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# End-tidal to arterial $\text{PCO}_2$ 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  $\text{PCO}_2$ , in equilibrium with pulmonary capillary  $\text{PCO}_2$ , is a central concept in the physiological dead space measurement. As it cannot be measured, it is surrogated by arterial  $\text{PCO}_2$  which, unfortunately, may be far higher than ideal alveolar  $\text{PCO}_2$ , when the right-to-left venous admixture is present. The “ideal” alveolar  $\text{PCO}_2$  equals the end-tidal  $\text{PCO}_2$  ( $P_{\text{ETCO}_2}$ ) only in absence of alveolar dead space. Therefore, in the perfect gas exchanger (alveolar dead space = 0, venous admixture = 0), the  $P_{\text{ETCO}_2}/\text{PaCO}_2$  is 1, as  $P_{\text{ETCO}_2}$ ,  $P_{\text{ACO}_2}$  and  $\text{PaCO}_2$  are equal. Our aim is to investigate if and at which extent the  $P_{\text{ETCO}_2}/\text{PaCO}_2$ , a comprehensive meter of the “gas exchanger” performance, is related to the anatomic 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  $P_{\text{ETCO}_2}/\text{PaCO}_2$ , measured at 5  $\text{cmH}_2\text{O}$  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  $P_{\text{ETCO}_2}/\text{PaCO}_2$  (lowest ratio, the worst = group 1, highest ratio, the best = group 4). The progressive increase  $P_{\text{ETCO}_2}/\text{PaCO}_2$  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, inhomogeneity index and increase of well-aerated tissue. The respiratory system elastance significantly improved from quartile 1 to 4, as well as the  $\text{PaO}_2/\text{FiO}_2$  and  $\text{PaCO}_2$ . The improvement of  $P_{\text{ETCO}_2}/\text{PaCO}_2$  was also associated with a significant decrease of physiological dead space and venous admixture. When PEEP was increased from 5 to 15  $\text{cmH}_2\text{O}$ , the greatest improvement of non-aerated tissue,  $\text{PaO}_2$  and venous admixture were observed in quartile 1 of  $P_{\text{ETCO}_2}/\text{PaCO}_2$  and the worst deterioration of dead space in quartile 4.

**Conclusion:** The ratio  $P_{\text{ETCO}_2}/\text{PaCO}_2$  is highly correlated with CT scan, physiological and clinical variables. It appears as an excellent measure of the overall “gas exchanger” status.

**Keywords:**  $P_{\text{ETCO}_2}$ , Acute respiratory distress syndrome, Severity, Monitoring

## 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  $\text{PCO}_2$  ( $\text{PACO}_2$ ). This ideal  $\text{PCO}_2$ , introduced by Riley, cannot be measured directly and it is assumed to be equal to the capillary  $\text{PCO}_2$  ( $\text{PcCO}_2$ ) [3] which leaves the ventilated/perfused pulmonary units [4]. As the  $\text{PcCO}_2$  cannot be measured directly, the arterial  $\text{PCO}_2$  ( $\text{PaCO}_2$ ) is assumed to be its surrogate. Therefore, the assumption on which the physiological dead space is computed is that  $\text{PACO}_2$ ,  $\text{PcCO}_2$  and  $\text{PaCO}_2$  have identical values. While this is nearly correct in the normal lung, in the diseased lung, as in ARDS, the  $\text{PaCO}_2$  is higher than  $\text{PcCO}_2$  and  $\text{PACO}_2$  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  $\text{PO}_2$  and  $\text{PCO}_2$  of the mixed venous blood). Consequently,  $\text{PaCO}_2$  is the result of the weighted average of blood coming from the ideal compartment ( $\text{PcCO}_2$ ) and of mixed venous  $\text{PCO}_2$  ( $\text{PvCO}_2$ ) [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  $\text{CO}_2$  ( $\text{P}_{\text{ET}}\text{CO}_2$ ) is representative of the actual alveolar gases. In this case, the  $\text{P}_{\text{ET}}\text{CO}_2$  is lower than the  $\text{PACO}_2$  depending on the amount of alveolar dead space.

