Establishing a gradient between partial pressure of arterial carbon dioxide and end-tidal carbon dioxide in patients with acute respiratory distress syndrome

Tariq Yousuf,[1] Taylor Brinton,[1] Ghulam Murtaza,[1] Daniel Wozniczka,[1] Khansa Ahmad,[1] Joy Iskandar,[1] Raju Mehta,[1] Hesam Keshmiri,[2] Tabassum Hanif[1]

[1]Department of Medicine, Advocate Christ Medical Center, Oak Lawn, Illinois, USA
[2]Department of Cardiology, Illinois Masonic Medical Center, Chicago, Illinois, USA

Correspondence to
Dr Tariq Yousuf, Department of Medicine, Advocate Christ Medical Center, 4440 W. 95th St., Oak Lawn, IL 60453, USA;
tmyousuf614@gmail.com

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ABSTRACT

End-tidal carbon dioxide ($ETCO_2$) monitoring is useful in many situations. However, $ETCO_2$ monitoring is unreliable in patients with acute respiratory distress syndrome (ARDS) due to widespread lung inflammation. In our study, we attempt to establish the gradient between the arterial pressure of carbon dioxide ($PaCO_2$) and $ETCO_2$ in patients with ARDS, which we defined as the $PaETCO_2$ gradient. The main objective of the study was to establish a $PaETCO_2$ gradient in each severity of ARDS. We analyzed 35 patients with ARDS and a total of 88 arterial blood gases were included. $PaCO_2$, PaO_2/FiO_2 and $ETCO_2$ were measured. Patients were stratified into mild, moderate and severe ARDS as classified by the Berlin ARDS criteria. $PaCO_2$ and $ETCO_2$ were compared at each severity stratification. The mean $PaCO_2$ was 50.0, the mean $ETCO_2$ was 26.6 and the gradient among all samples was 23.24 (±12.02). The mean gradient for each severity is as follows: mild: 19.3 (±9.9), moderate: 27.9 (±13.2) and severe: 23.9 (±7.8). The difference between the $PaETCO_2$ gradient of the mild to moderate ($p=0.001$) and mild to severe groups ($p=0.01$) reached statistical significance. However, the difference between the moderate to severe groups did not reach statistical significance ($p=0.48$). We found the gradient between $PaCO_2$ and $ETCO_2$ in patients with ARDS is vast and tends to worsen with increasing severity of ARDS. This indicates that the gradient between the 2 may be used as an indicator of increasing severity of ARDS.

Significance of this study

What is already known about this subject?

- We were unable to find literature that has specifically looked at $PaCO_2$ and $ETCO_2$ levels and/or compared their gradients in patients with acute respiratory distress syndrome.
- However, in 1987, a trial was performed on 17 patients who were intubated with respiratory failure from various causes and investigators found that $ETCO_2$ was a poor estimate of $PaCO_2$ in patients with respiratory failure.
- Similarly, a retrospective cross-sectional analysis was performed on pediatric patients who were intubated from November 2001 to June 2005 at Duke's Children's Hospital. The study showed that $ETCO_2$ values do closely correlate with $PaCO_2$ values at low dead space. With increasing dead space, results showed an increase in the $ETCO_2$ and $PaCO_2$ gradient.

What are the new findings?

- $PaCO_2$ and $ETCO_2$ values do not correlate in patients with acute respiratory distress syndrome (ARDS).
- The $PaETCO_2$ gradient ($PaCO_2$–$ETCO_2$) can be used to monitor progression of ARDS from mild–moderate and/or mild to severe.

INTRODUCTION

End-tidal carbon dioxide ($ETCO_2$) is the concentration of carbon dioxide (CO_2) exhaled from the lungs. This is measured via capnography, which is an instrument attached to the endotracheal tube of an intubated patient or to a nasal cannula of a patient breathing ambient air. It has been shown that this measurement closely approximates (by about 2 mm Hg) the partial pressure of carbon dioxide in the systemic arteries ($PaCO_2$) in patients with healthy lungs.[1] Studies have also shown that in critically ill patients, this relationship is broken. It is hypothesized that this is likely due to increased dead space (or non-ventilatory space) inside the lungs usually caused by inflammation and tissue damage.[2] This relationship has not been studied in patients with acute respiratory distress syndrome (ARDS).

