

THE NONINVASIVE CARBON DIOXIDE GRADIENT (NICO₂G) DURING HEMORRHAGIC SHOCK

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ABSTRACT—Hemorrhagic shock (HS) is a setting in which both pulmonary and cutaneous perfusion may be impaired. The goals of this study were to evaluate the relationship between end-tidal (etCO₂), transcutaneous (tPCO₂), arterial carbon dioxide (PaCO₂) and lactate during lethal HS and to assess the effect of progressive HS on those variables and on a new variable, the noninvasive CO₂ gradient ([NICO₂G] or the difference between tPCO₂ and etCO₂). Ten consciously sedated swine were hemorrhaged, by means of a computerized exponential protocol, of up to 80% estimated blood volume for 20 min. End-tidal carbon dioxide, tPCO₂, PaCO₂, and lactate measurements were taken at baseline and every 5 min thereafter, that is, after 25%, 44%, and 62% total blood volume hemorrhage (TBVH) and at cardiac arrest. Cardiac arrest occurred on average at 67% TBVH. Data were analyzed by linear regression and one-way repeated-measures analysis of variance and are presented as means ± SD. Forty-nine paired measurements were made. There was no overall relationship between NICO₂ variables and PaCO₂: PaCO₂ vs. tPCO₂ ($r^2 = 0.002$, $P = 0.78$); PaCO₂ vs. etCO₂ ($r^2 = 0.0002$, $P = 0.93$). Rather, NICO₂G increased at each level of blood loss: 4.0 ± 24.9 at baseline, 6.3 ± 35.7 at 25% TBVH, 25.0 ± 37.6 at 44% TBVH, 55.0 ± 33.9 at 62% TBVH, and 70.0 ± 33.2 at cardiac arrest ($P < 0.05$). Similarly, tPCO₂ increased and etCO₂ decreased at each level. Linear regression of NICO₂G and lactate showed a better correlation than was observed for the other two variables: NICO₂G, $r^2 = 0.58$; tPCO₂, $r^2 = 0.46$; etCO₂, $r^2 = 0.26$. During HS, NICO₂ monitors lose accuracy for approximating the PaCO₂ but gain usefulness as hemodynamic monitors. Also, by combining data from two different organ systems, NICO₂G demonstrated improved correlation with lactate than did either etCO₂ or tPCO₂ alone.

KEYWORDS—Transcutaneous carbon dioxide, end-tidal carbon dioxide, noninvasive carbon dioxide gradient, blood gas analysis, hemorrhage, swine

INTRODUCTION

Current recommendations for the management of trauma and post-cardiac arrest (CA) patients place significant emphasis on the maintenance of adequate ventilation and on the avoidance of hypocapnia or hypercapnia (1–3). To facilitate this, when arterial blood gas measurements are not readily available, two main types of noninvasive CO₂ (NICO₂) technologies have been developed: end-tidal (etCO₂) and transcutaneous CO₂ (tPCO₂) monitors.

End-tidal CO₂ monitoring has been encouraged in patients with traumatic brain injuries, targeting the range of 25 to 35 mmHg (3–5). However, etCO₂ does not always correlate linearly with PaCO₂ because a rise in physiologic dead space or a decrease in pulmonary perfusion results in an increase in the PaCO₂-etCO₂ gradient (6). Several recent studies conducted in

emergency departments revealed a poor correlation between etCO₂ and PaCO₂ in severely injured patients (7) as well as in nontrauma patients (8, 9).

An alternative NICO₂ monitoring technique uses transcutaneous measurements of the partial pressure of CO₂ (tPCO₂). Several studies reported a good correlation between tPCO₂ and PaCO₂ in adults under general anesthesia (10, 11). Similar results were described in critically ill patients (12–14). In addition, tPCO₂ appears to be a more accurate noninvasive substitute for PaCO₂ than etCO₂ in critically ill patients during interhospital transfer (15). However, decreased skin perfusion, for example, during hypovolemic shock, alters tPCO₂ relationship with PaCO₂.

Increasingly, both techniques are recognized not only as noninvasive correlates of PaCO₂ but also as indicators of the adequacy of pulmonary (etCO₂) and cutaneous (tPCO₂) perfusion. Several guidelines recommend using end-tidal capnometry for assessment of the adequacy of cardiopulmonary resuscitation and of the return of spontaneous circulation (1). It has been reported that during emergency trauma surgery, etCO₂ more than 27 mmHg and PaCO₂-etCO₂ gap less than 9 mmHg predicted survival (16). Alternatively, high tPCO₂ levels (>60 mmHg) were associated with 90% mortality in severely injured patients (17). In addition, an elevated tPCO₂-etCO₂ gap more than 26 mmHg as well as a tPCO₂-PaCO₂ gap more than 16 mmHg were reported to be associated with poor outcomes in patients with septic shock (18).

