

Assessment of gradient between partial pressure of arterial carbon dioxide and end-tidal carbon dioxide in acute respiratory distress syndrome

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Context End-tidal carbon dioxide (EtCO₂) is used as a noninvasive bedside test to assess the adequacy of ventilation and physiologic dead space in mechanically ventilated patients. The gradient difference between EtCO₂ and partial pressure of arterial carbon dioxide (PaCO₂) is directly related to an increase in the physiologic dead space.

Aim The aim of this study was to evaluate the role of measuring the gradient between EtCO₂ and PaCO₂ in adults with acute respiratory distress (ARDS).

Settings and design This was a prospective consecutive enrollment study.

Patients and methods Overall, 51 cases were recruited after the diagnosis of ARDS was made according to the Berlin definition. Patients were mechanically ventilated as per the lung-protective protocol. Daily arterial blood gases were collected and for every sample, the EtCO₂ value was collected electronically by capnography using an endotracheal tube for the first 5 days.

Results Cases were classified into survivors and nonsurvivors: 26 cases were because of extrapulmonary causes and 25 cases were because of pulmonary causes. The mean value of the APACHE II score for all cases on admission was 21.6. The mean length of ICU stay was 12.7

days. For all study cases, PaO₂/FiO₂ was the lowest at day 1 and the highest at day 5. We found a significant negative correlation between PaO₂/FiO₂ and the gradient at days 2, 4, and day 5, and a significant positive correlation between the gradient on admission and the APACHE II score ($r=0.4$, $P\leq 0.05$). Nonsurvivors had a significantly higher gradient and lower EtCO₂ and PaO₂/FiO₂ levels at all time intervals, whereas PaCO₂ alone was found to be nonsignificant.

Conclusion In ARDS, EtCO₂ and gradient are reliable indicators of severity.

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Keywords: acute respiratory distress syndrome, EtCO₂, P(a-et)CO₂, PaCO₂, PaO₂/FiO₂

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Introduction

According to Berlin guidelines [1], acute respiratory distress syndrome (ARDS) is classified as follows:

- (1) Mild: PaO₂/FiO₂ (200–300) with positive end expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) of at least 5 cmH₂O.
- (2) Moderate: PaO₂/FiO₂ (100–200) with PEEP of at least 5 cmH₂O.
- (3) Severe: PaO₂/FiO₂ (≤ 100) with PEEP of at least 5 cmH₂O.

For years, capnography has been used as a standard of care in the ICU to ensure correct placement and patency of the endotracheal tube. end-tidal carbon dioxide (EtCO₂) is also used in cardiopulmonary resuscitation to ensure that the proper technique is used. In healthy adults, EtCO₂ approaches the arterial carbon dioxide (PaCO₂); hence, capnography can provide quick real-time continuous monitoring of the levels of CO₂ (and hence ventilation) in patients. However, in diseases of the lungs causing ventilation perfusion mismatches, the relationship

between EtCO₂ and PaCO₂ becomes altered and many studies have shown that EtCO₂ alone cannot be used as a surrogate for PaCO₂ when the lungs are diseased [2].

Physiologic dead space is the part of ventilation that is not involved in the gas exchange process and it includes the anatomical dead space (airways) and the alveolar dead space (alveoli not receiving perfusion). In ARDS patients on mechanical ventilation, the dead space increases as the tidal volume reaches non perfused lung segments. Overdistension of the normally perfused segments by high tidal volumes or high ventilation pressures (PEEP) can also increase dead space. It has also been shown that in ARDS microemboli and endothelial damage occurs, which may also lead to the dead space effect. In patients with ARDS, dead space plays a prognostic role and can

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be used to control ventilator parameters. The gradient between arterial and EtCO₂ [P(a-et)CO₂] widens with increased dead space [3].

In our study, we attempted to study the P(a-et)CO₂ in ARDS patients and whether this gradient correlates with disease severity and outcome.

Our aim is to evaluate the role of measuring the gradient between EtCO₂ and PaCO₂ in ARDS mechanically ventilated patients as a detector of disease severity.

Patients and methods

Study design

This study is a consecutive prospective enrollment study that was carried out from January 2015 to January 2017 at the respiratory ICU.

