NONINVASIVE CARBON DIOXIDE MONITORING IN A PORCINE MODEL OF ACUTE LUNG INJURY DUE TO SMOKE INHALATION AND BURNS

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ABSTRACT In critically ill intubated patients, assessment of adequacy of ventilation relies on measuring partial pressure of arterial carbon dioxide (PaCO2), which requires invasive arterial blood gas analysis. Alternative noninvasive technologies include transcutaneous CO2 (tPCO2) and end-tidal CO2 (EtCO2) monitoring. We evaluated accuracy of tPCO2 and EtCO2 monitoring in a porcine model of acute lung injury (ALI) due to smoke inhalation and burns. Eight anesthetized Yorkshire pigs underwent mechanical ventilation, wood-bark smoke inhalation injury, and 40% total body surface area thermal injury. tPCO2 was measured with a SenTec system (SenTec AG, Therwil, Switzerland) and EtCO2 with a Capnostream-20 (Oridion Medical, Jerusalem, Israel). These values were compared with PaCO2 measurements from an arterial blood gas analyzer. Paired measurements of EtCO2-PaCO2 (n = 276) and tPCO2-PaCO2 (n = 250) were recorded in the PaCO2 range of 25 to 85 mmHg. Overlapping data sets were analyzed based on respiratory and hemodynamic status of animals. Acute lung injury was defined as PaCO2/PaCO2 ≤ 300 mmHg; hemodynamic instability was defined as mean arterial pressure ≤ 60 mmHg. Before ALI, EtCO2 demonstrated moderate correlation with PaCO2 (R2 = 0.45; P < 0.0001), which deteriorated after onset of ALI (R2 = 0.12; P < 0.0001). Before ALI, tPCO2 demonstrated moderate correlation (R2 = 0.51; P = < 0.0001), which was sustained after onset of ALI (R2 = 0.78; P < 0.0001). During hemodynamic stability, EtCO2 demonstrated moderate correlation with PaCO2 (R2 = 0.44; P < 0.0001). During hemodynamic instability, EtCO2 did not correlate with PaCO2 (R2 = 0.03; P = 0.29). tPCO2 monitoring demonstrated strong correlation with PaCO2 during hemodynamic stability (R2 = 0.80, P = < 0.0001), which deteriorated under hemodynamically unstable conditions (R2 = 0.39; P = < 0.0001). Noninvasive carbon dioxide monitors are acceptable for monitoring trends in PaCO2 under conditions of hemodynamic and pulmonary stability. Under unstable conditions, reevaluation of patient status and increased caution in the interpretation of results are required.

KEYWORDS Transcutaneous carbon dioxide, end-tidal carbon dioxide, blood gas analysis, acute lung injury, swine, burns, inhalation injury

INTRODUCTION

Measurement of the partial pressure of carbon dioxide in arterial blood (PaCO2) remains the criterion standard for evaluating the adequacy of ventilation. In certain populations, such as trauma patients with head injury, providing appropriate ventilation (avoiding either overventilation or underventilation) has been shown to save lives (1–2). Obtaining blood gas samples, however, is invasive and requires special equipment, which is often impractical in prehospital settings. Thus, a noninvasive means of estimating PaCO2 would be useful (3). Several such methods have been developed.

End-tidal carbon dioxide (EtCO2) monitoring is performed with increasing frequency in injured patients (4,5). However, this method may become inaccurate in unstable trauma patients (6). The PaCO2-EtCO2 gradient is related to the physiologic dead space as described by Enghoff modification of the Bohr equation (7). PaCO2-EtCO2 gradient increases with increasing physiologic dead space, due to lung injuries or decreased pulmonary perfusion.

Another noninvasive technique that can be used as a surrogate for PaCO2 is the measurement of the transcutaneous partial pressure of CO2 (tPCO2). This technique was pioneered by Severinghaus (8) in the 1960s using a temperature-stabilized heated electrode. Transcutaneous gas tension is a function of dermal capillary blood and in turn of arterial blood flow. Previous studies by Nishiyama et al. (9, 10) demonstrated good correlations between transcutaneous CO2 measurements and PaCO2 in adults undergoing general anesthesia. Several studies, performed in critically ill adults (11–14) as well as in adults undergoing noninvasive ventilation (15, 16), reported good correlation between tPCO2 measurements and PaCO2. Most notably, a study by Hinkelbein et al. (13) demonstrated the feasibility of tPCO2 monitoring in critically ill adults during interhospital transport.
**Noninvasive Carbon Dioxide Monitoring in a Porcine Model of Acute Lung Injury Due to Smoke Inhalation and Burns.**

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**ABSTRACT**

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Nevertheless, there is a paucity of studies comparing Et\textsubscript{CO\textsubscript{2}} and tPCO\textsubscript{2} monitoring in settings of evolving acute lung injury (ALI). Therefore, we carried out an animal study to evaluate the usability and accuracy of these methods in a clinically relevant porcine model of ALI secondary to smoke inhalation and burns.