The measurement of the  $\text{P}_{\text{ET}}\text{CO}_2$  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  $\text{P}_{\text{ET}}\text{CO}_2/\text{PaCO}_2$  ratio may be seen as a direct overall meter of the gas exchanger performance in a scale from 0 to 1. Indeed, a  $\text{P}_{\text{ET}}\text{CO}_2/\text{PaCO}_2$  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  $\text{CO}_2$  removal.

The aim of this study is to investigate whether the  $\text{P}_{\text{ET}}\text{CO}_2/\text{PaCO}_2$ , 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 cmH<sub>2</sub>O 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 cmH<sub>2</sub>O minus the fraction of non-aerated tissue at 45 cmH<sub>2</sub>O [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 cmH<sub>2</sub>O 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, ScvO<sub>2</sub> and arteriovenous O<sub>2</sub> content difference) and gas exchange variables (P<sub>ET</sub>CO<sub>2</sub>, PaO<sub>2</sub>, PaCO<sub>2</sub>, PaO<sub>2</sub>/PaCO<sub>2</sub> ratio, SaO<sub>2</sub>, venous admixture (Q<sub>s</sub>/Q<sub>t</sub>), physiological dead space fraction (V<sub>d</sub>/V<sub>t</sub>)). Tidal volume and FiO<sub>2</sub> were kept constant at these two PEEP levels. The volumetric capnography measurements were performed with COSMO (Respironics Novamatrix, 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 P<sub>ET</sub>CO<sub>2</sub>/PaCO<sub>2</sub> ratios determined during ventilation at 5 cmH<sub>2</sub>O 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 P<sub>ET</sub>CO<sub>2</sub>/PaCO<sub>2</sub> 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

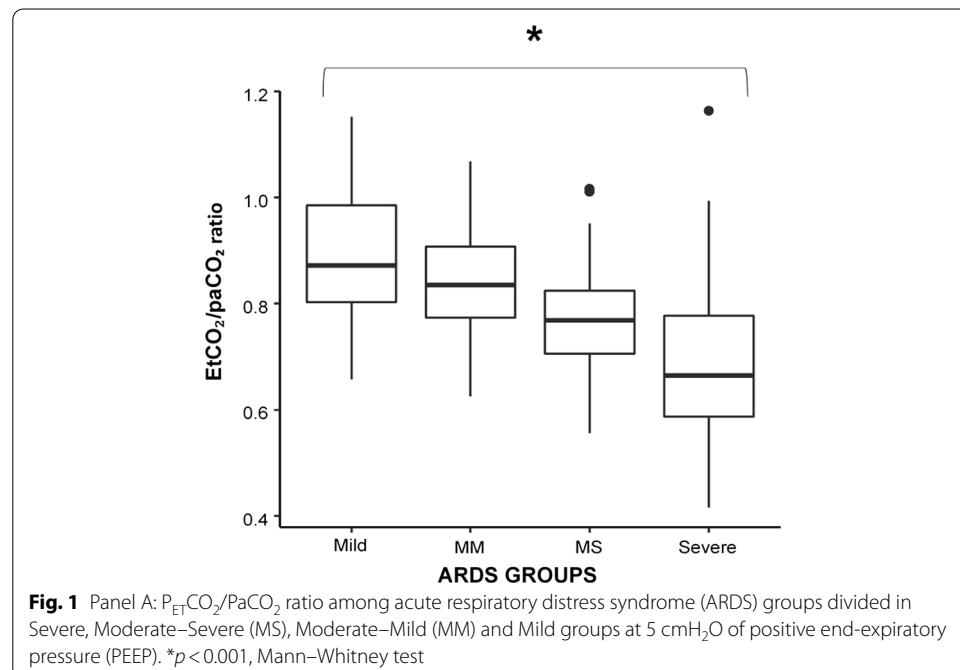
The main anthropometric and the physiological characteristics of the study population obtained at 5 cmH<sub>2</sub>O of PEEP are presented in Table 1. Figure 1, panel A shows the P<sub>ET</sub>CO<sub>2</sub>/PaCO<sub>2</sub> ratio as a function of ARDS severity. The ratio decreased linearly with increasing severity. In Fig. 2, we report the mortality rate observed in the quartiles of P<sub>ET</sub>CO<sub>2</sub>/PaCO<sub>2</sub> ratio.