Previously, our group performed a series of animal experiments to better understand the utility of these NICO₂ monitoring techniques. Swine models were chosen because their physiology

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14. ABSTRACT Purpose: Hemorrhagic shock (HS) is a setting in which both pulmonary and cutaneous perfusion may be impaired. The goals of this study were (1) to evaluate the relationship between end-tidal (etCO₂), transcutaneous (tPCO₂), arterial carbon dioxide (PaCO₂), and lactate during lethal HS; and (2) to assess the effect of progressive HS on those variables and on a new variable, the "non-invasive CO₂ gradient" (NICO₂G, or difference between tPCO₂ and etCO₂). Materials and Methods: Ten consciously sedated swine were hemorrhaged, by means of an computerized exponential protocol, of up to 80% estimated blood volume (EBV) over 20 min. EtCO₂, tPCO₂, PaCO₂, and lactate measurements were taken at baseline and every 5 min thereafter, i.e., after 25%, 44%, and 62% total blood volume hemorrhage (TBVH), and at cardiac arrest (CA). CA occurred on average at 67% TBVH. Data were analyzed by linear regression and one-way repeated measures analysis of variance (ANOVA) and are presented as means +/- SD. Results: 49 paired measurements were made. There was no overall relationship between non-invasive CO₂ variables and PaCO₂: PaCO₂ vs. tPCO₂ (r² = 0.002; p = 0.78); PaCO₂ vs. etCO₂ (r² = 0.0002; p = 0.93). Rather, NICO₂G increased at each level of blood loss: 4.0+/-24.9 at baseline, 6.3+/-35.7 at 25% TBVH, 25.0+/-37.6 at 44% TBVH, 55.0+/-33.9 at 62% TBVH, and 70.0+/-33.2 at CA (p < 0.05). Similarly, tPCO₂ increased and etCO₂ decreased at each level. Linear regression of NICO₂G and lactate showed a better correlation than was observed for the other 2 variables: NICO₂G r² = 0.58; tPCO₂ r² = 0.46; etCO₂ r² = 0.26. Conclusions: During HS, non-invasive CO₂ monitors lose accuracy for approximating the PaCO₂, but gain usefulness as hemodynamic monitors. Also, by combining data from 2 different organ systems, NICO₂G demonstrated improved correlation with lactate than did either etCO₂ or tPCO₂ alone. (C) 2014 by the Shock Society.		
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closely resembles that of humans. First, we explored the relationship between etCO_2 and PaCO_2 over a wide range of ventilator settings in a swine model of pulmonary contusion and hemorrhage. Before injury and, later, after resuscitation, there was an excellent correlation. During the immediate period after injury and during hemorrhage, this relationship broke down (19). Second, we evaluated both etCO_2 and tPCO_2 in a swine model of acute lung injury secondary to smoke inhalation injury and burns. We demonstrated that tPCO_2 monitoring was an acceptable surrogate for PaCO_2 under hemodynamically stable conditions but not during periods of hemodynamic instability. We also found that the relationship between etCO_2 and PaCO_2 was less linear early after lung injury and during rapid changes in lung function (20).

Based on these findings, we decided to further explore the effect of shock on etCO_2 and tPCO_2 . The present study extends our previous work by collecting data at several steps during a hemorrhage process that is, ultimately, lethal. In addition, we described the NICO₂ gradient (NICO₂G), which we define as the difference between etCO_2 and tPCO_2 . It takes advantage of the dual observations that etCO_2 decreases (16) and tPCO_2 increases (17) during hypovolemic shock, reminiscent of the work of Vallee and colleagues (18). We had two questions: 1) Can etCO_2 and/or tPCO_2 serve as surrogates for PaCO_2 in an exsanguinating subject? 2) Does etCO_2 , tPCO_2 , or NICO₂G correlate with the severity of hemorrhage-induced metabolic debt, as indicated by elevated arterial lactate? By addressing these questions, we aimed to better understand the utility and limitations of NICO₂ monitoring under conditions of life-threatening hemorrhagic shock (HS). Also, arterial lactate more than 4 mmol/L has been associated with hypoperfusion and with increased mortality (21); lactate has been used as a resuscitation index (22). Thus, in the present study, we also sought to understand the relationship between NICO₂ variables and lactate.

