The Ochsner Journal 15:418–422, 2015

Correlation Between Partial Pressure of Arterial Carbon Dioxide and End Tidal Carbon Dioxide in Patients with Severe Alcohol Withdrawal

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Background: Respiratory depression is a common adverse effect of benzodiazepine administration to patients with severe alcoholic withdrawal. This study was conducted to assess the value of end tidal carbon dioxide ($ETCO_2$) levels compared to partial pressure of arterial carbon dioxide ($PaCO_2$) levels in monitoring respiratory depression secondary to benzodiazepine treatment in patients with severe alcohol withdrawal.

Methods: We retrospectively analyzed 36 patients admitted to the intensive care unit for severe alcohol withdrawal who had been administered sedative agents.

Results: We observed a statistically significant correlation between $PaCO_2$ and $ETCO_2$ at time 1 ($r=0.74$, $P<0.01$) and time 3 ($r=0.52$, $P=0.02$) but not at time 2 ($r=0.22$, $P=0.31$).

Conclusion: Our study confirms a positive correlation between $PaCO_2$ and $ETCO_2$ levels in patients experiencing severe alcohol withdrawal.

Keywords: *Alcohol withdrawal delirium, blood gas analysis, capnography, respiratory insufficiency*

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INTRODUCTION

The management of patients with alcohol withdrawal is guided by the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) that is scaled from 0-67.[1] The goal of therapy is to prevent adverse outcomes of alcohol withdrawal, in particular delirium tremens (DT), and to support patients on their path to long-term recovery. The CIWA-Ar score plays an important role in determining the dose and frequency of medication and assessing whether the patient needs to be admitted to the intensive care unit (ICU). Patients with a score >20 are admitted to the ICU to effectively manage their withdrawal symptoms. High doses of benzodiazepines are routinely administered to manage symptoms of psychomotor agitation and to avert advancement of withdrawal symptoms. Benzodiazepines bind to and excite the gamma aminobutyric acid receptor, leading to a decrease in neuronal activity and inducing sedation. A common adverse reaction to benzodiazepines is respiratory depression, defined as insufficient ventilation to achieve the necessary gas exchange for normal metabolic function. During such states of hypoventilation, patients retain carbon dioxide (CO_2), become hypercapnic, and experience respiratory acidosis. To monitor for this unwanted outcome, the arterial blood gas (ABG) test is the standard of care to track the partial pressure of arterial CO_2 ($PaCO_2$).

The ABG test provides valuable information, although its application has several limitations. ABG tests are painful, expensive, time consuming, and not obtained without risk. Capnography is rapidly replacing the ABG test as a noninvasive measure of end tidal CO_2 ($ETCO_2$), the maximum CO_2 concentration or partial pressure at the end of each tidal breath. To assess disease severity and response to treatment, monitoring the changes in $ETCO_2$ with respirations is common practice. Capnography offers practitioners immediate information about metabolism, perfusion, and ventilation or how effectively CO_2 is produced, transported back to the lungs, and eliminated by the alveoli. Capnography has proved to be a valuable tool for patients receiving general anesthesia and care in the emergency department and in the ICU. In intubated patients, capnography can help verify proper placement of the endotracheal tube, predict the success of resuscitation during cardiac arrest, and help transition patients off mechanical ventilation. However, capnography is not limited

to intubated patients. In fact, in spontaneously breathing patients, capnography can help determine response to treatment during acute respiratory stress, offer prognostic signs in patients with sepsis, and determine the adequacy of ventilation in patients who are sedated. While it is known that abnormal changes in $ETCO_2$ levels can be found in patients with respiratory depression caused by excessive sedation,[2] research comparing ABG $PaCO_2$ to capnography for monitoring adverse respiratory events in this patient population is limited.