Ethical approval and consent to participate

The ethical committee of our university approved the study and, therefore, our study was carried out in accordance with the ethical standards of Declaration of Helsinki, laid down in 1964, and its later amendments. All candidates in the research signed an informed consent after an explanation was provided of the details of the study and the possibility of publication. Consent was signed by the patients or the legal next of kin.

Consent for publication

Informed consent on the data that were collected and/or published was explained and signed by each patient or the legal next of kin. All authors agreed to publish the data.

Patients

The study included 52 mechanically ventilated patients with ARDS. Patients were 18 years of age and older, recruited within 48 h of mechanical ventilation after the diagnosis of ARDS as per Berlin definition. We excluded patients who were hemodynamically unstable (mean arterial pressure of 64 mmHg despite the use of vasopressors), patients who previously had any chronic lung diseases leading to hypercapnia (PCO₂>45), hypoxemia (PO₂<5 mmHg), pulmonary hypertension (PAP>40 mmHg), polycythemia, morbid obesity (BMI>35), or home oxygen/ventilator dependence. Patients were enrolled between January 2016 and January 2017 in the ICU of our university hospitals.

Analytical methods

Mechanical ventilation

The mechanical ventilators used, Puritan Bennett 840 Ventilator, (Medtronocs, Minneapolis, MN, USA)

and Dräger EVITA V500 (Drägerwerk AG & Co. KGaA, Lübeck, Germany), had airway graphic monitors and were calibrated according to the manufacturer's recommendations. Ventilators were set to the standard lung-protective mechanism protocol (tidal volume: 6 ml/kg, maximum plateau pressure 30 mmHg, PEEP between 8 and 12 mmHg personalized according to patients' BMI and oxygenation, respiratory rate 20–30/min, bed head elevation >30°).

Data collection

The APACHE II score was calculated on admission and daily during the first 5 days of mechanical ventilation. Daily arterial blood gases were collected and for every sample, the EtCO₂ value was collected electronically by mainstream capnography using an endotracheal tube through a Philips IntelliVue MP70 ECG Monitor (Koninklijke Philips N.V. High Tech Campus 55656 AE, Eindhoven, The Netherlands), a General Electric CARESCAPE B650 (GE Healthcare, Milwaukee, USA), and a Dräger Infinity Patient Monitor (Drägerwerk AG & Co. KGaA, Lübeck, Germany). We collected those simultaneous arterial blood gas and EtCO₂ readings every morning for the first 5 days. The gradient was calculated by mathematically subtracting the EtCO₂ from the PaCO₂.

Statistical methods

We used mean±SD, median and range, or frequencies and percentages to describe data. Student's *t*-test was used to compare the numerical variables between groups. Pearson's moment correlation equation was used for linear relations and Spearman's rank correlation equation for non-normal variables. *P* values less than 0.05 were considered statistically significant. All statistical calculations were carried out using the computer program SPSS (SPSS Inc., Chicago, Illinois, USA) release 15 for Microsoft Windows (2006).

Results

The study included 51 patients. There were 27 (53%) male and 24 (47%) female patients. All of them were mechanically ventilated patients with ARDS; 26 (51%) cases were because of extrapulmonary causes and 2 (49%) cases were because of pulmonary causes. Nineteen (37.3%) cases had survived ARDS and 32 (62.7%) cases did not survive. The mean age of the study cases was 48.04±9.3 years. The mean value of the APACHE II score for all cases on admission was 21.69±5.97. The mean length of stay in ICU was 12.76±5.08

days; the shortest time of stay was for a case who died 3 days after admission. All descriptive data are shown in Table 1.

Nonsurvivors had a significantly higher gradient and lower EtCO₂ and *P/F* levels at all time intervals. PaCO₂ alone was not found to be significantly different between survivors and nonsurvivors. These findings are shown in Table 2 and Fig. 1.