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 used a convenience sample collected prospectively from the first 10 consecutive animals used in the larger study of exsanguination and CA caused by lethal hemorrhage. All 19 animals from the parent protocol were female nonpregnant Yorkshire pigs, purchased from Midwest Research Swine (Gibbon, Minn), *Sus scrofa* species, and bred for research. The parent protocol consisted of a single group of animals instrumented and treated identically. Animals were fasted overnight with water *ad libitum*. At the beginning of the experiment, animals were anesthetized with Telazol (tiletamine/zolazepam 4–6 mg/kg) by i.m. injection. Analgesia was provided using buprenorphine hydrochloride i.m. (0.25 mg/kg). Venous access was established with an 18- to 22-gauge catheter placed in a peripheral ear vein. Subsequently, animals were endotracheally intubated, and anesthesia was maintained during the surgical procedure using isoflurane (2%–4%) in 100% oxygen. The animals were placed supine on the operating table for surgical instrumentation. Surgery included tracheostomy and placement of catheters in an external jugular vein, carotid artery, femoral artery, and femoral vein. In addition, surgical steel wires were placed subcutaneously for electrocardiography in a lead II configuration. Before placement, the tissues around the catheter and steel wire sites were infiltrated with 2% bupivacaine for local anesthesia. To assess the level of sedation, bispectral index (BIS) electrodes (Aspect Medical Systems, Newton, Mass) were placed on the forehead.

After completion of the surgical procedure, isoflurane was discontinued and continuous i.v. infusion of midazolam (0.6–2.5 mg/kg per h) was initiated to maintain conscious sedation titrated to a BIS level of 70 to 80. Postprocedurally, analgesia coverage was provided by the buprenorphine hydrochloride i.m. and 2% bupivacaine local injections administered earlier. In all 10 animals enrolled in this study, the SenTec digital monitor with V-sign sensor (SenTec Ag, Therwil, Switzerland) were used for tPCO_2 monitoring. The V-sign sensor was attached to the right auricle using a single-use attachment ring. Before the sensor placement, the area was cleansed with isopropyl alcohol. One drop of SenTec contact gel was applied to the center of the membrane. The V-sign sensor was heated to 43.5°C during use. A Capnostream 20 device with a FilterLine H Set CO₂ sidestream sampling line and an airway adapter (Oridion Medical, Jerusalem, Israel) were used for etCO_2 monitoring. Arterial blood gas analysis was performed with i-STAT system (Abbot Point of Care, Princeton, NJ). CG4 cartridges were used to measure pH, PaCO_2 , and lactate values.

After surgery, animals were recovered for approximately 30 min. A set of baseline measurements was taken. Animals were then bled up to 80% of the estimated blood volume for 20 min using the computerized exponential protocol previously described by Burns et al. (23) (Fig. 1). A computer-controlled withdrawal system, based on a Masterflex peristaltic pump (Thermo Fisher Scientific, Waltham, Mass), was used for the hemorrhage. Throughout the experiment, animals were allowed to breathe spontaneously on continuous positive airway pressure at 5 cm H₂O. Once an animal developed respiratory arrest, defined as a respiratory rate less than 6 breaths per minute or a minute ventilation less than 25% of the baseline for more than 30 s, controlled mechanical ventilation was initiated with a tidal volume of 10 mL/kg, a fraction of inspired oxygen (FiO_2) of 100%, and a respiratory rate adjusted between 12 and 20 breaths per min to maintain PaCO_2 between 35 and 45 mmHg. Arterial blood gas samples and corresponding tPCO_2 and etCO_2 values were recorded at baseline, at 5 min (~25% total blood volume hemorrhage [TBVH]), at 10 min (~44% TBVH), at 15 min (~62% TBVH), and at CA (~67% TBVH). Cardiac arrest was defined as a sustained aortic diastolic pressure of 20 mmHg or less, as measured by the Millar transducer. The study was terminated at death, which was defined as a mean arterial pressure of 0 mmHg and an etCO_2 less than 8 mmHg.

Statistical analysis

Analyses were performed using SigmaPlot Version 12.0 for Windows (Systat Software, San Jose, Calif) and SAS version 9.2 (SAS Institute Inc., Cary, NC). Linear regression and Bland-Altman analysis were used to determine the correlation between PaCO_2 and several continuous variables, to include tPCO_2 and etCO_2 . Variables were tested for normality using the Shapiro-Wilk test. One-way repeated-measures analysis of variance (ANOVA) with *post hoc* Dunnett tests were used to analyze changes over time for normally distributed data. Those that did not meet the criteria for normality were analyzed using Friedman nonparametric test for repeated measures. Fisher exact test was used to