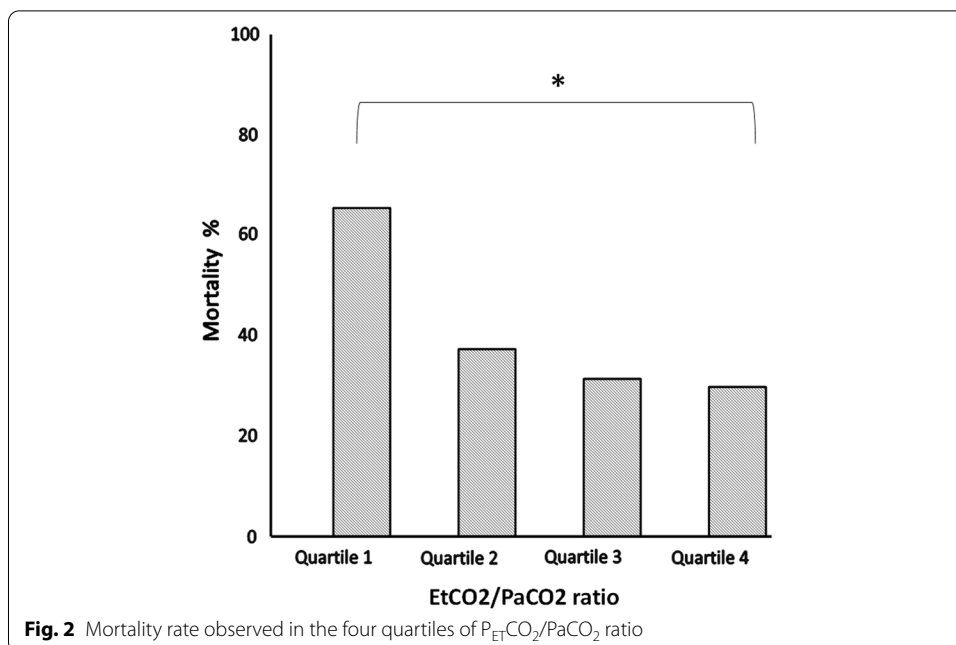
Table 2 gives the quantitative CT scan variables obtained at 5 cmH<sub>2</sub>O PEEP stratified as quartiles of P<sub>ET</sub>CO<sub>2</sub>/PaCO<sub>2</sub>. As shown, the well-aerated tissue increased with the P<sub>ET</sub>CO<sub>2</sub>/PaCO<sub>2</sub> ratio. The poorly inflated, non-aerated tissue, the inhomogeneity index [10] and recruitability all significantly decrease throughout the P<sub>ET</sub>CO<sub>2</sub>/PaCO<sub>2</sub> quartiles. As shown in Table 3, the P<sub>ET</sub>CO<sub>2</sub>/PaCO<sub>2</sub> 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; 76.0]	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, cmH <sub>2</sub> O	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
E <sub>rs</sub> , cmH <sub>2</sub> O/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
PaO <sub>2</sub> /FiO <sub>2</sub> ratio	230 [218; 255]	173 [160; 183]	122 [108; 139]	79.6 [66.7; 87.4]	<0.001
PaO <sub>2</sub> , 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
FiO <sub>2</sub>	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
PaCO <sub>2</sub> , 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)	

P for one-way Anova and Kruskal–Wallis test. MM mild–moderate, MS moderate–severe, SAPS Simplified Acute Physiology Score, BMI body mass index, E<sub>rs</sub> respiratory system elastance





**Table 2** Computed tomography quantitative variables at 5 cmH<sub>2</sub>O of end-expiratory pressure among the P<sub>ET</sub>CO<sub>2</sub>/PaCO<sub>2</sub> ratio quartiles