Table 1 Descriptive characteristics of the cases included in the study

	<i>n</i> (%)
Sex	
Female	24 (47)
Male	27 (53)
Cause of ARDS	
Extrapulmonary	26 (51)
Pulmonary	25 (49)
Smoking history	
Smokers	25 (49)
Nonsmokers	26 (51)
Mortality [<i>n</i> (%)]	
No	19 (37.3)
Yes	32 (62.7)
Age (mean±SD)	48.04±3.9
APACHE score (mean±SD)	21.69±5.9
LOS (mean±SD)	12.76±5.08

ARDS, acute respiratory distress syndrome; LOS, length of stay.

We found a significant negative correlation between the *P/F* ratio and the arterio-EtCO₂ gap at days 2, 4, and day 5 as shown in Fig. 2.

Figure 3 shows that a significant positive correlation was found between the gradient on admission and APACHE ($r=0.4$, $P\leq 0.05$).

ROC analysis of the EtCO₂ gradient and predicted mortality showed a cut-off value for the EtCO₂ gradient to predict mortality of 17.5 on day 1 [area under the curve (AUC)=0.77, 80% sensitivity, 40% specificity], 17.5 on day 2 (AUC=0.73, 74% sensitivity, 42% specificity), 15.5 on day 3 (AUC=0.78, 87% sensitivity, 42% specificity), 16.5 on day 4 (AUC=0.83, 84% sensitivity, 36% specificity, and 15.5 on day 5 (AUC=0.86, 96% sensitivity, and 47% specificity) (Fig. 4).

Discussion

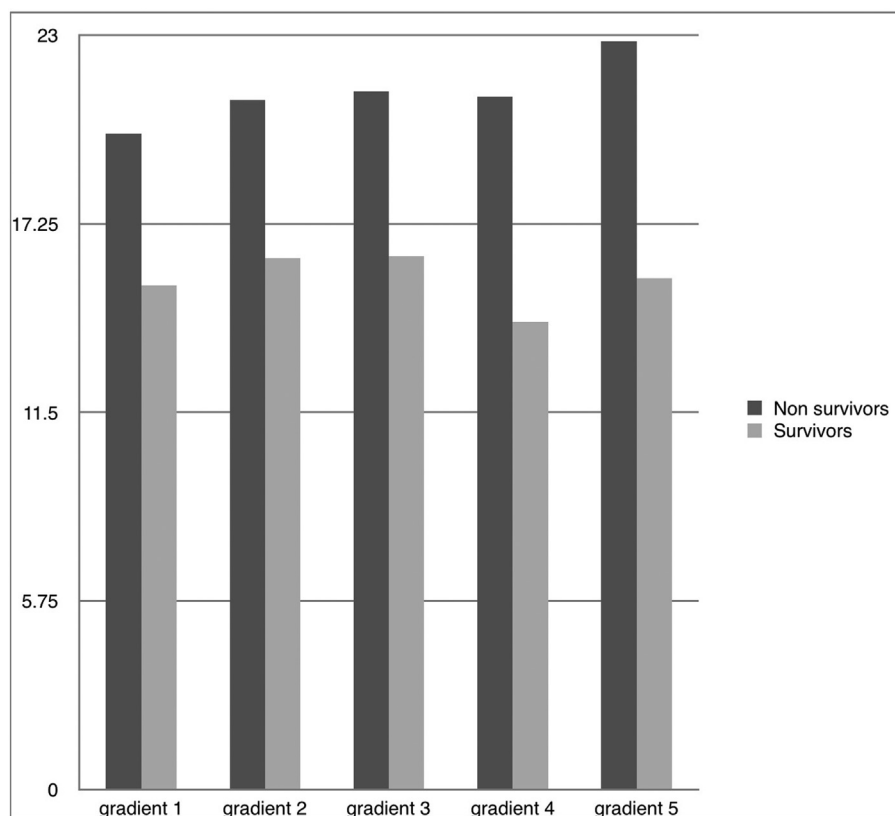
Our main finding was that nonsurvivors had higher gradients and lower EtCO₂ at all study days compared with survivors and that the gradient and EtCO₂ were significantly related to *P/F* ratios (the higher the gradient, the lower the *P/F*); hence, the gradient increased as ARDS worsened, whereas PaCO₂ alone

