CORRELATION BETWEEN CAPNOGRAPHY AND ARTERIAL CARBON DIOXIDE BEFORE, DURING, AND AFTER SEVERE CHEST INJURY IN SWINE

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ABSTRACT  The relationship between end-tidal carbon dioxide (EtCO₂) and arterial carbon dioxide (PaCO₂) if better defined could facilitate the difficult task of ventilation in prehospital trauma patients. We aimed to study the PaCO₂-EtCO₂ relationship before, during, and after chest trauma, hemorrhage, and resuscitation in swine. Twenty-four swine were intubated, anesthetized, and monitored in an animal intensive care unit during three phases: phase 1 (day 1, healthy animals); phase 2 (day 2, injury), which consisted of blunt chest trauma, hemorrhage, and resuscitation; and phase 3 (day 2, after injury). “Respiratory maneuvers” (changes in respiratory rate and tidal volume [TV], intended to vary the PaCO₂ over a range of 25 to 85 mmHg, were performed during phases 1 and 3. End-tidal CO₂ and PaCO₂ were recorded after each respiratory maneuver and analyzed using linear regression. During phase 1, PaCO₂ and EtCO₂ were strongly correlated (r² 0.97, P < 0.01). During phase 2, animals developed decreased oxygenation (PaO₂/FiO₂ [fraction of inspired oxygen] ratio < 200) and hypotension (mean arterial pressure, 20–50 mmHg); the PaCO₂-EtCO₂ relationship deteriorated (r² 0.25, P < 0.0001). During phase 3, oxygenation, hemodynamics, and the PaCO₂-EtCO₂ relationship recovered (r² 0.92, P < 0.01). End-tidal CO₂ closely correlates to PaCO₂ in healthy animals and after injury/resuscitation across a wide range of respiratory rates and tidal volumes. Once oxygenation and hemodynamics are restored, EtCO₂ can be used to predict PaCO₂ following chest trauma/hemorrhage and should be considered for patient monitoring. This work demonstrated that EtCO₂ alone can reliably be used to estimate PaCO₂ in uninjured subjects and in those subjects who have been resuscitated from severe injury. Immediately after blunt chest injury, the correlation between EICO₂ and PaCO₂ is temporarily unstable. Under these circumstances (with abnormal oxygenation and/or hemodynamics), greater caution and other monitoring tools may be required.

KEYWORDS  End-tidal carbon dioxide, pulmonary contusion, pulmonary dead space, swine, blood gas analysis, carbon dioxide

INTRODUCTION

After experiencing severe trauma, patients may require advanced airway control for respiratory support before reaching the hospital. In a large retrospective study (n = 9,018) concerning prehospital transport of trauma patients, endotracheal intubation occurred in the field 16.7% of the time (1). In addition to securing a patent airway, first responders must attempt to achieve adequate ventilation, as hyperventilation or hypoventilation can have adverse effects on the patient’s acid-base status. Davis and colleagues (2) showed a higher mortality in head-injured patients who were hyperventilated or hypoventilated (n = 890 intubated and n = 2,709 nonintubated) before hospital arrival. Adverse effects of ventilation are especially noticeable in the setting of traumatic brain injury (TBI); hyperventilation can worsen outcomes by reducing intracranial blood flow and parenchymal perfusion, whereas hypoventilation causes decreased oxygen delivery (3, 4). Additional risks associated with hyperventilation include overinflation of airspaces and potential worsening of airway injury by barotrauma. Overinflation could also worsen a tension pneumothorax and lead to cardiovascular collapse. In the setting of cardiac arrest, hyperventilation can worsen coronary perfusion by increasing intrathoracic pressure (5). These scenarios highlight the need for normoventilation and normocapnia during prehospital transport of trauma patients to decrease mortality and improve outcomes.