ARDS is a progressive and diffuse inflammatory process that takes place inside the lungs and is usually caused by pneumonia or sepsis.

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Significance of this study

How might these results change the focus of research or clinical practice?

- Although arterial blood gases are most useful to assess partial pressure of oxygen (PaO_2) and to calculate the P/F ratio to determine severity of acute respiratory distress syndrome (ARDS), differences between the $PaCO_2$ and $ETCO_2$ or the '$PaETCO_2$' gradient can further aid clinicians in determining the severity such as an increasing gradient can point towards worsening of ARDS. Our sample size was small and only included patients in one intensive care unit setting. Larger clinical trials are needed to truly assess the benefit of using the $PaETCO_2$ gradient and determine if it helps in early detection of ARDS and whether it can be used along with P/F ratios to determine severity of ARDS.

Other causes of ARDS include pancreatitis, toxic inhalation, aspiration and transfusion of blood products. It is characterized by severe hypoxemia and hypercapnia. Diffuse bilateral infiltrates are seen on a chest X-ray, which can be seen with pulmonary edema due to heart failure. However, the diagnosis of ARDS also requires exclusion of heart failure as a cause.[3] The condition is so severe that nearly all patients are intubated and placed on mechanical ventilation due to acute respiratory failure, with mortality rates >30%.[4]

The Berlin criteria for ARDS were recently established and are the guideline by which ARDS is diagnosed. Patients are stratified into categories of mild, moderate and severe. This categorization utilizes the PaO_2/FiO_2 ratio. PaO_2 is the partial pressure of oxygen in the systemic arteries, and FiO_2 is the fraction of inspired air, that is, oxygen. A normal PaO_2 is 100 and the fraction of inspired ambient air, that is, oxygen, is 21%.[5] Therefore, a normal PaO_2/FiO_2 ratio (abbreviated to P/F ratio) of 100/0.21 is about 500. The classification for ARDS severity is as follows: mild: P/F ratio 200–300 (mortality rate 27%), moderate: P/F ratio 100–200 (mortality rate 32%) and severe: P/F ratio <100 (mortality rate 45%). All three categories require that the patient receive a positive end-expiratory pressure (PEEP) of five or greater. PEEP is a positive force delivered by the ventilator during exhalation, which recruits collapsed alveoli within the lung and allows for enhanced oxygenation.[6]

This classification system does not take into account end-tidal carbon dioxide, because it is yet to be studied. Our study attempts to not only establish that $ETCO_2$ is not an accurate measure of $PaCO_2$ in patients with ARDS, but also looks to discover whether the gradient between the two, what we are calling the $PaETCO_2$ gradient, increases with increasing severity of ARDS based on the Berlin criteria. Our hypothesis is that when ARDS is most severe and, theoretically, dead space is at its maximum, this gradient should be very wide, and wider than seen with milder disease. If this is true, the $PaETCO_2$ gradient could be added to the criteria for classifying ARDS patients and could be used as a real-time monitor for progression of disease. One reason for the importance of this is that in order to measure arterial oxygen content, arterial blood gas (ABG) must be sampled either through an arterial blood draw or via a catheter placed in a peripheral artery, both of which are invasive measures. End-tidal CO_2, a non-invasive measure, could therefore be considered the '6th vital sign' in a patient with ARDS.

METHODS

Data from 35 patients, including 88 samples of ABGs, were included in the study, which was approved by a local IRB review board. Data were analyzed in a retrospective fashion from a cohort of patients from 2014 to 2015 at the Medical Intensive Care Unit at Advocate Christ Medical Center in Oak Lawn, Illinois, USA. Inclusion criteria were that the patient must be on a ventilator, diagnosed with ARDS as defined by the Berlin criteria and be over the age of 18. Exclusion criteria were active heart failure and patients ventilated via tracheostomy. The capnography instrument used at our institution is a sidestream capnographer.

The primary outcome of the study was the mean $PaETCO_2$ gradient at each severity of ARDS. The secondary outcome was the mean $PaETCO_2$ gradient among all samples. In our institution, all mechanically ventilated patients have continuous monitoring of end-tidal CO_2, and the reading is automatically recorded into the electronic medical record every hour. This reading was compared with ABGs that were taken at the same time. The $ETCO_2$ measurement was subtracted by the $PaCO_2$, as measured by the ABG, to calculate the $PaETCO_2$ gradient. Other data collected included age, sex, comorbid conditions, length of stay (LOS), cause of ARDS and preexisting pulmonary disease in the form of chronic obstructive pulmonary disease (COPD), asthma or pulmonary fibrosis.