Table 2 Comparison between survivors and nonsurvivors

	Total (<i>N</i> =51)	Survivors (<i>N</i> =19)	Nonsurvivors (<i>N</i> =32)	<i>P</i> value
<i>P/F</i>				
D1	188.53	236	160	<0.05
D2	199.14	278	152	<0.05
D3	193.22	286	137	<0.05
D4	230.43	325	174	<0.05
D5	237.37	335	179	<0.05
EtCO ₂				
D1	20.22	23.8	20	<0.05
D2	19.57	22.9	19.5	<0.05
D3	23.22	23	17	<0.05
D4	19.92	24.45	16.9	<0.05
D5	18.71	23.8	18.7	<0.05
Gradient				
D1	18.27	15.3	20	<0.05
D2	19.24	16.2	21	<0.05
D3	15.45	16.2	21.2	<0.05
D4	18.57	14.2	21.2	<0.05
D5	20.12	15.5	22.8	<0.05
PaCO ₂				
D1	38.49	39.2	38	≥0.05
D2	38.80	39.1	38.5	≥0.05
D3	38.67	39.3	38.2	≥0.05
D4	38.49	39.2	38	≥0.05
D5	38.82	39.4	38.4	≥0.05

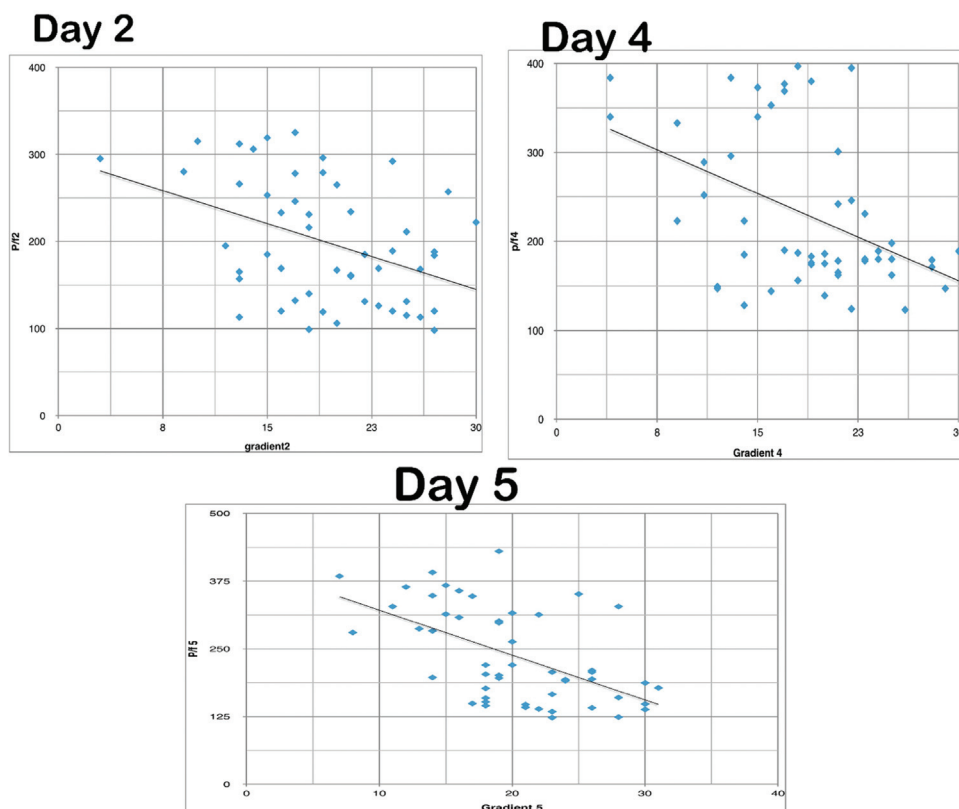
D, day; EtCO₂, end-tidal carbon dioxide; gradient, gradient between PaCO₂ and EtCO₂; *P/F*, PaO₂/FiO₂; PaCO₂, partial pressure of arterial carbon dioxide.