P <sub>ET</sub> CO <sub>2</sub> /PaCO <sub>2</sub> quartiles	I	II	III	IV	p value
Ranges	[0.416,0.709]	[0.709,0.796]	[0.796,0.886]	[0.886,1.16]	
Number of patients	N=52	N=51	N=48	N=49	
Not aerated lung tissue, g	864 [534; 1321]	570 [417; 824]	510 [343; 692]	459 [314; 664]	<0.001
Poorly aerated lung tissue, g	545 [342; 761]	398 [271; 552]	423 [284; 584]	356 [264; 440]	0.001
Normally aerated lung tissue, g	281 [189; 414]	288 [220; 452]	363 [243; 487]	356 [260; 500]	0.021
Hyperinflated lung tissue, g	0.32 [0.02; 2.72]	0.16 [0.01; 1.10]	0.24 [0.02; 2.47]	0.19 [0.01; 1.05]	0.739
Inhomogeneity index	0.20 [0.15; 0.24]	0.16 [0.13; 0.23]	0.15 [0.12; 0.18]	0.14 [0.12; 0.20]	0.007
Possibly recruitable tissue, g	336 [168; 583]	253 [109; 462]	171 [89.8; 295]	117 [54.4; 219]	<0.001

Data are expressed in medians and IQR. P for Mann–Whitney test

system elastance, alveolar ventilation and VCO<sub>2</sub>. These variables improved when the P<sub>ET</sub>CO<sub>2</sub>/PaCO<sub>2</sub> ratio approached unity. The gas exchange variables under the same conditions are presented in Table 4. As shown, the PaCO<sub>2</sub> progressively decreased with the concurrent increase of P<sub>ET</sub>CO<sub>2</sub>/PaCO<sub>2</sub> ratio, while the PaO<sub>2</sub>/FiO<sub>2</sub> ratio and saturation increased. Both venous admixture and dead space significantly decreased throughout the P<sub>ET</sub>CO<sub>2</sub>/PaCO<sub>2</sub> quartiles.

**P<sub>ET</sub>CO<sub>2</sub>/PaCO<sub>2</sub> ratio at different airway pressures**

Figure 3 illustrates how lung tissue aeration changed in the different P<sub>ET</sub>CO<sub>2</sub>/PaCO<sub>2</sub> ratio quartiles when airway pressure was increased from 5 to 15 and 45 cmH<sub>2</sub>O. The amount of non-aerated tissue decreased steadily from 5 to 45 cmH<sub>2</sub>O in all quartiles, while the amount of normally aerated tissue increased.

**Table 3** Respiratory mechanics and hemodynamics across  $P_{ET}CO_2/PaCO_2$  ratio quartiles

$P_{ET}CO_2/PaCO_2$ quartiles	I	II	III	IV	<i>p</i> value
Range	[0.416,0.709]	(0.709,0.796]	(0.796,0.886]	(0.886,1.16]	
Number of patients	<i>N</i> =52	<i>N</i> =51	<i>N</i> =48	<i>N</i> =49	
<i>Respiratory variables</i>					
$E_{rs}$ , cmH <sub>2</sub> O/L	27.9 [21.4; 33.5]	23.6 [20.4; 30.0]	25.7 [20.1; 30.1]	22.3 [18.1; 27.4]	0.015
Tidal volume, mL	480 [420; 550]	520 [455; 598]	510 [451; 600]	540 [485; 598]	0.064
RR, bpm	18.0 [14.8; 20.0]	16.0 [13.0; 19.0]	16.0 [13.0; 18.0]	15.0 [14.0; 18.0]	0.414
MAP, cmH <sub>2</sub> O	12.0 [10.0; 13.0]	11.0 [9.00; 13.0]	11.0 [10.0; 12.0]	10.0 [9.83; 11.5]	0.130
$V_A$ L/min	3.18 [2.74; 4.75]	3.99 [2.86; 5.12]	4.25 [3.44; 5.60]	4.72 [3.33; 5.74]	0.003
$VCO_2$ , mL/min	117 [81.2; 137]	144 [112; 174]	164 [129; 189]	180 [144; 200]	<0.001
<i>Hemodynamics</i>					
HR, bpm	87.0 [71.0; 105]	89.0 [70.5; 96.0]	89.0 [81.0; 106]	96.0 [82.0; 108]	0.245
Mean arterial pressure, mmHg	77.0 [69.5; 86.7]	83.0 [73.7; 90.3]	79.0 [72.0; 87.5]	81.7 [73.2; 89.2]	0.210
CVP, mmHg	11.0 [9.00; 14.0]	11.0 [9.00; 13.0]	12.0 [9.50; 14.0]	12.0 [9.00; 14.0]	0.822