$ETCO_2$ can be monitored via mainstream or sidestream monitors. Mainstream monitors detect the concentration of air flowing directly through the endotracheal tube, whereas sidestream monitors analyze a sample of the expired air. Mainstream monitors are more accurate than sidestream monitors but are less versatile and more difficult to supply. Sidestream monitors are slightly less accurate than mainstream monitors—because the air sample is smaller—but are more versatile and easier to supply. Sidestream monitors can be used on prone and awake patients and do not require repeated sterilization.

This retrospective study was conducted to assess the value of $ETCO_2$ levels compared to $PaCO_2$ levels from ABG tests in monitoring respiratory depression secondary to benzodiazepine treatment in patients with alcohol withdrawal. Our aim was to investigate for a surrogate marker that is cost effective, rapid, and less labor intensive than the ABG test.

METHODS

This single-center, retrospective study was conducted at Advocate Christ Medical Center in Oak Lawn, IL. Data were collected for this study via an electronic medical record review of 36 patients. Medical records were reviewed for the following inclusion criteria: adult patients experiencing severe alcohol withdrawal who were admitted to the ICU. Medical records were evaluated for patients experiencing respiratory depression as measured by ABG tests and $ETCO_2$ monitoring simultaneously. ABG tests were drawn per the Medical Intensive Care Unit Severe Alcohol Withdrawal Protocol. The protocol states that an ABG test should be drawn 30 minutes after the patient reaches a total bolus dose of 650 mg intravenous phenobarbital and at the time the patient reaches 30 mg/h of lorazepam infusion to monitor early signs of respiratory depression. ABG tests are also drawn when clinically indicated. $ETCO_2$ was recorded at the time of every arterial blood draw and every hour until the patient was no longer experiencing DT. $ETCO_2$ was measured by sampling the exhaled air through an endotracheal tube for patients who required mechanical ventilation or through a nasal cannula or facemask for nonmechanically ventilated patients. The device used was an Oridion Microstream Filterline (Covidien) sidestream capnographer. Additional variables extracted from the medical record included medical history, ICU course, vital signs, CIWA-Ar score at the time the ABG test was drawn, and $PaCO_2$ and $ETCO_2$ values. Institutional review board approval was obtained prior to data collection.

Categorical variables are summarized with frequencies and percentages, and continuous variables are summarized with means and standard deviations. The association between $PaCO_2$ and $ETCO_2$ values at the first 3 time points was analyzed using the Pearson product moment correlation coefficient and displayed as difference scores ($PaCO_2$–$ETCO_2$). Analysis was performed using SPSS v.22 (IBM), and statistical significance was determined at $P<0.05$.

RESULTS

The Table displays demographics and clinical parameters for the study population (n=36). The sample was predominantly male (n=31, 86.1%), with a mean age of 46.0 years (SD=10.2). The mean CIWA-Ar score was 14.8 (SD=9.9), the mean temperature was 36.8°C (SD=2.8), the mean heart rate was 87.0 beats per minute (SD=18.0), and the mean respiratory rate was 20.0 breaths per minute (SD=7.0).

Mean differences between $PaCO_2$ and $ETCO_2$ are displayed in Figure 1 for the first 3 time points when these scores were measured. $PaCO_2$ was 9.4-10.3 mmHg higher on average than $ETCO_2$: for time 1, the mean difference was 10.3 mmHg (95% confidence interval [CI]=7.9-12.6); for time 2, the mean difference was 9.7 mmHg (95% CI=6.7-12.6); for time 3, the mean difference was 9.4 mmHg (95% CI=6.3-12.6). A statistically significant correlation between $PaCO_2$ and $ETCO_2$ was seen for time 1 (r=0.74, $P<0.01$) and time 3 (r=0.52, $P=0.02$) but not for time 2 (r=0.22, $P=0.31$) (Figure 2).