Figure 1



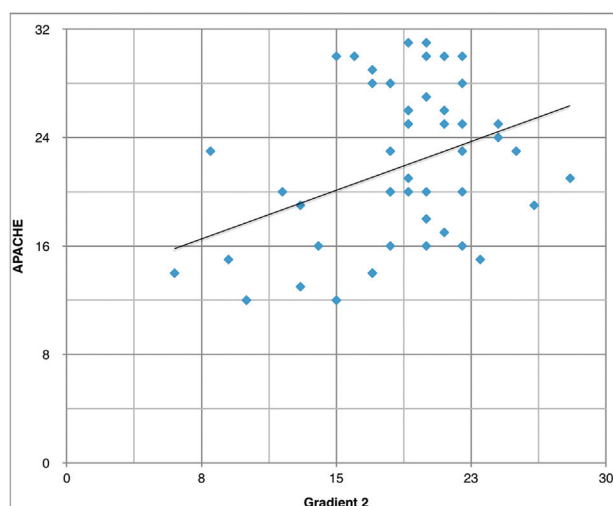
Gradient difference in survivors and nonsurvivors.

Figure 2



P/F and gradient correlation on days 2, 4, and 5 of the study.

Figure 3



APACHE score and gradient correlation on day 2 of the study.

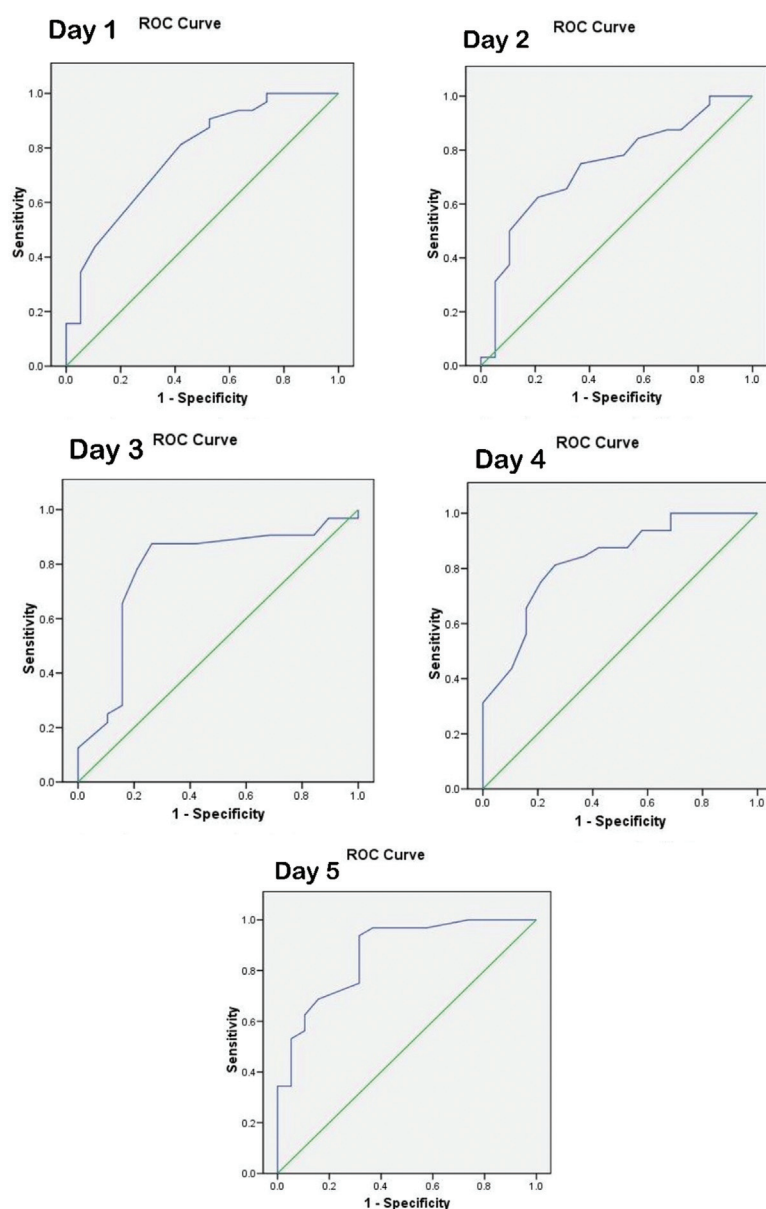
did not change significantly in nonsurvivors. To our knowledge, very limited studies have been carried out to assess the gradient in adult patients with ARDS.