**MATERIALS AND METHODS**

This study was approved by the US Army Institute of Surgical Research Animal Care and Use Committee. It was conducted in compliance with the Animal Welfare Act and the implementing Animal Welfare Regulations and in accordance with the principles of the Guide for the Care and Use of Laboratory Animals.

**Animal preparation**

For this study, we selected a subgroup of eight female, nonpregnant, Yorkshire pigs from an ongoing study that investigates treatment of acute respiratory distress syndrome (ARDS) due to smoke inhalation and burns. Total intravenous anesthesia with ketamine HCL (20 30 mg/kg per hour), midazolam HCL (1.0 1.5 mg/kg per hour), and propofol (100 μg/kg per hour) was used during the experiment. All animals underwent tracheostomy and placement of central and arterial lines. After instrumentation, animals were allowed to recover for 2 to 3 h. After stabilization, they received inhalation injury with 22 breaths of pine bark smoke at room temperature (Table 1). This model of smoke inhalation injury has been described previously (17). Smoke injury was followed immediately by a 40% total body surface area, full thickness flame burn. Upon completion of smoke inhalation and burn, animals were transferred to the animal intensive care unit where they were continuously monitored for the duration of the experiment. Total intravenous anesthesia levels were adjusted to effect as needed to attain no response to painful stimuli. In addition, buprenorphine HCL (0.1 mg/kg) was administered intramuscularly every 6 h for analgesia for the duration of the study. Resuscitation with lactated Ringer’s solution was performed by means of a computerized burn resuscitation decision support system for the first 24 h after burn. Subsequently, the fluid rate was adjusted for pulmonary toilet was performed at 1, 2, 6, 12, and 24 h after injury, every 24 h thereafter, and anytime airway obstruction was clinically suspected. During suctioning and bronchoscopies, FIO\textsubscript{2} was increased to 100%. After the onset of ARDS, animals were transitioned to low tidal volume CMV, and further ventilator changes, including adjustments of positive end-expiratory pressure and FIO\textsubscript{2}, were made in accordance with the ARDSnet protocol (18). The study was designed to continue for up to 7 days after injury. Experiments were terminated earlier if ARDS did not develop in 72 h after injury or if an animal reached terminal cardiopulmonary failure before 7 days. Animals were killed with intra venous injection of 20 mL Fatal Plus (Vortech Pharmaceuticals, Dearborn, Mich).

**RESULTS**

A total of 454 h of animal intensive care unit care were provided during this study. We recorded 276 paired measurements of PacO\textsubscript{2} and EtCO\textsubscript{2}, and 250 paired measurements of PacO\textsubscript{2} and tPCO\textsubscript{2}, from eight animals. The average duration of monitoring was 56.8 ± 40.9 h. EtCO\textsubscript{2} and tPCO\textsubscript{2} measurements were made across a PacO\textsubscript{2} range of 25 to 85 mmHg. Animal data are presented in Table 1.

![SHOCK Vol. 39, No. 6](image-url)
Two partially overlapping sets of data were analyzed based on (i) pulmonary status (before vs. after the onset of ALI) and (ii) cardiovascular status (hemodynamically stable vs. unstable). The results of this analysis, describing the EtCO2-Paco2 and tPCO2-Paco2 relationships, are presented in Table 2 and are described in the following sections.

**Before versus after the onset of ALI**

Linear regression analysis of 105 EtCO2-Paco2 pairs, recorded before the onset of ALI (Fig. 2A), demonstrated moderate correlation: \( \text{Paco2} = 13.45 + 0.68 \times \text{EtCO2} \left( R^2 = 0.45, P < 0.0001 \right) \). There was systemic underreading by capnography \( (P = 0.02) \). Bland-Altman analysis revealed a mean bias of 0.91 ± 3.77 mmHg (Fig. 2B).

Analysis of 171 EtCO2-Paco2 pairs, recorded after ALI (Fig. 3A), demonstrated low correlation: \( \text{Paco2} = 41.51 + 0.34 \times \text{EtCO2} \left( R^2 = 0.12, P < 0.0001 \right) \). There was systemic underreading by capnography \( (P < 0.001) \). Mean bias increased to 14.84 ± 11.76 mmHg (Fig. 3B).

Analysis of 88 tPCO2-Paco2 pairs, recorded before the onset of ALI (Fig. 2A), revealed moderate correlation: \( \text{Paco2} = 17.01 + 0.56 \times \text{tPCO2} \left( R^2 = 0.51, P < 0.0001 \right) \). No systemic difference was observed \( (P = 0.85) \). Mean bias was 0.09 ± 4.56 mmHg (Fig. 2C).