DISCUSSION

In normal healthy lungs, CO_2 is an end product of tissue metabolism that is transported to the lungs where it diffuses across the capillary membrane via perfusion. Alveolar ventilation then eliminates CO_2 from the body. This close relationship between ventilation and perfusion subsequently manifests in a constant and predictable gradient between $PaCO_2$ and $ETCO_2$ levels.[2,3] To calculate the $ETCO_2$–$PaCO_2$ gradient—normally 2-5 mmHg—an ABG test must be sampled at the same time an $ETCO_2$ measurement is acquired.[4] In patients who do not have significant cardiopulmonary disorders or a ventilation/perfusion (V/Q) mismatch, $ETCO_2$ levels can be used as a surrogate marker for $PaCO_2$ levels.

In our review of the literature, we found no studies indicating that $ETCO_2$ levels could not be used as a surrogate marker for $PaCO_2$ levels in patients who are facing alcohol withdrawal symptoms and are being treated with benzodiazepines. Our hypothesis is that this cannot be disproved because although these patients are experiencing respiratory depression secondary to therapy, no V/Q mismatch is present, and therefore the $ETCO_2$–$PaCO_2$ gradient will be normal and consistent at approximately 2-5 mmHg. Other studies assessed patients with cardiopulmonary pathology in whom a V/Q mismatch was present.[3,5,6] In these patients, the $ETCO_2$–$PaCO_2$ gradient increases, and therefore correlating the two measurements is not a reliable measure of the true CO_2 level in the blood. In conditions with increased dead space ventilation, such as a pulmonary embolism, parts of the lungs are well ventilated but not perfused. On the other hand, in conditions such as atelectasis or increased alveolar fluid, areas of the lung are well perfused but not ventilated. Studies have shown that $ETCO_2$ levels are a poor predictor of $PaCO_2$ levels in these conditions of respiratory failure.[3,7]

Based on a 2013 study, an emerging trend in the treatment of acute alcohol withdrawal syndrome is com-

Table. Demographics and Clinical Parameters of the Study Population (n=36)

Variable	Value
Male, n (%)	31 (86.1)
Age, years (SD)	46.0 (10.2)
CIWA-Ar score during admission (SD)	14.8 (9.9)
$PaCO_2$, mmHg (SD)	39.9 (7.1)
$ETCO_2$, mmHg (SD)	30.4 (6.1)
Temperature, °C (SD)	36.8 (2.8)
Heart rate, beats per minute (SD)	87.0 (18.0)
Respiratory rate, breaths per minute (SD)	20.0 (7.0)

CIWA-Ar, Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised; $ETCO_2$, end tidal carbon dioxide; $PaCO_2$, partial pressure of arterial carbon dioxide.

bined barbiturate and benzodiazepine therapy for prevention of severe DT.[8] In that study, only 1 patient of a possible 102 patients was intubated. It is unclear if this intubation was because of respiratory depression or refractory agitation. Another study showed that escalating doses of phenobarbital decreased the amount of intubations required.[9] To our knowledge, no studies have been performed on $ETCO_2$ monitoring of patients receiving barbiturates for alcohol withdrawal.

Patients experiencing respiratory depression from excessive sedation require careful monitoring of their oxygenation and ventilation. In respiratory depression, patients have decreased ventilation that leads to an abnormal retention of CO_2. To monitor the adverse effects of hypoventilation, ICU protocols require trends in CO_2 levels to be tracked using ABG tests and $ETCO_2$ measurements. The purpose of this study was to assess whether $ETCO_2$ levels could be used as a reliable surrogate for $PaCO_2$ levels once a baseline gradient between the two values was established. Tracking $ETCO_2$ levels may reduce the need for frequent ABG sampling, allowing for continuous, safe, comfortable, and less-invasive monitoring. Our results showed a positive correlation between the $ETCO_2$–$PaCO_2$ gradient in patients undergoing alcohol withdrawal and requiring benzodiazepine therapy. The results indicate a constant gradient of 9.5 mmHg (95% CI=6.7-12.6) between the two values, a higher gradient than has been reported in previous studies on other populations.[3,4,7] This difference was consistent throughout our population's hospital course, as 3 different data sets indicate a mean difference of approximately 9.5 mmHg. The gradient trend is significant because it can be used as an active clinical tool to assess the adequacy of treatment. A reduction in the gradient can indicate that treatment has been effective. An elevation in the gradient can indicate that the pulmonary condition is worsening, and further diagnostic and therapeutic measures should be considered. The $ETCO_2$ level may also be used reliably to indicate $PaCO_2$ level trends in patients with healthy lungs. For example, declining $ETCO_2$ levels may indicate a developing underlying process such as metabolic acidosis.