The criterion standard by which to assess arterial carbon dioxide (PaCO₂) levels is to perform arterial blood gas (ABG) analysis. However, in the early stages of trauma casualty extraction and transport (prehospital), ABG analysis is not feasible (6). Capnography has emerged as a noninvasive surrogate for PaCO₂. Use of continuous capnography with adaptive ventilation strategies in the prehospital setting has shown improvement in achieving normocapnia in trauma patients (7). Helm and colleagues (7) compared anesthetist delivery of prehospital ventilation either using continuous capnography versus no capnography. Patients with head and chest trauma, hemodynamic instability, or a higher injury severity score arrived more frequently in the normocapnic range when ventilation was guided using capnography compared with using no capnography monitor. In light of these findings, capnography represents a potential method by which to improve ventilation during the prehospital phase of care in trauma victims.

The correlation between end-tidal CO₂ (EtCO₂) and PaCO₂ is well known, and a PaCO₂-EtCO₂ gradient (defined as PaCO₂ − EtCO₂) of 5 to 10 mmHg is expected in an otherwise healthy patient. This gradient is a function of pulmonary dead space and
Correlation between capnography and arterial carbon dioxide before, during, and after severe chest injury in swine

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Experimental protocol: respiratory maneuvers (phases 1 and 3)

We performed a sequence of ventilator changes across a wide range of minute ventilations by altering either RR or TV to hyperventilate or hypoventilate the animal. We termed these changes “respiratory maneuvers,” and we completed them during both the uninjured (day 1, phase 1) and injured states (day 2, phase 3) in all animals. After baseline measurements, each animal was randomized to one of four groups to determine the sequence by which the animal would undergo the respiratory maneuvers. These groups are listed in Table 1. All animals went through every ventilator change, but because of randomization, the sequence of respiratory maneuvers differed among animals. Before respiratory maneuvers, animals were determined to have adequate anesthetic depth without response to painful stimuli. Animals were then administered boluses of vecuronium (1 mg/kg) to ensure absence of spontaneous respirations during the maneuvers. Two sets of data were collected, and the results averaged after each respiratory maneuver.

Experimental protocol: phase 2

All animals underwent injury on day 2. Injury consisted of right sided PC delivered as previously described using a modified captive bolt humane stunner (model MKL, Karl Schermer; Packers Engineering, Omaha, Neb) (10). Immedi-ately after PC, a chest tube was placed on the side of impact. Ten minutes after PC, constant rate hemorrhage was performed, for a total volume of 12 mL/kg over 10 min. The blood was removed through an arterial line and stored in citrated blood collection bags (Terumo, Somerset, NJ). The animal was observed for 30 min following the end of hemorrhage. Then, a pressure bag was used to administer warm lactated Ringer’s (LR) solution at a volume of three times the volume of shed blood over a 10 min period. After administration of LR solution, the animals were transfused with the previously collected blood. Administration of LR solution was then started at a rate of two times the body weight per hour and titrated to achieve a urine output of at least 1 mL/kg per hour. It should be noted that no respiratory maneuvers were performed during this phase. The animals were then returned to the sternal recumbent position, and respiratory maneuvers were again performed as described above.

Statistical analysis

All data are means (±SEM) of MAP, PFR, EtCO2, or PaCO2 at each respiratory maneuver during phases 1 and 2 and were analyzed for statistical differences using a Wilcoxon signed rank test. Phase 2 data were recorded over time, and a two way analysis of variance with repeated measures was performed on EtCO2 and PaCO2 to determine if time from injury had any impact on the relationship between them. Variables suspected to play a role in pre dicting PaCO2 were MAP, PFR, and EtCO2. We used those variables in step wise linear regression to model the relationship between EtCO2 and PaCO2 during phases 1, 2, and 3. All statistics were completed using Stata (StataCorp, College Station, Tex) or SAS (SAS Institute Inc, Cary, NC) software.