Analysis of 140 tPCO2-Paco2 pairs, recorded after the onset of ALI (Fig. 3A), revealed strong correlation: \( \text{Paco2} = 7.74 + 0.83 \times \text{tPCO2} \left( R^2 = 0.78, P < 0.0001 \right) \). Slight systemic underreading was present \( (P = 0.026) \). Mean bias was 0.03 ± 5.44 mmHg (Fig. 3C).

**Hemodynamically stable versus unstable**

We repeated the analysis based on hemodynamic status. Linear regression of 233 EtCO2-Paco2 pairs under hemodynamically stable conditions (Fig. 4A) demonstrated moderate correlation: \( \text{Paco2} = 5.32 + 1.03 \times \text{EtCO2} \left( R^2 = 0.44, P < 0.0001 \right) \). There was systemic underreading by capnography. The mean bias was 6.74 ± 8.26 mmHg (Fig. 4B).

Analysis of 41 EtCO2-Paco2 pairs under hemodynamically unstable conditions (Fig. 5A) did not demonstrate a linear relationship: \( \text{Paco2} = 61.4 - 0.16 \times \text{EtCO2} \left( R^2 = 0.03, P = 0.29 \right) \). Systemic underreading was present \( (P < 0.001) \). Mean bias was 25.59 ± 15.30 mmHg (Fig. 5B).

Analysis of 212 tPCO2-Paco2 pairs under hemodynamically stable conditions (Fig. 4A) demonstrated strong correlation: \( \text{Paco2} = 7.86 + 0.82 \times \text{tPCO2} \left( R^2 = 0.80, P < 0.0001 \right) \). There was no systemic difference between the two techniques \( (P = 0.29) \). Mean bias was −0.35 ± 4.75 mmHg (Fig. 4C).

Finally, analysis of 38 tPCO2-Paco2 pairs under hemodynamically unstable conditions (Fig. 5A) demonstrated poor correlation: \( \text{Paco2} = 33.60 + 0.3 \times \text{tPCO2} \left( R^2 = 0.39, P < 0.0001 \right) \). There was systemic overreading \( (P < 0.001) \). Mean bias was −11.32 ± 14.87 mmHg (Fig. 5C).

**DISCUSSION**

In this study, we evaluated the utility of two commonly used noninvasive carbon dioxide monitoring technologies in a severely injured, mechanically ventilated porcine model of ALI due to smoke inhalation and burns. Our principal findings were (i) the period of time between smoke/burn injury and the onset of ALI was characterized by pulmonary instability, manifested by a steady decrease in the PFR and by frequent ventilator changes and other interventions; (ii) both EtCO2 and tPCO2 were moderately correlated with Paco2 during this period; (iii) after

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HD indicates hemodynamically.
the onset of ALI, EtCO₂ became relatively inaccurate, whereas tPCO₂ did not; (iv) hemodynamic instability caused EtCO₂ values to lose their linear relationship with Paco₂. Based on these observations, we conclude that both methods can be useful in the monitoring of patients with developing severe lung injury, but that caution should be used in the interpretation of results when patients are changing rapidly.

Good correlation between EtCO₂ and Paco₂ across all ranges of dead space was reported by McSwain et al. (7). Our previous study (26) demonstrated close correlation between EtCO₂ and Paco₂ in a porcine model of severe chest injury during periods of hemodynamic stability and during settings of hyperventilation and hyperventilation induced by varying tidal volumes and different respiratory rates in healthy swine. At the same time, results were not as promising when accuracy of capnography was evaluated in trauma patients (6). In addition, several studies compared accuracy of end-tidal and tPCO₂ monitoring in human patients (13, 27, 28), favoring tPCO₂. In our study, EtCO₂ systemically underestimated Paco₂. Presence of systemic bias was confirmed by paired Student t test results (Table 2). This is to be expected, particularly in patients with developing ALI, in whom dead space progressively increases, thereby leading to an increase in Paco₂-EtCO₂ gradient.

There was moderate correlation between tPCO₂ and Paco₂ ($R^2 = 0.51$) before ALI. This correlation became more linear ($R^2 = 0.78$) after onset of ALI. We expected better correlation during pre-ALI stage, and such findings were surprising. We speculate that lower tPCO₂-Paco₂ correlation before onset of ALI was possibly due to more frequent ventilator changes; approximately $3.07 \pm 1.53$ changes per hour in the initial phase of the experiment, compared with $1.84 \pm 1.68$ changes per hour after the onset of ALI. Also, more frequent suctioning was required in the first 24 h after injury due to copious secretions. Because it can cause alveolar collapse and loss of recruitment, repeated suctioning may have had a destabilizing effect on Paco₂ correlation. In addition, the tPCO₂ sensor was more frequently disconnected and removed from the animals during the first 24 h of the experiment to accommodate bronchoscopies.

