arterial blood pressures, central venous pressure, heart rate, ScvO2 and arteriovenous O2 content difference) and gas exchange variables (PETCO2, PaO2, PaCO2, PaO2/PaCO2 ratio, SaO2, venous admixture (Qs/Qt), physiological dead space fraction (Vd/Vt)). Tidal volume and FiO2 were kept constant at these two PEEP levels. The volumetric capnography measurements were performed with COSMO (Respironics Novametrix, Wallingford, USA).

The first analysis was done grouping the patients according to their ARDS severity (mild, moderate–mild, moderate–severe, severe) [11]. An additional analysis was performed dividing the patients into four groups (~50 patients per group) based on the equal-count quartiles of their PETCO2/PaCO2 ratios determined during ventilation at 5 cmH2O of PEEP. For details regarding the calculated variables, please refer to Additional File 1.

Statistical methods
The normal distribution of the data was assessed by the Shapiro–Wilk test. Physiological, CT scan variables and PETCO2/PaCO2 ratio were compared among groups with one-way analysis of variance or Kruskal–Wallis test as appropriate. Multiple comparisons were performed with Bonferroni correction. Two tailed, p values < 0.05 were considered statistically significant. These statistical analyses were performed with R (R Foundation for Statistical Computing version 3.7).

Results
The main anthropometric and the physiological characteristics of the study population obtained at 5 cmH2O of PEEP are presented in Table 1. Figure 1, panel A shows the PETCO2/PaCO2 ratio as a function of ARDS severity. The ratio decreased linearly with increasing severity. In Fig. 2, we report the mortality rate observed in the quartiles of PETCO2/PaCO2 ratio.

Table 2 gives the quantitative CT scan variables obtained at 5 cmH2O PEEP stratified as quartiles of PETCO2/PaCO2. As shown, the well-aerated tissue increased with the PETCO2/PaCO2 ratio. The poorly inflated, non-aerated tissue, the inhomogeneity index [10] and recruitability all significantly decrease throughout the PETCO2/PaCO2 quartiles. As shown in Table 3, the PETCO2/PaCO2 ratio was strongly associated with respiratory
Table 1  Baseline characteristics among ARDS groups

| ARDS severity | Mild | MM  | MS  | Severe | P         |
|---------------|------|-----|-----|--------|-----------|
| Number of patients | N = 33 | N = 54 | N = 70 | N = 43 |
| Age           | 59.0 [43.0; 69.0] | 66.0 [53.2; 70.0] | 61.0 [45.2; 70.5] | 63.0 [52.0; 72.5] | 0.382 |
| Sex           | 0.905 |
| Female        | 13 (39.4) | 16 (29.6) | 23 (32.9) | 13 (30.2) |
| Male          | 20 (60.6) | 38 (70.4) | 46 (65.7) | 30 (69.8) |
| BMI           | 25.6 [22.2; 28.0] | 25.0 [23.1; 27.8] | 24.2 [21.9; 26.7] | 26.1 [22.2; 32.0] | 0.107 |
| SAPS II       | 41.5 [27.8; 46.2] | 40.0 [31.0; 54.2] | 39.0 [33.0; 52.0] | 43.0 [35.0; 54.5] | 0.416 |
| Tidal volume, ml/kg | 540 [500; 600] | 550 [480; 600] | 502 [432; 560] | 500 [428; 590] | 0.082 |
| Respiratory Rate, bpm | 15.0 [12.0; 18.0] | 15.0 [13.0; 18.0] | 18.0 [14.0; 20.0] | 18.0 [15.0; 20.0] | 0.110 |
| Plateau pressure, cmH2O | 19.0 [16.1; 21.3] | 17.0 [14.5; 20.0] | 18.5 [16.3; 21.0] | 18.0 [15.9; 21.0] | 0.121 |
| Ers, cmH2O/L | 23.1 [17.6; 29.2] | 22.3 [19.1; 25.6] | 26.9 [21.4; 31.7] | 26.9 [21.0; 33.2] | 0.005 |
| PaO2/FiO2 ratio | 230 [218; 255] | 173 [160; 183] | 122 [108; 139] | 79.6 [66.7; 87.4] | < 0.001 |
| PaO2, mmHg | 96.2 [83.0; 109] | 75.2 [65.8; 81.9] | 67.2 [62.0; 71.9] | 60.0 [54.0; 71.3] | < 0.001 |
| FiO2 | 0.40 [0.40; 0.45] | 0.40 [0.40; 0.50] | 0.55 [0.50; 0.60] | 0.85 [0.70; 0.92] | < 0.001 |
| PaCO2, mmHg | 40.9 [38.2; 44.2] | 42.9 [38.2; 49.8] | 44.5 [39.7; 50.3] | 52.0 [43.2; 55.0] | < 0.001 |
| Arterial pH | 7.39 [7.35; 7.46] | 7.39 [7.35; 7.43] | 7.38 [7.31; 7.42] | 7.36 [7.30; 7.40] | 0.024 |
| ARDS causes, no. (%): | | | | | |
| Aspiration   | 1 (3.03) | 5 (9.26) | 7 (10.0) | 2 (4.65) |
| Other        | 5 (15.2) | 5 (9.26) | 11 (15.7) | 5 (11.6) |
| Pneumonia    | 8 (24.2) | 21 (38.9) | 35 (50.0) | 28 (65.1) |
| Sepsis       | 15 (45.5) | 18 (33.3) | 14 (20.0) | 7 (16.3) |
| Trauma       | 4 (12.1) | 5 (9.26) | 3 (4.29) | 0 (0.00) |