Eighty-eight data points were measured as independent variables as the ABGs were collected on separate days with different lung physiology and different P/F ratio values due to the dynamic nature of the disease process. The data were stratified into mild, moderate and severe categories based on the Berlin criteria, and a mean gradient with an SD was calculated. This mean gradient was then compared with the other groups to determine if a statistically significant difference existed. This statistical significance was obtained via t-test of the two groups, and statistical significance defined as a p value of <0.05.

RESULTS

The baseline characteristics of the patients in the study are presented in table 1. The mean age was 60.6 years. The most common causes for ARDS in our group of patients were sepsis and healthcare-associated pneumonia. The average LOS was ~13 days. Of all the patients studied, 51.4% of the patients had underlying lung disease (COPD, asthma, pulmonary fibrosis).

The analysis was performed using the POWER procedure and the overall F test for one-way ANOVA. The α was 0.05, nominal power was 0.8 and SD of 1. The mean $PaCO_2$ reading was 50.0, and $ETCO_2$ reading was 26.6 for a gradient among all samples of 23.24 (+12.02) with a mean P/F ratio of 197.7. In the mild cohort, the mean gradient was 19.3 (+9.9) with an N of 40 and a mean P/F

ratio of 262.7. In the moderate severity group, the mean gradient was 27.9 (±13.2) with an N of 39 and a mean P/F ratio of 155.1. For the severe group, the mean gradient was 23.9 (+7.8) with an N of 11 and a mean P/F ratio of 81.1. Therefore, the difference between the $PaETCO_2$ gradient of the mild and moderate (p=0.001) and mild and severe groups (p=0.01) reached statistical significance. However, the difference between the moderate and severe groups did not reach statistical significance (p=0.48) (see figure 1).

DISCUSSION

Capnography is an indispensable tool in an intubated patient in the intensive care unit (ICU) as it allows for continuous assessment of a patient's ventilatory status. It also allows for detection of warning signs such as inadvertent extubation, kinking of the ET tube, ventilator disconnection and cardiac arrest. It also decreases the frequency of ABG monitoring.[7] While the $ETCO_2$ obtained from capnography correlates well with $PaCO_2$ in patients with normal physiological space, in patients with ARDS, the levels do not correlate well as evidenced by our study. Hence, $ETCO_2$ is a poor predictor of $PaCO_2$ in patients with respiratory failure.[8]

This study shows that the $PaETCO_2$ gradient in ARDS is vast and $ETCO_2$ is not reliable in this clinical situation to estimate $PaCO_2$. This is likely due to the severe tissue damage caused by widespread inflammation in the lung. However, this gradient tends to worsen with worsening severity of ARDS, at least between mild and moderate and mild and severe. The difference between moderate and severe is not statistically significant potentially due to the low number of samples in the severe cohort. This low number may be due to the high mortality in the cohort. One reason for the high mortality in severe ARDS may be due to late recognition. At the very least, this study highlights that $ETCO_2$ levels do not reflect accurate $PaCO_2$ levels and that there is a big difference between the two across all severities of ARDS.

The treatment of ARDS is mostly directed towards preventing its complications, including volutrauma and barotrauma, which are due to high volumes and high pressures inside the lung, respectively. This leads to pneumothoraces, pneumomediastinum and fibrosis all of which lead to death. This can be prevented, in some cases, with lung protective ventilation as described by the ARDSnet trials.[9 10] This involves decreasing the tidal volume delivered by the ventilator to 6 mL/kg of ideal body weight, increasing PEEP, and more recently, positioning the patient prone.