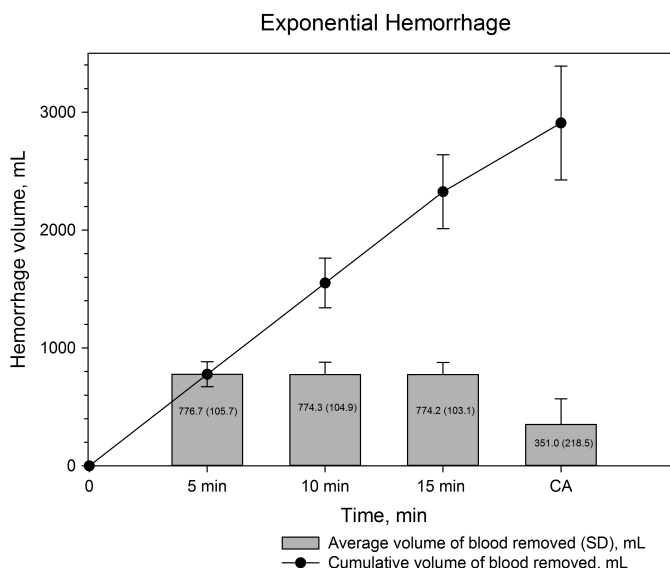


FIG. 1. Exponential hemorrhage volume in milliliters recorded after 25%, 44%, and 62% TBVH and at CA.

TABLE 1. Vital sign and blood gas changes during hemorrhage

	Baseline	25% TBVH	44% TBVH	62% TBVH	CA
Temp	38.5 ± 0.5	38.6 ± 0.7	38.7 ± 0.7	38.8 ± 0.7	38.6 ± 0.8
HR	104.2 ± 25.2	116.1 ± 32.3	128.3 ± 34.0	160.9 ± 56.1	116.2 ± 79.0
MAP	102.3 ± 16.0	67.1 ± 15.4 [‡]	43.5 ± 20.3 [‡]	26.7 ± 13.7 [‡]	10.5 ± 13.6 [‡]
CVP	5.3 ± 5.2	1.0 ± 3.6 [§]	0.9 ± 4.7 [§]	2.1 ± 5.9	1.2 ± 3.0
PAP	19.8 ± 5.3	11.5 ± 8.1 [§]	15.1 ± 17.3 [§]	11.6 ± 5.9 [§]	7.3 ± 5.1
Arterial pH	7.32 ± 0.07	6.88 ± 1.0	7.24 ± 0.27	7.33 ± 0.11	7.19 ± 0.36
Lactate	4.0 ± 2.8	4.3 ± 3.2	5.5 ± 3.1	7.7 ± 2.9 [§]	7.8 ± 2.4 [§]
PaCO ₂	51.8 ± 3.7	60.5 ± 23.2	51.3 ± 25.8	38.9 ± 15.7	54.7 ± 38.6
PmvCO ₂	59.0 ± 5.2	54.5 ± 13.1	61.9 ± 14.2	66.7 ± 22.0	75.9 ± 20.4
tPCO ₂	56.2 ± 23.1	54.9 ± 33.7	61.9 ± 35.0	75.7 ± 35.2 [†]	78.3 ± 35.5 [‡]
etCO ₂	52.2 ± 5.2	48.6 ± 5.4	36.9 ± 7.2 [‡]	20.8 ± 12.0 [‡]	8.3 ± 7.2 [‡]

TBVH indicates total blood volume hemorrhage; CA, cardiac arrest; Temp, core body temperature (in degrees Celsius); HR, heart rate; MAP, mean arterial pressure (in millimeters mercury); CVP, central venous pressure (in millimeters mercury); PAP, mean pulmonary artery pressure (in millimeters mercury); BE, arterial base excess (in millimolar); Lactate, arterial lactate level (in millimolar); PaCO₂, arterial pressure of carbon dioxide (in millimeters mercury); PmvCO₂, partial pressure of carbon dioxide in mixed venous blood (in millimeters mercury); tPCO₂, transcutaneous carbon dioxide (in millimeters mercury); etCO₂, end-tidal carbon dioxide (in millimeters mercury).

* $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$ by ANOVA with *post hoc* Dunnett tests compared with baseline.

§ $P < 0.05$; || $P < 0.01$ by Friedman test compared with baseline.

compare categorical variables. All results are expressed as means ± SD. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Data were recorded from 10 animals with an average weight of 61.9 ± 10.3 kg. Average time to CA was 22 min 19 sec ± 4 min 2 sec. Average blood loss at CA was $67\% \pm 9\%$ of the estimated TBV. Measurements ($n = 49$) of PaCO₂, tPCO₂, and etCO₂ were recorded. Figure 1 demonstrates cumulative hemorrhage volumes during the experiment. Table 1 presents vital signs and laboratory values with data grouped and evaluated based on the percentage of TBVH.