The limitations of this study were as follows: this study was performed using a patient population at 1 hospital and may not represent the population as a whole, the study did not compare $ETCO_2$ levels from a healthy population to the $ETCO_2$ levels of patients enrolled in the study, and this was a retrospective study with a relatively small sample size.

CONCLUSION

This study confirms a positive correlation between $PaCO_2$ and $ETCO_2$ levels in patients experiencing severe alcohol withdrawal. However, the gradient between the two measurements was larger in our study than in previous studies that have indicated a normal gradient of 2-5 mmHg. The $ETCO_2$ level in our study was, on average, 9.5 mmHg lower than the $PaCO_2$ level and was consistent throughout the patients' hospital course. Capnography can be a potential form of cardiopulmonary monitoring for patients who do not

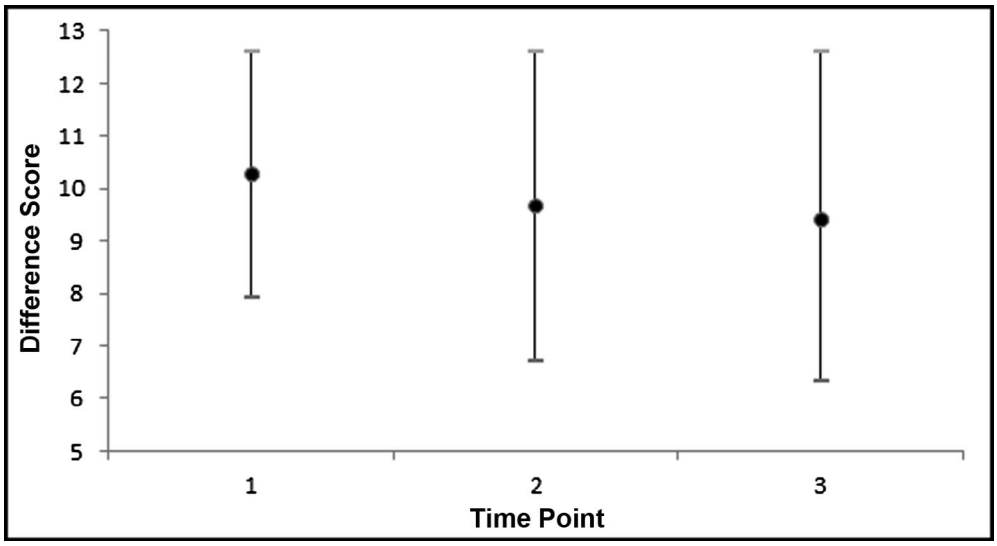

Figure 1. Mean differences between partial pressure of arterial carbon dioxide ($PaCO_2$) and end tidal carbon dioxide ($ETCO_2$). Mean difference scores with 95% confidence interval between $PaCO_2$ and $ETCO_2$ levels for the first 3 time points were measured.