* for one-way Anova and Kruskal–Wallis test. MM mild–moderate, MS moderate–severe, SAPS Simplified Acute Physiology Score, BMI body mass index, Ers respiratory system elastance

Fig. 1  Panel A: P_{ETCO2}/PaCO2 ratio among acute respiratory distress syndrome (ARDS) groups divided in Severe, Moderate–Severe (MS), Moderate–Mild (MM) and Mild groups at 5 cmH2O of positive end-expiratory pressure (PEEP). *p < 0.001, Mann–Whitney test
system elastance, alveolar ventilation and VCO₂. These variables improved when the \( P_{ET\,CO_2}/PaCO_2 \) ratio approached unity. The gas exchange variables under the same conditions are presented in Table 4. As shown, the \( PaCO_2 \) progressively decreased with the concurrent increase of \( P_{ET\,CO_2}/PaCO_2 \) ratio, while the \( PaO_2/FiO_2 \) ratio and saturation increased. Both venous admixture and dead space significantly decreased throughout the \( P_{ET\,CO_2}/PaCO_2 \) quartiles.

### \( P_{ET\,CO_2}/PaCO_2 \) ratio at different airway pressures

Figure 3 illustrates how lung tissue aeration changed in the different \( P_{ET\,CO_2}/PaCO_2 \) ratio quartiles when airway pressure was increased from 5 to 15 and 45 cmH₂O. The amount of non-aerated tissue decreased steadily from 5 to 45 cmH₂O in all quartiles, while the amount of normally aerated tissue increased.
In Table 5, we report the changes of CT scan, respiratory mechanics and gas exchange variables through the quartiles of P_{ET}CO_{2}/PaCO_{2} when PEEP was increased from 5 to 15 cmH_{2}O. As shown, the greatest improvement of non-aerated tissue, PaO_{2} and venous admixture were observed in quartile 1 of P_{ET}CO_{2}/PaCO_{2} and the worst deterioration of dead space in quartile 4.

Discussion
In this study, we found that the P_{ET}CO_{2}/PaCO_{2} ratio is strongly associated with most of the morphological and physiological characteristics of ARDS, resulting as an easy and appealing measure of the status and the performance of the lung.
Fig. 3 Portions of lung tissue classified as not aerated, poorly aerated, normally aerated and hyperinflated among $\text{PETCO}_2/\text{PaCO}_2$ ratio quartiles to the response of step increase of PEEP at 5, 15 and 45 cmH$_2$O. The asterisk denotes $p < 0.001$ among the portions of tissue throughout $\text{PETCO}_2/\text{PaCO}_2$ ratio quartiles for Mann–Whitney test. The dollar denotes $p < 0.001$ among portions of lung tissue to the response to PEEP for Wilcoxon test.

Table 5 Changes in CT scan, respiratory mechanics and gas exchange variables in response to PEEP increase from 5 to 15 cmH$_2$O among $\text{PETCO}_2/\text{PaCO}_2$ ratio quartiles