Variables are expressed in medians and IQR. *P* for Mann–Whitney test.  $E_{rs}$  respiratory system elastance, *RR* respiratory rate, *PEEP* end-expiratory pressure, *MAP* mean airway pressure,  $V_A$  alveolar ventilation, *HR* heart rate, *CVP* central venous pressure

**Table 4** Gas exchange across  $P_{ET}CO_2/PaCO_2$  ratio quartiles

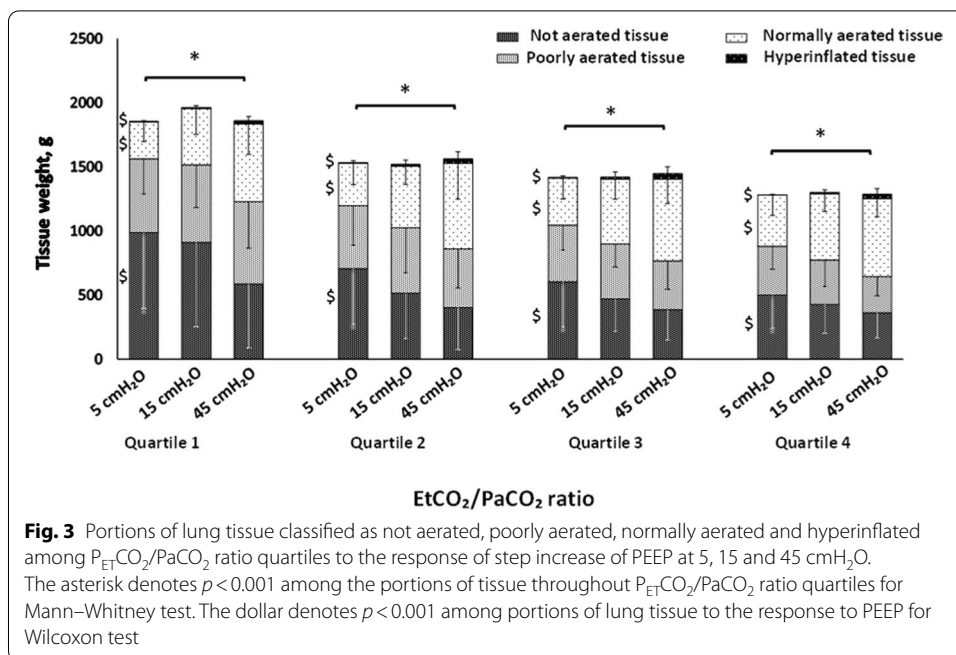
$P_{ET}CO_2/PaCO_2$ quartiles	I	II	III	IV	<i>p</i> value
Ranges	[0.416,0.709]	[0.709,0.796]	[0.796,0.886]	[0.886,1.16]	
Number of patients	<i>N</i> =52	<i>N</i> =51	<i>N</i> =48	<i>N</i> =49	
$PaO_2$ , mmHg	62.6 [55.0; 73.6]	71.0 [63.5; 81.2]	75.0 [65.8; 89.7]	71.8 [65.0; 83.0]	0.001
$PaCO_2$ , mmHg	48.1 [43.3; 53.8]	46.0 [41.1; 52.4]	44.7 [40.4; 50.1]	39.9 [36.5; 43.2]	<0.001
$PaO_2/FiO_2$	103 [76.7; 131]	117 [102; 158]	164 [139; 203]	171 [143; 207]	<0.001
Arterial pH	7.36 (0.07)	7.37 (0.07)	7.38 (0.08)	7.40 (0.07)	0.009
$SaO_2$	90.8 [87.5; 94.0]	92.4 [90.5; 95.3]	94.1 [92.0; 96.2]	94.7 [92.7; 96.8]	<0.001
Venous pH	7.34 (0.07)	7.35 (0.06)	7.36 (0.07)	7.37 (0.05)	0.141
$PvO_2$ , mmHg	42.1 [39.8; 45.6]	42.0 [39.2; 44.1]	40.8 [37.2; 49.0]	42.9 [40.0; 47.7]	0.667
$PvCO_2$ , mmHg	50.2 [46.9; 56.9]	52.0 [46.8; 55.3]	49.8 [45.0; 56.5]	45.8 [41.0; 47.3]	<0.001
$SvO_2$	73.5 [70.1; 76.5]	74.3 [71.4; 77.7]	76.4 [70.0; 80.6]	77.7 [72.6; 81.0]	0.073
<i>v-a</i> difference	2.31 [1.30; 2.83]	2.46 [1.92; 2.83]	2.65 [2.00; 3.26]	2.10 [1.56; 2.53]	0.036
$Q_s/Q_t$	0.54 [0.40; 0.66]	0.42 [0.36; 0.48]	0.35 [0.27; 0.43]	0.39 [0.30; 0.46]	<0.001
$V_d/V_t$	0.74 [0.67; 0.80]	0.63 [0.60; 0.68]	0.56 [0.51; 0.61]	0.47 [0.44; 0.55]	<0.001