RESULTS

Twenty-four animals underwent experimental procedures. More than 700 h of animal ICU care were used to complete this protocol. Four animals died after phase 1, of whom two died immediately following PC as a direct result of the impact. Necropsy revealed massive pulmonary parenchymal and vascular injury, which was deemed to be the cause of death. The other two animals died on day 1 from spontaneous dysrhythmias attributed to the indwelling pulmonary artery catheter. Each animal developed ventricular tachycardia and subsequent pulseless electrical activity. Necropsy revealed small clots and endocardial irritation within the right atrium with evidence of trauma due to the pulmonary artery catheter. Cardiac irritation was deemed to be the cause for the fatal dysrhythmias and hence death. For the final analysis, all 24 animals were used to examine phase 1 data, and the 20 animals surviving to the end of study were used to examine phase 3 data. Data were recorded continuously during phase 2 for 13 animals and constituted the subset of animals used for phase 2 analysis.
Phase 1
Multivariate stepwise linear regression to model PaCO₂ was done using the following variables: MAP, PFR, and EtCO₂ in the healthy animal (phase 1). End-tidal CO₂ had the strongest association with PaCO₂. Adding MAP did not show an increase in correlation and was therefore left out of the final model. Ratio of PaO₂ to FiO₂ was not associated with PaCO₂. Using EtCO₂ alone as the independent variable and including all ventilator changes (RR and TV) on day 1, the association with PaCO₂ was strong: PaCO₂ = -0.98 + 0.96 * EtCO₂ (r² = 0.97, P < 0.05) (Fig. 1).

Phase 2
Immediately upon impact, MAP decreased dramatically. Mean arterial pressure then decreased again during the hemorrhage period (Figs. 2, 2–3) and slowly recovered during the shock period (Figs. 2, 3–4), resuscitation with LR solution (Figs. 2, 4–5), and transfusion (Figs. 2, 5–6). Ratio of PaO₂ to FiO₂ decreased markedly from baseline (Fig. 3, 0) to 10 min following impact (Figs. 2 and 3) and remained 300 or less during the entire injury/resuscitation sequence.

Figure 4 shows EtCO₂ and PaCO₂ during phase 2. Within seconds of impact, the PaCO₂ remained relatively constant,