Limitations of our study

The main limitations of our study are that although we studied the P/F ratio, we did not stratify patients into those with mild, moderate, and severe ARDS; hence, we did not establish a relationship between $P(a-et)CO_2$ and the degree of ARDS as per the Berlin classification. Also, we did not study the level of PEEP and its effects on dead space and hence $P(a-et)CO_2$.

These data are in agreement with a study carried out by Brinton and colleagues, who studied 35 patients with various degrees of ARDS and concluded that the gradient widens with increasing ARDS severity [4].

Figure 4

Receiver operating characteristic analysis of the $EtCO_2$ gradient and predicted mortality.

A similar study by Yousuf and colleagues in 2016 established P(a-et)CO₂ in ARDS patients. The aim of this study was to detect a gradient in each grade of severity of ARDS; PaCO₂, PaO₂/FiO₂, and EtCO₂ were measured. This study found that the gradient between PaCO₂ and EtCO₂ in ARDS worsened with increasing severity of ARDS, which indicates the value of gradient as an indicator of the severity of ARDS [5].

A study was carried out by Mehta and colleagues in neonatal and pediatric ICUs of a tertiary care children hospital. The study included 101 mechanically ventilated patients (35 children and 66 neonates). EtCO₂ and PaCO₂ were reported and data were analyzed. The researchers concluded that EtCO₂ is a good predictor of PaCO₂, and the correlation between EtCO₂ and PaCO₂ was affected significantly by the *P/F* ratio [6]. In 2012, another study detected a positive correlation between EtCO₂ and PaCO₂ through all modes of mechanical ventilation and even while the candidates were on a T tube. Their final conclusion was that EtCO₂ is an accurate predictor of PaCO₂ in mechanically ventilated patients and the use of EtCO₂ may reduce the need for invasive monitoring and/or repeated arterial blood gases [7].

Although studies in this field are limited and although our study was also limited by the number of patients and the fact that the PEEP effect was not studied, most data of the studies carried out are in agreement. More studies on a greater number of patients are required.

Conclusion

The gradient between EtCO₂ and PaCO₂, and EtCO₂ plays a good role in predicting severity and prognosis in patients with ARDS and its determination is recommended as a noninvasive, reliable predictor in mechanically ventilated patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

- 1 Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, *et al.* The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med* 2012; **38**:1573–1582.
- 2 McSwain SD, Hamel DS, Smith PB, Gentile MA, Srinivasan S, Meliones JN, Cheifetz IM. End-tidal and arterial carbon dioxide measurements correlate across all levels of physiologic dead space. *Respir Care* 2010; **55**:288–293.
- 3 Yamanaka MK, Sue DY. Comparison of arterial-end tidal PCO₂ difference and dead space/tidal volume ratio in respiratory failure. *Chest* 1987; **92**:832–835.
- 4 Brinton T, Yousuf T, Iskandar J, Nepal R, Mehta R, Hanif T. End-tidal CO₂ correlation with PaCO₂ in acute respiratory distress syndrome american thoracic society conference 2016, C49. Respiratory failure: clinical and translational aspects of vili and lung protective MV. *Am J Respir Crit Care Med* 2016; **193**:A5252.
- 5 Yousuf T, Brinton T, Murtaza G, Wozniczka D, Ahmad K, Iskandar J, *et al.* Establishing a gradient between partial pressure of arterial carbon dioxide and end-tidal carbon dioxide in patients with acute respiratory distress syndrome. *J Investig Med* 2017; **65**:338–341.
- 6 Mehta H, Kashyap R, Trivedi S. Correlation of end-tidal and arterial carbon-dioxide levels in critically ill neonates and children. *Indian J Crit Care Med* 2014; **18**:833–834.
- 7 Razi E, Moosavi GA, Omid K, Khakpour Saebi A, Razi A. Correlation of end-tidal carbon dioxide with arterial carbon dioxide in mechanically ventilated patients. *Arch Trauma Res* 2012; **1**:58–62.