Variables are expressed in medians and IQR or means  $\pm$  SD according to distribution. *P* for Mann–Whitney test or one-way Anova.  $Q_s/Q_t$ : shunt fraction;  $V_d/V_t$ : dead space fraction

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<sub>2</sub>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

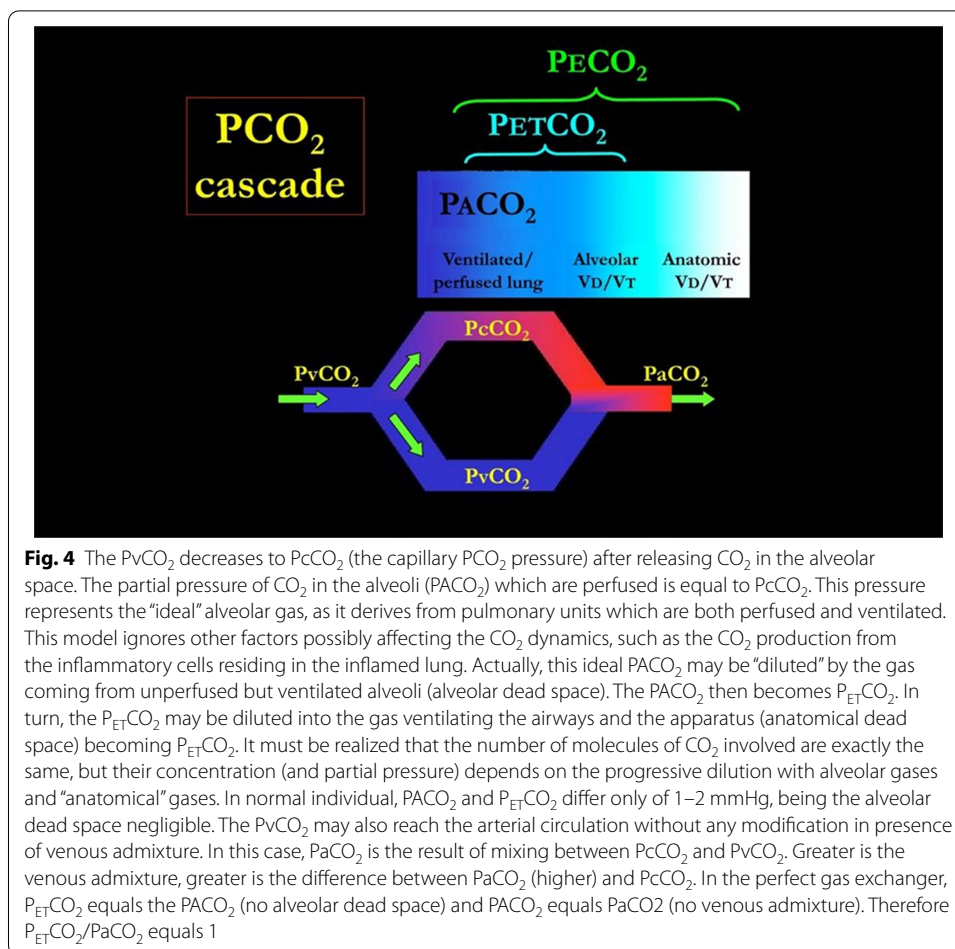
In this study, we found that the  $P_{ET}CO_2/PaCO_2$  ratio is strongly associated with most of the morphological and physiological characteristics of ARDS, resulting as an easy and appealing measure of the status and the performance of the lung.