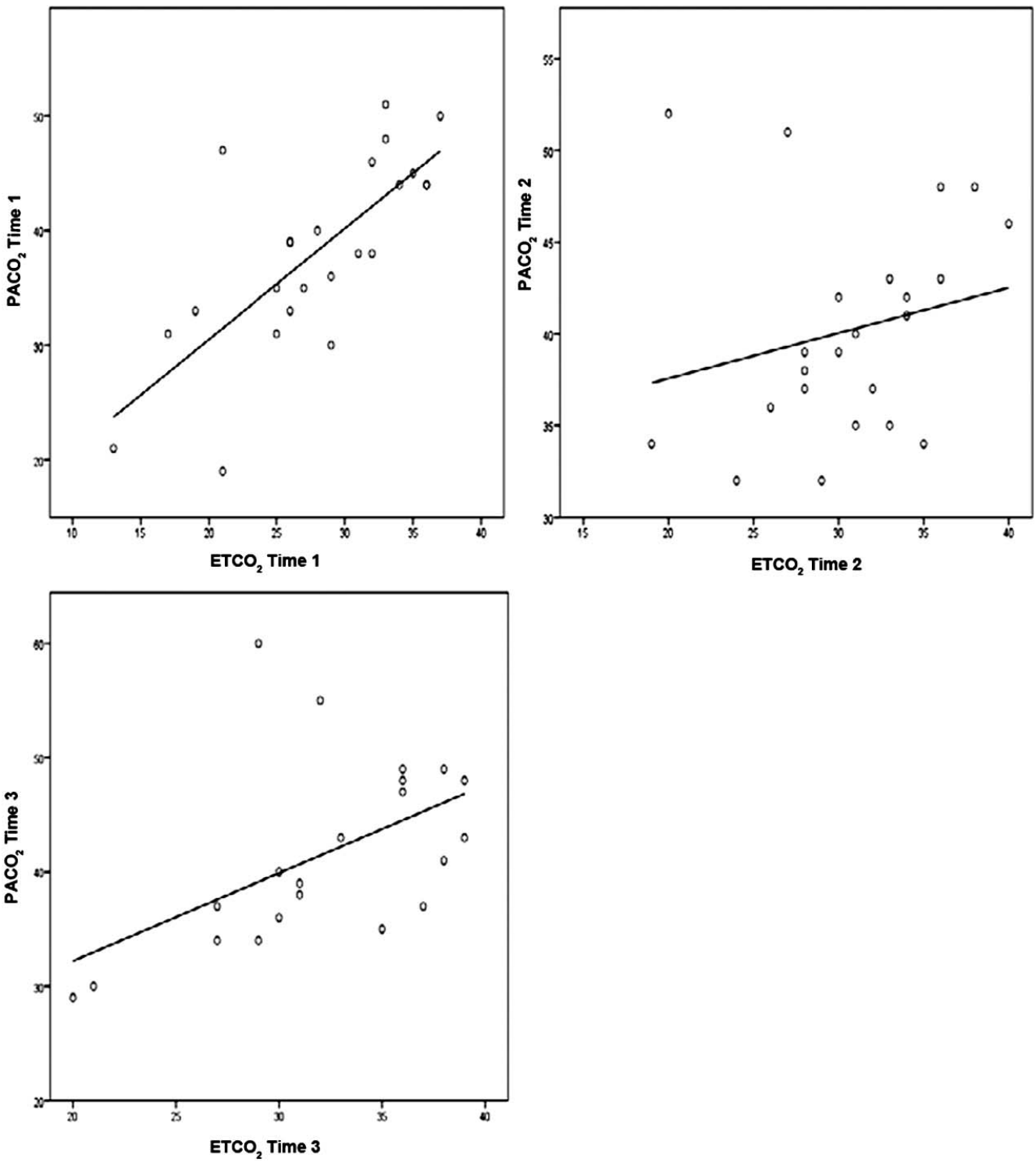

Figure 2. Scatterplots of the correlation between partial pressure of arterial carbon dioxide ($PACO_2$) and end tidal carbon dioxide ($ETCO_2$) levels at time points 1, 2, and 3.

have a V/Q mismatch and offers more convenient, noninvasive monitoring than ABG testing.

ACKNOWLEDGMENTS

The authors have no financial or proprietary interest in the subject matter of this article.

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