Recent studies have shown that prone positioning, when used in severe ARDS in conjunction with lung protective ventilation, decreases mortality significantly. Patients must be proned quickly when they enter the severe category of ARDS to receive such benefit.[11 12] Additional therapies that have shown benefit in patients with ARDS include the use of neuromuscular blocking agents. In patients with severe ARDS, early administration of a neuromuscular blocking agent improved the adjusted 90-day survival.[13]

Table 1 Baseline characteristics of patients

Characteristics	All patients (n=35)
Age (mean)	60.68
Females–no. (%)	18 (51.0)
Males	17 (49.0)
Diabetes	13 (37.0)
Hypertension	21 (60.0)
Chronic kidney disease	6 (17.1)
Cerebrovascular accident	8 (22.9)
Hyperlipidemia	8 (22.9)
Chronic obstructive pulmonary disease	17 (48.6)
Restrictive lung disease	1 (2.9)
Congestive heart failure	3 (8.6)
Coronary artery disease	5 (14.3)
Weight in kg (mean)	84.16
Average length of stay in days	12.94
Cigarette smoking	15 (42.9)
Cause of ARDS	
Sepsis	13 (37.1)
Healthcare-associated pneumonia	13 (37.1)
Pneumonia	2 (5.7)
Alcohol withdrawal	2 (5.7)
Severe pancreatitis	2 (5.7)
Cardiac arrest	1 (2.9)
Chemical ingestion	1 (2.9)
Pulmonary blastomycosis	1 (2.9)

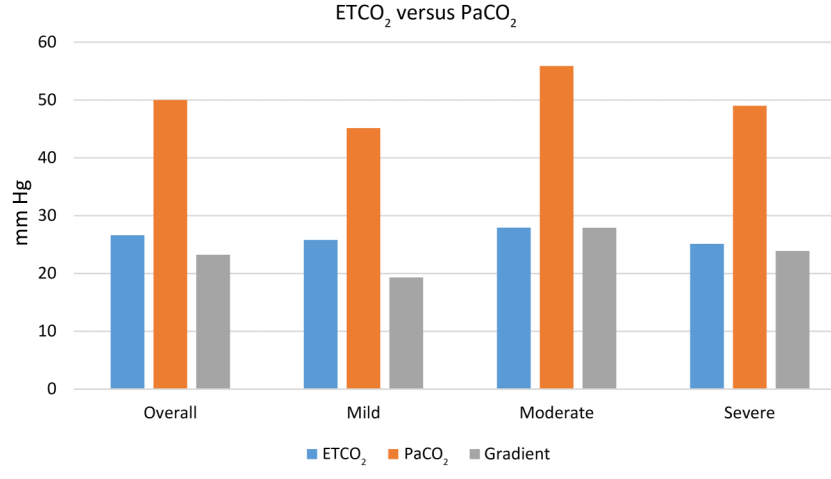

Figure 1 The $PaETCO_2$ gradient in each severity of acute respiratory distress syndrome (ARDS). Relationship between the $PaCO_2$, $ETCO_2$ and $PaETCO_2$ gradient among the severities of ARDS (mild, moderate and severe) and overall.

A reason for delayed recognition of severe ARDS is the need for frequent arterial blood gas sampling. Our study indicates that a worsening $PaETCO_2$ gradient correlates with increasing severity of ARDS and a clinical application of this could be that if a clinician notices a declining/improving gradient, he/she may be alerted that the patient is deteriorating/improving. On calculation of the $PaETCO_2$ gradient from the initial ABG, clinicians can monitor the $ETCO_2$ in real time and if end-tidal CO_2 is declining, that can imply that the dead space is worsening/ARDS is progressing and warrant a repeat ABG to calculate the new $PaETCO_2$ gradient and consider lifesaving maneuvers such as neuromuscular blockade and prone positioning.

There were several limitations to our study. The first was that this was a small study involving one ICU setting, with only 35 patients and 88 total data points. Future studies should be aimed at a larger population that could include more data points in the severe cohort. This may show a statistically significant gradient between moderate and severe ARDS. In addition, our study did not consider the changing severity in each patient, but instead each data point was looked at as a separate entity. Finally, ventilator settings were not considered when collecting data points.

CONCLUSION

Our study shows that with increasing severity of ARDS, the gradient between arterial carbon dioxide content and end-tidal carbon dioxide tends to worsen. A positive correlation is shown between $PaETCO_2$ gradient and mild–moderate and mild–severe ARDS. The study also confirms that $ETCO_2$ is not an accurate estimate of $PaCO_2$ in ARDS. The $PaETCO_2$ gradient has many potential applications, including alerting the clinician to deteriorating lung function when the gradient increases, leading to potential lifesaving maneuvers. However, larger prospective studies are needed to determine if this gradient can be used in conjunction with the P/F ratio in ARDS to further risk stratify patients and direct therapy.

Competing interests None declared.

Ethics approval IRB.

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