Linear regressions of tPCO₂ or etCO₂ with PaCO₂ are presented in Figure 2A. There was no relationship between PaCO₂ and tPCO₂ ($r^2 = 0.002$, $P = 0.78$). Similarly, there was no relationship between PaCO₂ and etCO₂ ($r^2 = 0.0002$, $P = 0.93$). In addition, a Bland-Altman analysis was performed. For tPCO₂, bias was -13.5 ± 41.8 mmHg (Fig. 2B). For etCO₂, bias was 18.1 ± 30.4 mmHg (Fig. 2C).

Changes over time in various gradients, to include the NICO₂G, are presented in Table 2. Figure 3 illustrates the observed divergence between tPCO₂, etCO₂, and NICO₂G values with each hemorrhage step.

Linear regression of etCO₂, tPCO₂, and NICO₂G with lactate was also performed. These data are presented in Figure 4, A to C. Here, note that the correlation for etCO₂ was quite low, $r^2 = 0.26$ ($P < 0.001$); for tPCO₂, it was better, $r^2 = 0.46$ ($P < 0.001$); and for NICO₂G, it was best, $r^2 = 0.58$ ($P < 0.0001$).

In view of the observed relationship between NICO₂G and lactate, the variables were categorized into dichotomies, as follows: lactate greater than or less than 4 mmol/L; NICO₂G greater than or less than 0; tPCO₂ greater than or less than 50 mmHg; and etCO₂ greater than or less than 20 mmHg. A Fisher exact test was performed, which disclosed that the relationships between lactate and the other categorical variables were highly significant ($P < 0.001$). Noninvasive CO₂G greater than 0 had a sensitivity of 88%, a specificity of 73%, and an accuracy of 85% for detecting lactate greater than 4 mmol/L. In

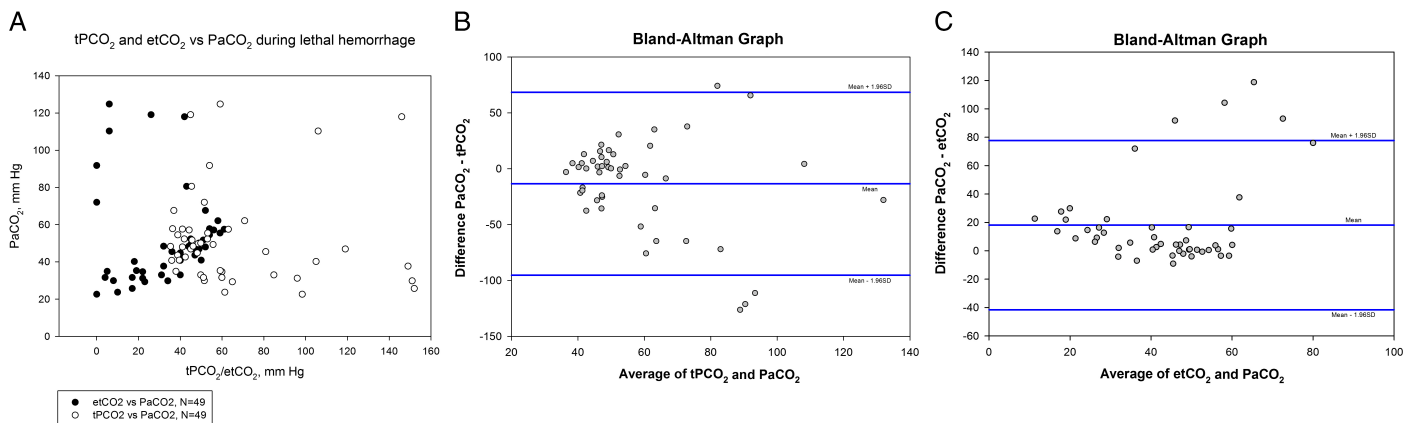


FIG. 2. A, Linear regression of PaCO₂ and tPCO₂ or etCO₂ ($n = 49$). Neither tPCO₂ ($r^2 = 0.002$, $P = 0.78$) nor etCO₂ ($r^2 = 0.0002$, $P = 0.93$) correlated with PaCO₂. B and C, Bland-Altman analysis of PaCO₂ and tPCO₂ or etCO₂. The middle solid line represents the mean difference (bias), and the outer solid lines represent limits of agreement (mean ± 1.96 SD) between the two methods. For tPCO₂, bias was -13.5 ± 41.8 mmHg; for etCO₂, it was 18.1 ± 30.4 mmHg ($n = 49$).