| Table 1. Order by which animals underwent ventilator changes |
|---------------------------------|------------------------------------------|
| Group no.: No. animals in each group | Description of sequence of respiratory maneuvers RR, TV | Example |
| Group 1: eight animals | Each ventilator change is separated by seven min: | Start: TV = 10 mL/kg, RR = 14 |
| | 1. Increase RR by 2/min to maximum of 30/min | 1. TV hold at 10 mL/kg; increase RR = 16, 18, 20, ...; RR = 30 |
| | 2. Change RR back to baseline settings and increase TV to 20 mL/kg | 2. Change RR = 14, TV = 20 mL/kg |
| | 3. Decrease TV by 2 mL/kg until 4 mL/kg is reached | 3. RR hold at 14; decrease TV = 20 mL/kg, = 18 mL/kg, = 16 mL/kg, ... = 4 mL/kg |
| | 4. Change TV back to 10 mL/kg and decrease RR to 6/min | 4. Change TV = 10 mL/kg, RR = 6 |
| | 5. Increase RR by 2/min until baseline setting is reached | 5. TV hold at 10 mL/kg; increase RR = 6, 8, 10, 12, 14 |
| Group 2: five animals | Each ventilator change is separated by seven min: | Start: TV = 10 mL/kg, RR = 14 |
| | 1. Increase TV by 2 mL/kg until a maximum of 20 mL/kg is reached | 1. RR hold at 14/min; Increase TV to = 12 mL/kg, = 14 mL/kg, ... = 20 mL/kg |
| | 2. Change TV back to 10 mL/kg and increase RR to 30/min | 2. Change TV = 10 mL/kg, RR = 30 |
| | 3. Decrease RR by 2/min until 6/min is reached | 3. TV hold at 10 mL/kg, decrease RR = 30, 28, 26, ... = 6 |
| | 4. Change RR back to baseline settings and decrease TV to 4 mL/kg | 4. Change RR = 14, TV = 4 mL/kg |
| | 5. Increase TV by 2 mL/kg until 10 mL/kg is reached | 5. RR hold at 14, increase TV = 4 mL/kg, = 6 mL/kg, ... = 10 mL/kg |
| Group 3: six animals | Each ventilator change is separated by 7 min | Start: TV = 10 mL/kg, RR = 14 |
| | 1. Decrease RR by 2/min to a minimum of 6/min | 1. TV hold at 10 mL/kg; decrease RR = 14, = 12, ... = 6 |
| | 2. Change RR back to baseline settings and decrease TV to 4 mL/kg | 2. Change TV to 4 mL/kg, RR = 14 |
| | 3. Increase TV by 2 mL/kg until 20 mL/kg is reached | 3. RR hold at 14; increase TV = 4 mL/kg, = 6 mL/kg, = 8 mL/kg, ... = 20 mL/kg |
| | 4. Change TV back to 10 mL/kg and increase RR to 30/min | 4. Change TV = 10 mL/kg, RR = 30 |
| | 5. Decrease RR by 2/min until baseline setting is reached | 5. TV hold at 10 mL/kg; decrease RR = 30, 28, 26, ... = 6 |
| Group 4: five animals | Each ventilator change is separated by 7 min | Start: TV = 10 mL/kg, RR = 14 |
| | 1. Decrease TV by 2 mL/kg until a minimum of 4 mL/kg is reached | 1. RR hold at 14/min; Decrease TV to = 8 mL/kg, = 6 mL/kg, ... = 4 mL/kg |
| | 2. Change TV back to 10 mL/kg and decrease RR to 6/min | 2. Change TV = 10 mL/kg, RR = 6 |
| | 3. Increase RR by 2/min until 30/min is reached | 3. TV hold at 10 mL/kg, increase RR = 6, 8, 10, ... = 30 |
| | 4. Change RR back to baseline settings and increase TV to 20 mL/kg | 4. Change RR = 14, TV = 20 mL/kg |
| | 5. Decrease TV by 2 mL mL/kg until 10 mL/kg is reached | 5. RR hold at 14, decrease TV = 18 mL/kg, = 16 mL/kg, ... = 10 mL/kg |

Note that although animals underwent changes in different orders, they all rotated through every possible ventilator change.
whereas EtCO₂ decreased dramatically. Over the next 10-minute period, EtCO₂ recovered partially. No interaction was noted between the PaCO₂-EtCO₂ gradient and time until the start of blood transfusion (Figs. 4, 5). After this time point, EtCO₂ and PaCO₂ began to converge as time progressed.

Univariate regression of EtCO₂ and PaCO₂ during phase 2 indicated a weaker association than during the other phases (1 and 3), and an increase in the gradient: PaCO₂ = 26.8 + 0.49 * EtCO₂ \( (r^2 = 0.25, P < 0.0001, n = 13) \). The relationship is illustrated in Figure 5. Mean arterial pressure and PFR were found to have a stronger association with PaCO₂ than during phases 1 or 3 and could be included in a multivariate linear regression model. Using all variables (MAP, PFR, and EtCO₂), the equation is PaCO₂ = 23.9 + (0.52 * EtCO₂) + (0.04 * PFR) + (0.19 * MAP). Despite inclusion of these other variables, the association remained weaker than observed either before injury or after transfusion \( (r^2 = 0.51, P < 0.0001) \).

Phase 3

Overall, MAP was lower (considering both sets of respiratory maneuvers together) during phase 3 than during phase 1 \( (P < 0.0001) \). Despite PC and hemorrhage, the PFR recovered to greater than 300 during phase 3. However, the PFR was higher during phase 1 compared with phase 3 \( (P < 0.0001) \). Hypoventilation adversely affected PFR, particularly at the lower end of TV, during both phases 1 and 3; ventilation with 4 mL/kg caused PFR of less than 300 in both injured and uninjured.