| $\text{PETCO}_2/\text{PaCO}_2$ quartiles | I        | II       | III      | IV       | $p$ value |
|----------------------------------------|----------|----------|----------|----------|-----------|
| Ranges                                 | [0.4160; 0.709] | [0.709; 0.796] | [0.796; 0.886] | [0.886; 1.16] |           |
| Number of patients                     | $N = 52$ | $N = 51$ | $N = 48$ | $N = 49$ |           |
| $\Delta$ Lung volume, mL               | 579 [417; 775] | 602 [436; 719] | 588 [467; 735] | 586 [443; 823] | 0.98      |
| $\Delta$ Lung gas, mL                  | 546 [451; 816] | 598 [413; 711] | 551 [456; 700] | 564 [395; 810] | 0.99      |
| $\Delta$ Lung tissue, g                | 10.9 [−42; 53] | 26 [−5.1; 53] | 20 [6.4; 43.4] | 22.6 [−23; 56] | 0.87      |
| $\Delta$ Not aerated tissue, mL        | −170 [−282; −78] | −87.7 [−160; −42.3] | −70.1 [−124.4; −40.3] | −23.5 [−91.5; 0.3] | < 0.001 |
| $\Delta$ Poorly aerated tissue, mL     | 7.3 [−50; 171] | −42.4 [−97.1; 14.1] -37.2 [−105.7; 15] | −73 [−112; 17] | 0.02      |
| $\Delta$ Normally aerated tissue, mL   | 140 [82; 241] | 153 [68; 226] | 143 [94; 197] | 134 [87; 199] | 0.96      |
| $\Delta$ Hyperinflated tissue, mL      | 1.5 [0.17; 4] | 0.85 [0.13; 1.8] | 0.5 [0.04; 3.44] | 0.5 [0.11; 5.4] | 0.92      |
| $\Delta$ $Q_s/Q_t$                    | −0.13 [−0.2; −0.08] | −0.08 [−0.13; −0.04] | −0.08 [−0.14; −0.01] | −0.07 [−0.13; −0.03] | 0.01      |
| $\Delta$ $V_d/V_t$                     | 0.01 [0.0; 0.03] | 0.02 [−0.01; 0.04] | 0.01 [0.0; 0.04] | 0.03 [0.02; 0.06] | 0.03      |
| $\Delta$ $\text{PaO}_2$, mmHg         | 32 [18.5; 46] | 23 [10.2; 58.4] | 21.2 [4.3; 36] | 16 [4.4; 28] | 0.01      |
| $\Delta$ $E_{RS}$, cmH$_2$O/L         | 0.07 [−4.0; 3.4] | −0.2 [−2.2; 4.1] | 0.3 [−1.1; 2.4] | 0.0 [−2.5; 2.2] | 0.85      |

Differences were computed as the variable at PEEP 15 cmH$_2$O minus the variable at PEEP 5 cmH$_2$O. Variables are expressed in medians and IQR. $p$ for Mann–Whitney test. $Q_s/Q_t$: shunt fraction; $V_d/V_t$: dead space fraction; $P/F$: $\text{PaO}_2$/FiO$_2$ ratio; $E_{RS}$: respiratory system elastance; SvO$_2$: central venous oxygen saturation; $\text{PETCO}_2$: end-tidal CO$_2$. 

The physiological meaning of the $\text{PETCO}_2/\text{PaCO}_2$ ratio may be easily understood when one considers CO$_2$ kinetics through the anatomical space from the pulmonary capillaries to the airway opening. Figure 4 shows that, in the ideal lung, $\text{PaCO}_2$ is equal to $\text{PcCO}_2$ (venous admixture fraction = 0). Similarly, $\text{PETCO}_2$ is equal to $\text{PACO}_2$ (alveolar dead space fraction = 0). Therefore, in this “ideal” setting the ratio of $\text{PETCO}_2$ to $\text{PaCO}_2$ would be 1. This ratio will depart progressively from 1 in the presence of a venous admixture and/or alveolar dead space. Consequently, the $\text{PETCO}_2/\text{PaCO}_2$ ratio is a rather unspecific variable, as it is linked to both CO$_2$ and O$_2$ exchange impairment, but for the same reason it may give an immediate warning of an overall impairment of gas exchange. The potential role of monitoring the $\text{PETCO}_2/\text{PaCO}_2$ ratio in order to follow and understand the disease course is emphasized by its close association with the overall severity of ARDS and the mortality.