TABLE 2. CO₂ gradients during hemorrhage

	Baseline	25% TBVH	44% TBVH	62% TBVH	CA
NICO ₂ G	4.0 ± 24.9	6.3 ± 35.7	25.0 ± 37.6*	55.0 ± 33.9 [‡]	70.0 ± 33.2 [‡]
PaCO ₂ -tPCO ₂	-4.4 ± 24.6	1.6 ± 18.0	-14.2 ± 48.8	-34.9 ± 45.5	-27.3 ± 53.8
PaCO ₂ -etCO ₂	-0.4 ± 2.6	7.9 ± 24.6	10.8 ± 28.0	20.1 ± 24.8 [§]	42.7 ± 38.9
PaCO ₂ -PmvCO ₂	-7.2 ± 2.2	7.5 ± 27.1	-8.6 ± 31.2	-24.5 ± 18.7	-34.6 ± 14.9

TBVH indicates total blood volume hemorrhage; CA, cardiac arrest; NICO₂G, noninvasive carbon dioxide gradient, that is, tPCO₂-etCO₂ (in millimeters mercury); PaCO₂, partial pressure of carbon dioxide in arterial blood (in millimeters mercury); tPCO₂, transcutaneous carbon dioxide (in millimeters mercury); etCO₂, end-tidal carbon dioxide (in millimeters mercury); PmvCO₂, partial pressure of carbon dioxide in mixed venous blood (in millimeters mercury).

**P* < 0.05; [‡]*P* < 0.01; [‡]*P* < 0.001 by ANOVA with *post hoc* Dunnett tests compared with baseline.

[§]*P* < 0.05; ^{||}*P* < 0.01; ^{||}*P* < 0.001 by Friedman test compared with baseline.

addition, tPCO₂ greater than 50 mmHg had a sensitivity of 89%, a specificity of 57%, and an accuracy of 75% for detecting lactate greater than 4 mmol/L. Finally, etCO₂ less than 20 mmHg had a sensitivity of 100%, a specificity of 56%, and an accuracy of 60% for detecting lactate greater than 4 mmol/L.

DISCUSSION

We evaluated the utility of NICO₂ monitoring in an animal model of lethal hemorrhage. We found that neither tPCO₂ nor etCO₂ correlated with PaCO₂ in this setting. These results indicate that NICO₂ monitoring methods alone are not reliable for guiding ventilation management in patients who are actively exsanguinating. Rather, these sensors performed better as indicators of shock state. The tPCO₂ increased and the etCO₂ decreased with progressive blood loss. Furthermore, the NICO₂G, defined as the difference between tPCO₂ and etCO₂ measurements, increased with progressive hemorrhage and correlated better with arterial lactate levels than either tPCO₂ or etCO₂ alone. The sensitivity of a positive NICO₂G for detecting arterial lactate level greater than 4 was 88%, and the specificity was 73%. This gradient was more accurate and specific for detecting elevated lactate (>4 mmol/L) than its individual components tPCO₂ and etCO₂.

Previous reports on the relationship between NICO₂ surrogates and PaCO₂ in critically ill patients were mixed. For example, poor etCO₂ correlation with PaCO₂ was demonstrated in severely injured intubated patients (7). On the other hand, several reports (12, 13) indicated an acceptable correlation between tPCO₂ and PaCO₂ in critically ill adults. Our own previous work in swine models indicates the utility of etCO₂ monitoring in patients who are stable from a hemodynamic and pulmonary standpoint. Caution should be exercised when a patient is rapidly deteriorating from either standpoint (19, 20). The present study confirms those findings in an animal model of lethal hemorrhage, that is, with hemodynamic instability taken to an extreme.

Despite encouraging results, the current generation of tPCO₂ monitors demonstrates some shortcomings, which include the need for frequent calibration with a tank of standardized calibration gas (24), relative bulk, need for a heated sensor, and more gradual onset of changes (compared with etCO₂) in response to a change in PaCO₂ (20). Hopefully, the next generation of tPCO₂ sensors, currently under development, will address several of these problems. However, like etCO₂, we would not

expect tPCO₂ to serve as an effective substitute for PaCO₂ under conditions of severe hypovolemic shock as in the present study.

Rather, we find etCO₂ and tPCO₂ to show promise as non-invasive shock monitors. Weil and colleagues (25) were pioneers in the application of CO₂ monitoring to resuscitation. In the 1980s, they reported that the mixed-venous partial pressure of CO₂ (PmvCO₂) was increased and the etCO₂ was decreased in a porcine model of CA. They also found that cardiac output was linearly related to etCO₂. Thus, the difference between mixed venous and etCO₂ could be explained by a decreased cardiac output (decreased pulmonary blood flow) (25). Another consequence of low cardiac output is a high gradient between mixed-venous PCO₂ and arterial PCO₂ during cardiopulmonary resuscitation (26).