**Table 5** Changes in CT scan, respiratory mechanics and gas exchange variables in response to PEEP increase from 5 to 15  $cmH_2O$  among  $P_{ET}CO_2/PaCO_2$  ratio quartiles

$P_{ET}CO_2/PaCO_2$ quartiles	I	II	III	IV	p value
$\Delta$					
Ranges	[0.416,0.709]	[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
$\Delta PaO_2$ , mmHg	32 [18.5; 46]	23 [10.2; 58.4]	21.2 [4.3; 36]	16 [4.4; 28]	0.01
$\Delta E_{RS}$ , $cmH_2O/L$	0.07 [- 4.0; 3.4]	- 0.2 [- 2.2; 4.1]	0.3 [- 4.1; 2.4]	0.0 [- 2.5; 2.2]	0.85

Differences were computed as the variable at PEEP 15  $cmH_2O$  minus the variable at PEEP 5  $cmH_2O$ . 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;  $P/F$ :  $PaO_2/FiO_2$  ratio;  $E_{RS}$ : respiratory system elastance;  $SvO_2$ : central venous oxygen saturation;  $P_{ET}CO_2$ : end-tidal  $CO_2$



The physiological meaning of the  $P_{ET}CO_2/PaCO_2$  ratio may be easily understood when one considers CO<sub>2</sub> kinetics through the anatomical space from the pulmonary capillaries to the airway opening. Figure 4 shows that, in the ideal lung, PaCO<sub>2</sub> is equal to PpCO<sub>2</sub> (venous admixture fraction = 0). Similarly, P<sub>ET</sub>CO<sub>2</sub> is equal to PACO<sub>2</sub> (alveolar dead space fraction = 0). Therefore, in this “ideal” setting the ratio of P<sub>ET</sub>CO<sub>2</sub> to PaCO<sub>2</sub> would be 1. This ratio will depart progressively from 1 in the presence of a venous admixture and/or alveolar dead space. Consequently, the  $P_{ET}CO_2/PaCO_2$  ratio is a rather unspecific variable, as it is linked to both CO<sub>2</sub> and O<sub>2</sub> 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  $P_{ET}CO_2/PaCO_2$  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  $P_{ET}CO_2/PaCO_2$  ratio. With regard to the morphological variables, the  $P_{ET}CO_2/PaCO_2$  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  $P_{ET}CO_2/PaCO_2$  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  $P_{ET}CO_2/PaCO_2$  ratio, alveolar dead space and venous admixture accounts for its high sensitivity in detecting an overall impairment in gas exchange. The  $P_{ET}CO_2/PaCO_2$  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  $P_{ET}CO_2/PaCO_2$  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  $P_{ET}CO_2/PaCO_2$  ratio. Therefore, an altered  $P_{ET}CO_2/PaCO_2$  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  $P_{ET}CO_2/PaCO_2$  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 overdilatation of pulmonary units relative to their perfusion. An increase in alveolar dead space would tend to reduce  $P_{ET}CO_2$ , while a decrease of right-to-left venous admixture would tend to reduce  $PaCO_2$ . The  $P_{ET}CO_2/PaCO_2$  ratio is related to the two variables, and its changes may reflect these physiopathological mechanisms. Moreover, we showed that patients starting with a lower  $P_{ET}CO_2/PaCO_2$  ratio had a more favorable response to PEEP.

The  $P_{ET}CO_2/PaCO_2$  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  $P_{ET}CO_2/PaCO_2$  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  $P_{ET}CO_2/PaCO_2$  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 PaCO<sub>2</sub> that one can have a more complete picture of the lung structure and function [13]. Finally, the P<sub>ET</sub>-CO<sub>2</sub>/PaCO<sub>2</sub> 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 of the gas exchange alteration, both dead space and venous admixture must be measured.

## Conclusions

In this study, we evaluated the P<sub>ET</sub>-CO<sub>2</sub>/PaCO<sub>2</sub> 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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## Availability of data and materials

Dataset available upon reasonable request.

## Ethics approval and consent to participate

The ethics committee was notified and permission to use the data was granted (Göttingen Antragsnummer 14/12/12).

## Consent for publication

All authors have approved the manuscript.

## Competing interests

The authors have no conflict of interest to disclose.

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