End-tidal CO₂ was statistically different (between phases 1 and 3) during changes in RR and TV \( (P < 0.05) \). By contrast, PaCO₂ values were not different comparing phase 1 with phase 3 during the same changes in RR and TV \( (P > 0.05) \). As in phase 1, higher PaCO₂ and EtCO₂ were noted during low TV ventilation compared with low RR ventilation.

During phase 3, linear regression was again performed to model the PaCO₂-EtCO₂ relationship. The equation for this phase was PaCO₂ = 2.52 + 0.97 * EtCO₂ (Fig. 6). The association
between EtCO2 and PaCO2 was again shown to be strong ($r^2 = 0.92, P < 0.05$), although slightly weaker than for phase 1 data. Ratio of PaO2 to FiO2 was not associated with PaCO2, and the addition of MAP to the model did not improve it.

**DISCUSSION**

The principal findings in this study are as follows: (a) EtCO2 and PaCO2 were closely correlated in uninjured, mechanically ventilated pigs across a wide range of TVs and RRs; (b) EtCO2 and PaCO2 were also correlated in injured and resuscitated pigs with a difference of approximately 2.5 mmHg across a similar range of TVs and RRs; (c) EtCO2 and PaCO2 showed a weaker correlation during the immediate postinjury period, with a gradient of 22 mmHg.

Capnography is a vital tool in the armamentarium of aeromedical teams and first responders (11). Some health care providers who are involved in the prehospital transport of casualties are now relying on continuous EtCO2 monitoring rather than one-time capnometry for verification of correct placement of an airway. In their prospective observational study, Silvestri et al. (12) examined patients ($n = 153$) who were intubated before facility arrival. In those whose intubation was monitored using continuous capnography (93/153), the rate of unrecognized displaced endotracheal tubes was 0%, whereas the rate for the patients without continuous monitoring (60/153) was 9%. Kober et al. (13) demonstrated capnography’s utility in nonintubated trauma victims ($n = 70$) when they compared sensor malfunction rate during transport between pulse oximetry and capnography. Capnography was not found to be more inconvenient to the patients and gave disruption alerts only 0.8% of the transport time, compared with 13.2% for the pulse oximeter (13). Despite these demonstrated benefits of continuous capnography, it is currently not being fully utilized during the prehospital phase of trauma care.

Prehospital casualty retrieval and transport involve advanced airway control in a significant percentage of patients either by endotracheal intubation, bag-valve-mask, laryngeal mask airway, Combitube, or other apparatus (14, 15). Controlling CO2 levels and ventilation adequacy during this period can improve short-term acid-base status and improve long-term outcomes in trauma patients (1, 16, 17). Arguably, TBI patients can most benefit from tight control of blood CO2 levels so as to improve brain perfusion during the crucial 24 to 48 h after injury (18). Current recommendations from the literature include targeting PaCO2 levels between 35 and 40 mmHg so as to achieve optimal outcomes in these situations (19–21). Several studies indicate that a sizeable number of patients with TBI reach the hospital having been inappropriately ventilated (22, 23). Hyper-ventilation and hyperventilation during this period, especially in the setting of TBI, increase mortality rates (2, 3). Dumont et al. (16) retrospectively examined 77 patients with TBI admitted to a level I trauma center over a period of 7 years (January 2000 to January 2007) to determine if PaCO2 level on arrival was associated with in-hospital mortality. Patients with normocapnia had a lower mortality rate (15%) compared with those who were hypercapnic (61%) or hypocapnic (77%) ($P = 0.045$ between groups) (16).

The use of continuous capnography during prehospital transport has already been shown in some studies to improve ventilation adequacy (7). Davis (3) demonstrated that using continuous capnography reduces hyperventilation but does not eliminate it. However, creating a specific algorithm to achieve tight control can improve normoventilation even further. Helm and colleagues (7) have also shown that using continuous capnography during the prehospital care of trauma patients increases the likelihood that the patient will arrive at the hospital normocapnic. In their study, patients with chest trauma or hemodynamic instability were more likely to be normoventilated on hospital arrival when capnography was used to guide ventilation (7).