The CA studies led to other shock studies. Weil's group corroborated the relationship between etCO₂ and cardiac output in pigs with hemorrhagic, septic, and cardiogenic shock (27). Van der Linden et al. (28) demonstrated a venous-arterial gradient for PCO₂ in hemorrhaged dogs. There was an abrupt widening of this gradient when VO₂ became supply dependent, along with an increase in lactate and a decrease in etCO₂ (28). Dubin et al. (29) performed studies in dogs with stepwise hemorrhage. The etCO₂ was logarithmically related to cardiac output and linearly to CO₂ production. In other words, the greatest decrease in etCO₂ was seen at the lowest levels of cardiac output. This implied that, at low cardiac output, decreased etCO₂ may reflect

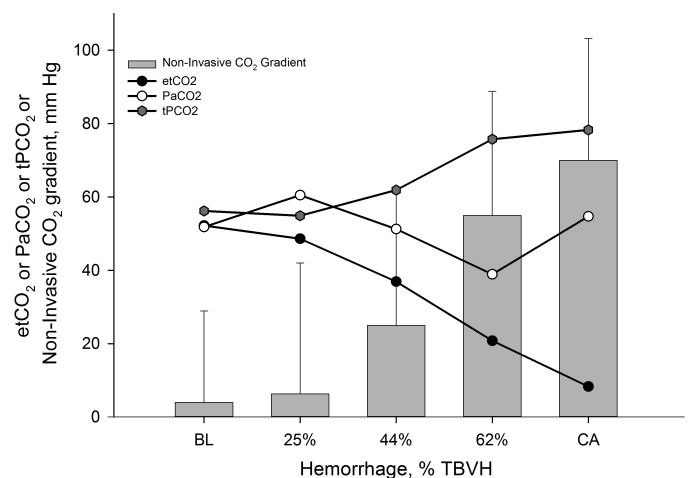


FIG. 3. The tPCO₂, etCO₂, PaCO₂, and NICO₂G as functions of time during hemorrhage. For tPCO₂, etCO₂, and PaCO₂, means during each hemorrhage step are depicted. For NICO₂G, vertical bars represent means during each hemorrhage step and error bars are $\pm$ SD (n = 49).

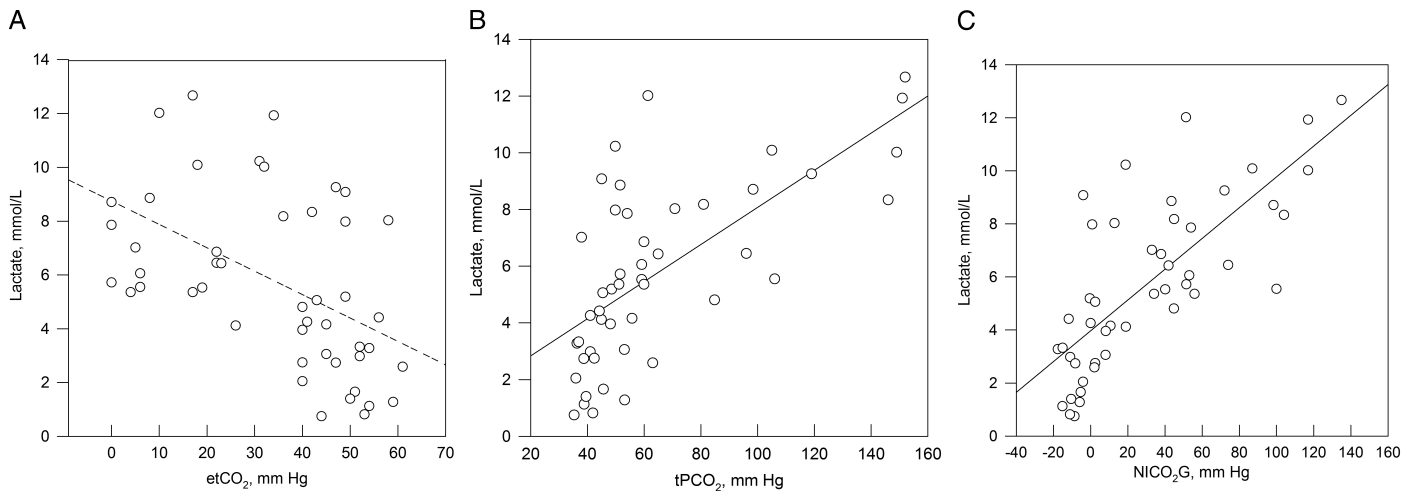


FIG. 4. **Linear regression analysis.** A, etCO_2 and lactate ($r^2 = 0.26$, $P < 0.001$, $n = 48$). B, tPCO_2 and lactate ($r^2 = 0.46$, $P < 0.001$, $n = 48$). C, NICO_2G and lactate ($r^2 = 0.58$, $P < 0.0001$, $n = 48$).

not only decreased pulmonary blood flow but also decreased CO_2 production (29).