When the tPCO₂-Paco₂ relationship was examined based on hemodynamic status, it was strongly linear ($R^2 = 0.80$) with
minimal bias (−0.35 ± 4.75 mmHg) as long as MAP remained greater than 60 mmHg. Our results confirm those reported previously in human studies (11, 13, 20, 27, 28) that demonstrated similar correlation. tPCO₂ had a less linear correlation to PaCO₂ during hemodynamic instability (R² = 0.39). In addition, transcutaneous monitoring tended to overestimate PaCO₂ under these conditions. Previous reporting (29, 30) indicated that vasoactive medications did not have a significant effect on tPCO₂ monitoring accuracy. However, our results were different, possibly because of the sensor location on the right auricle. Although the animals were hypotensive, their ears were cold to touch, and there was a visible area of vascular congestion. Preferred locations for tPCO₂ monitoring have been reported in humans (9, 10), but no such location has been defined in pigs.

Because we used a subset of animals for this work from a larger study, which pursued treatment of ARDS due to smoke inhalation and burns, the samples we obtained were convenience samples. This limited our ability to further investigate effects of suctioning, ventilator changes, and sensor disconnections on stabilizations/steady state times of the measured variables. Future studies designed specifically to address these limitations may be warranted.

Based on our data, transcutaneous capnometry is an acceptable trend-monitoring tool in settings of lung injury in hemodynamically stable patients and may be useful in a prehospital environment. However, the current generation of tPCO₂ sensors has some limitations. First, the tPCO₂ sensor requires stabilization time after placement. Several articles (31, 32) recommended a 20-min stabilization time while using the SenTec Monitor. Second, to maintain accuracy, the sensor has to be regularly recalibrated in vitro. Recalibration frequency appears to depend on sensor temperature. At 43.5°C, recalibrations were required every 6 to 8 h. On average, recalibration can be completed in approximately 3 min. Afterward, the sensor is repositioned on a patient and again requires stabilization time. In our experience, about 25 to 30 min was spent on moving, cleaning, recalibrating, replacing, and waiting for the sensor to stabilize. In this study, because of previously described limitations, we could not establish the precise stabilization timing necessary for improved accuracy; further study should be considered to

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**Fig. 4.** A, Scatter plot and linear regression analysis between ETCO₂ and PaCO₂ as well as tPCO₂ and PaCO₂ during hemodynamic stability (HD stable). Solid line represents linear regression between tPCO₂ and PaCO₂. Dashed line represents linear regression between ETCO₂ and PaCO₂. B and C demonstrate Bland-Altman analysis between ETCO₂, PaCO₂, and tPCO₂, PaCO₂ pairs; middle solid line indicates the mean difference (bias), and outer solid lines represent limits of agreement (mean ± 1.96 SD) between two methods.

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**Fig. 5.** A, Scatter plot and linear regression analysis between ETCO₂ and PaCO₂ as well as tPCO₂ and PaCO₂ during hemodynamic instability (HD unstable). Solid line represents linear regression between tPCO₂ and PaCO₂. Dashed line represents linear regression between ETCO₂ and PaCO₂. B and C demonstrate Bland-Altman analysis between ETCO₂, PaCO₂, and tPCO₂, PaCO₂ pairs; middle solid line indicates the mean difference (bias), and outer solid lines represent limits of agreement (mean ± 1.96 SD) between two methods.
address this issue. Also, we should point out that a prolonged stabilization time may limit utilization of tPCO2 monitors in prehospital environments. Finally, the sensor membrane requires replacement every 42 days and between patients. Currently, several companies are developing next-generation solid-state tPCO2 sensors that may overcome these shortcomings. Given promising results obtained from the use of a transcutaneous CO2 sensor, these new developments will be a welcomed addition to critical care monitoring armamentarium as well as potentially opening new possibilities for servo controlling mechanical ventilators and extracorporeal life support devices.

CONCLUSIONS

In a porcine model of ALI due to smoke inhalation and burns, transcutaneous CO2 monitoring is an acceptable noninvasive surrogate for PaCO2 under hemodynamically stable conditions and can be useful as a trend monitoring tool. However, tPCO2 readings should be correlated with PaCO2 with increased frequency when a patient’s condition is dynamically changing, for example, during periods of hemodynamic instability. End-tidal CO2 monitoring offers an ease-of-use advantage over the current generation of transcutaneous CO2 monitors. However, EtCO2 readings should be correlated with PaCO2 with increased frequency during evolution of lung injury (changes in dead space).

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