This is not really surprising, as almost all variables characterizing the ARDS are related to the $\text{PETCO}_2/\text{PaCO}_2$ ratio. With regard to the morphological variables, the $\text{PETCO}_2/\text{PaCO}_2$ ratio is related to the extent of non-aerated and aerated tissue, the size of the baby lung as well as to the extent of recruitability. No other gas exchange variable exhibits such a large number of correlations with lung morphology. Indeed, venous admixture and physiological dead space were only related to the non-aerated
tissue and to the normally aerated tissues, respectively. Therefore, the relative non-specificity of the $P_{ET}\text{CO}_2/Pa\text{CO}_2$ ratio, which reflects the overall gas exchange (both for oxygen and carbon dioxide), explains its correlation with all the morphological components of the lungs, of which some are more related to oxygen while others are more related to CO$_2$ exchange. On the other hand, the linkage between the $P_{ET}\text{CO}_2/Pa\text{CO}_2$ ratio, alveolar dead space and venous admixture accounts for its high sensitivity in detecting an overall impairment in gas exchange. The $P_{ET}\text{CO}_2/Pa\text{CO}_2$ ratio was inversely associated with respiratory system elastance and directly correlated with alveolar ventilation, while no relationship was found with hemodynamic variables. The low specificity but high sensitivity of the $P_{ET}\text{CO}_2/Pa\text{CO}_2$ ratio to reflect an overall impairment of gas exchange is strikingly shown by the correlation we found with the gas exchange variables. Indeed, as shown in Table 4, all measured or computed variables related either with oxygenation or carbon dioxide clearance were strongly associated with the $P_{ET}\text{CO}_2/Pa\text{CO}_2$ ratio. Therefore, an altered $P_{ET}\text{CO}_2/Pa\text{CO}_2$ ratio, as such, is associated both with the morphology and, the function of gas exchange, suggesting it as a sensitive, easily available marker, of changes in lung conditions. Interestingly, we found that the VCO$_2$ significantly increased throughout the quartiles. We believe that this is due to an improved alveolar ventilation, with greater elimination of carbon dioxide. Indeed, the low VCO$_2$ measured in quartile 1 possibly represents only a fraction of the metabolic CO$_2$ production which is partly retained. Increased alveolar ventilation throughout the quartiles leads to a normalization or even a higher than normal (metabolic) CO$_2$ clearance [12].

The $P_{ET}\text{CO}_2/Pa\text{CO}_2$ ratio may be also considered to anticipate the PEEP response. The PEEP response in gas exchange is a balance between the decrease of venous admixture and increase in alveolar dead space. The venous admixture decrease could either be due to recruitment, better mechanical conditions of pulmonary units already open, or to a decrease in cardiac output, while the alveolar dead space increase may be due to an overdistention of pulmonary units relative to their perfusion. An increase in alveolar dead space would tend to reduce $P_{ET}\text{CO}_2$, while a decrease of right-to-left venous admixture would tend to reduce PaCO$_2$. The $P_{ET}\text{CO}_2/Pa\text{CO}_2$ ratio is related to the two variables, and its changes may reflect these physiopathological mechanisms. Moreover, we showed that patients starting with a lower $P_{ET}\text{CO}_2/Pa\text{CO}_2$ ratio had a more favorable response to PEEP.

The $P_{ET}\text{CO}_2/Pa\text{CO}_2$ ratio is obviously related to the physiological dead space, although it may be considered a “positive variable” (greater the ratio, better the gas exchange) rather than “negative” (greater the dead space, worse the gas exchange). Indeed, any change of the $P_{ET}\text{CO}_2/Pa\text{CO}_2$ ratio toward the value of 1 indicates an improvement of the whole gas exchanger condition, which may then be easily monitored after any manoeuvre on the respiratory system, change of ventilator setting and pharmacological intervention. Indeed, the daily monitoring of this easy to use variable may show a progressive increase towards the unity, giving some evidence that the lung conditions are improving. In contrast, any change of this ratio towards lower values immediately indicates an overall decrease of the gas exchange performances. The $P_{ET}\text{CO}_2/Pa\text{CO}_2$ ratio also helps the clinician to be more aware of the dynamics of CO$_2$. Too often oxygenation represents the concern at the bedside of an ARDS patient, but it is only considering
also PaCO₂ that one can have a more complete picture of the lung structure and function [13]. Finally, the \( P_{ET}CO_2/\text{PaCO}_2 \) ratio finds in its strength as an overall meter of gas exchange impairment also its weakness. Indeed, to fully understand the various components of the gas exchange alteration, both dead space and venous admixture must be measured.

**Conclusions**
In this study, we evaluated the \( P_{ET}CO_2/\text{PaCO}_2 \) ratio as a clinical tool to comprehensively evaluate the gas exchange lung function. The ratio was associated with most of the physiological variables that can be measured at the bedside and, therefore, it can represent a useful parameter for the daily monitoring of the ARDS patient.

**Supplementary Information**
The online version contains supplementary material available at https://doi.org/10.1186/s40635-021-00377-9.

**Additional file 1.** Additional methods and formulas.

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**Authors’ contributions**
Conception and design: MB, MQ, DC, LG. Data collection: FR, MB, MMP, IS, SG. Analysis and interpretation: KM, MMQ, DC. Drafting the manuscript for important intellectual content: all authors. All authors read and approved the final manuscript.

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**Consent for publication**
All authors have approved the manuscript.

**Competing interests**
The authors have no conflict of interest to disclose.

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