In the present study, we found, like Weil and Van der Linden did, that decreases in etCO_2 occurred stepwise with progressive hemorrhage. We also found a widened PaCO_2 - PmvCO_2 gradient, which became statistically significant at CA (Table 2). These two findings, taken together, support the concept that, in profound HS or CA, pulmonary blood flow is insufficient to maintain adequate expiration of CO_2 . Clinically, this means that a falling etCO_2 (in a patient with a patent airway and constant ventilation) may indicate HS (or another cause of decreased pulmonary blood flow, such as a pulmonary embolism) (30, 31). Compared with other monitors, etCO_2 has the advantage of being continuous, referable to the central circulation, and non-invasive (32).

Recently, a prospective study of etCO_2 monitoring in acutely injured patients with penetrating trauma was reported, which suggests that etCO_2 is useful before near-arrest conditions are reached. There was a linear relationship between etCO_2 and lactate ($r^2 = 0.74$). The odds of operative intervention were higher in patients with a low etCO_2 (odds ratio, 20) than they were in patients with a high lactate (odds ratio, 4). Systolic blood pressure was related neither to the lactate level nor to the odds of operation (33). Similarly, in the present study, etCO_2 correlated with lactate (discussed further below).

Insofar as the skin is particularly susceptible to decreased perfusion during hypovolemic shock, tPCO_2 may have value as a shock monitor. Previous work by Cancio et al. (34) demonstrated decreased skin oxygenation (by hyperspectral imaging) and decreased skin blood flow (by laser Doppler imaging) during HS in pigs. The observation that tPCO_2 changes with HS is reminiscent of the large body of work that demonstrates the value of gastrointestinal, esophageal, and sublingual/buccal capnometry during shock and resuscitation. Transcutaneous PCO_2 monitoring would have the advantage of being entirely noninvasive and immediately accessible.

We observed that, after 25% TBVH, tPCO_2 measurements rose whereas etCO_2 values decreased. This prompted us to explore changes in the difference between the tPCO_2 and the etCO_2 , or NICO_2G . There was a statistically significant increase

in NICO_2G with each subsequent hemorrhage step above 25% TBVH. Furthermore, NICO_2G outperformed etCO_2 or tPCO_2 in linear regression versus lactate. As a diagnostic test for an elevated lactate (>4 mmol/L), NICO_2G had an accuracy of 85%, which was higher than its individual components. We think that NICO_2G performed better because it combines the features of both component variables into one. Those features are, physiologically, a decrease in pulmonary perfusion causing a decrease in the etCO_2 and a decrease in cutaneous perfusion causing an increase in the tPCO_2 . Additional work is planned to evaluate the response of NICO_2G to fluid resuscitation and transfusion in this hemorrhage model.

Our study had the following limitations. Animals were hypercapnic and hyperlactatemic at baseline. Most likely, these findings were caused by global hypoperfusion secondary to animals being placed and remaining in the supine position during the study. Furthermore, these animals breathed spontaneously at baseline and were placed on mechanical ventilation only after the onset of hypoventilation. The rationale for avoiding mechanical ventilation at baseline was to eliminate the effect of this intervention on hemodynamics during early hemorrhage. The trade-off was that this introduced variability into animal management during the course of the experiment. On the other hand, prehospital and emergency department management of severely injured patients often does involve changes in ventilation mode, which complicate data analysis. This makes our study design more relevant to actual early trauma care.

CONCLUSIONS

This and other studies indicate that NICO_2 monitors provide critical information that must, however, be interpreted contextually. In this study, we demonstrated that neither transcutaneous nor end-tidal capnometry served as an accurate noninvasive PaCO_2 surrogate in animals sustaining rapid exsanguinating hemorrhage. Instead, a rapid drop in etCO_2 and/or a rise in tPCO_2 in a bleeding patient, whose ventilation is controlled, may indicate a critical decrease in volume status rather than a change in the PaCO_2 (31, 32). This concept was demonstrated in the present study by the NICO_2G , defined as the difference

between the etCO₂ and the tPCO₂. This gradient increased with hemorrhage and correlated well with arterial lactate levels, even as PaCO₂ remained constant. The NICO₂G may be useful in monitoring the severity of HS.

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