Our study makes use of a controlled large animal model before, during, and after isolated chest trauma, hemorrhage, and resuscitation—with time points intended to simulate injury, extraction, transport, and resuscitation. Our data demonstrate a close association between PaCO2 and EtCO2 during periods of hemodynamic stability in both uninjured animals and injured animals with a history of chest trauma in which adequate...
oxygenation (PFR >300) has been restored. Immediately after injury (during the first 90 min after PC), oxygenation (PFR) and hemodynamics (MAP) are shown to play a role in the gradient between PaCO₂ and EtCO₂. The relationship between EtCO₂ and PaCO₂ is related to physiologic dead space, ventilation-perfusion (V/Q) matching, and CO (24, 25). This has been shown by McSwain and colleagues (8) in a retrospective cross-sectional study in which they examined pediatric ICU patients comparing PaCO₂ and EtCO₂ gradient as it relates to the ratio of physiologic dead space (Vₐ) to tidal volume (Vₜ). They showed that a strong correlation (ρ = 0.95) exists between the PaCO₂-EtCO₂ relationship at low physiologic dead space (Vₐ/Vₜ ≤0.4) and that the correlation remains strong (ρ = 0.86) to moderately strong (ρ = 0.78) at increasing levels of dead space (Vₐ/Vₜ = 0.56–0.7 and Vₐ/Vₜ > 0.7, respectively). The PC model used by us has been shown to lead to increased Vₐ/Vₜ and thus seems to provide an appropriate setting to test the dynamics of the PaCO₂-EtCO₂ gradient (9, 10).

The use of capnography in trauma patients has been discouraged because of some studies that showed a lack of correlation between EtCO₂ and PaCO₂ in this population. Russell and Graybeal (26) examined the correlation between EtCO₂ and PaCO₂ in nine trauma patients in an ICU setting. In 78% of patients, a significant (P < 0.05) relationship was found between these two variables. However, individual gradients ranged from −2 to 36 with a mean of 14 ± 11 mmHg, and the correlations were not always positive or negative. A larger gradient between these two variables was found in situations of decreasing oxygenation, an observation that we made from our data as well. Belpomme and colleagues (27) examined the gradient between EtCO₂ and PaCO₂ in the prehospital setting in both trauma and nontrauma patients, and they concluded that EtCO₂ could not be used to reliably estimate PaCO₂. The patients in their study were quite hypoxic, however, and required on average 72% ± 19% to 78% ± 20% FIO₂. The study included eight trauma patients, whereas the remaining 92 patients had a variety of other medical disorders, some with compromised lung mechanics. Both these factors would decrease the correlation between EtCO₂ and PaCO₂ as evidenced by our model during the acute injury period (phase 2).

To optimize the usefulness of continuous capnography in trauma, we must specifically define how the PaCO₂-EtCO₂ relationship changes after different levels of injury and with regard to the area of body injured. No study has examined this gradient in patients with history of trauma, who regain hemodynamic stability after resuscitation. Our study in swine simulated bilateral chest injury model. Our data indicate that, in healthy animals, the gradient between PaCO₂ and EtCO₂ was approximately −1 mmHg (i.e., slightly higher EtCO₂ than PaCO₂). Several potential explanations exist for a negative gradient. Rebreathing of previously exhaled air in the ventilator circuit could create a mixture of previously exhaled CO₂ and newly exhaled CO₂. In addition, low (but finite) V/Q lung units may also decrease the gradient. Fletcher and colleagues (28) outline the physiology behind this finding and state, “the negative... gradient implies compensation by perfusion for early emptying, overventilated alveoli.”

Finally, we concede that patients most likely will not have indwelling arterial catheters in the prehospital setting. Venous blood gas analysis could also be a viable method by which to estimate a patient’s acid-base status. In our current model, we did not measure real-time concordant venous blood gases, but this practice should be further investigated in view of our current findings and explored as a potential tool by which to facilitate capnography-driven ventilation control.

REFERENCES


