Buccal capnometry to guide management of massive blood loss

Gianluca A. A. M. Cammarata,1 Max Harry Weil,1,2 Michael Fries,1 Wanchun Tang,1,2 Shijie Sun,1,2 and Carlos J. Castillo1

1Weil Institute of Critical Care Medicine, Rancho Mirage; and 2The Keck School of Medicine, University of Southern California, Los Angeles, California

Submitted 5 November 2004; accepted in final form 15 August 2005

Cammarata, Gianluca A. A. M., Max Harry Weil, Michael Fries, Wanchun Tang, Shijie Sun, and Carlos J. Castillo. Buccal capnometry to guide management of massive blood loss. J Appl Physiol 100: 304–306, 2006. First published September 1, 2005; doi:10.1152/japplphysiol.01247.2004.—In both clinical and experimental settings, tissue PCO2 measured in the oral mucosa is a practical and reliable measurement of the severity of hypoperfusion. We hypothesized that a threshold level of buccal tissue PCO2 (PCO2B U) would prognosticate the effects of volume repletion on survival. Twenty pentobarbital-anesthetized Sprague-Dawley male breeder rats, each weighing ~0.5 kg, were randomly assigned to one of four groups. Animals were bled over an interval of 30 min in amounts estimated to be 25, 30, 35, or 40% of total blood volume. One-half hour after the completion of bleeding, each animal received an infusion of Ringer lactate solution over the ensuing 30 min in amounts equivalent to two times the volume of blood loss. PCO2B U was measured continuously with an optical PCO2 sensor applied noninvasively to the mucosa of the left cheek. Arterial pressure and end-tidal CO2 were measured over the same interval. Neurological deficit and 72-h survival were recorded. Aortic pressures were restored to near baseline values for each of the four groups after fluid resuscitation. This contrasted with the improvement of PCO2B U, which differentiated between animals with short and long durations of postintervention survival. After electrolyte fluid resuscitation in rats subjected to rapid bleeding, noninvasive measurement of PCO2B U was predictive of outcomes. Neither noninvasive end-tidal Pco2 nor invasive aortic pressure measurements achieved such discrimination. Accordingly, PCO2B U fulfills the criterion of a noninvasive and reliable measurement to guide fluid management of hemorrhagic shock.

DURING HEMORRHAGIC SHOCK, decreases of blood flow account for tissue hypoxia and multiple organ failure, even after hemostasis and initially successful resuscitation with fluid (5, 10, 12). Arterial pressure is considered to be the most consistent and widely used measurement for estimating the severity of hemorrhagic shock and to guide its management. However, even this capability is constrained when very low arterial pressure values cannot be reliably measured by noninvasive methods. Furthermore, other noninvasive techniques, such as subcutaneous PO2, have proven unreliable in emergency settings (21).

Tissue PCO2 has been introduced as a potentially useful guide to the diagnosis of circulatory shock states (6) and as a quantitative indicator of its severity. It also provides a rapid response measurement for confirmation of the effectiveness of interventions.

Although the stomach and the gut were regarded as “canaries” of systemic hypoperfusion (4), increases in sublingual and buccal tissue CO2 were approximately the same as those in the stomach and gut during low-flow states (9, 15, 17–20). At each of these sites, tissue Pco2 was closely correlated with decreases in tissue blood flows (9, 17).

The purpose of the present study was to investigate continuously recorded changes in buccal Pco2 (PCO2B U) during and after volume repletion in relationship to the severity of rapid blood losses. PCO2B U was compared with continuous measurement of systolic, diastolic, and integrated mean central aortic pressure and with end-tidal CO2 (PteCO2). We hypothesized that PCO2B U would identify a threshold level above which fluid resuscitation decreases, rather than increases, the duration of survival. We further hypothesized that Pco2B U serves as a better predictor of the severity of volume deficit compared with other currently used methods.

METHODS

The study was approved by the Institutional Animal Care and Use Committee of the Weil Institute of Critical Care Medicine. All animals received humane care in compliance with the Principles of Laboratory Animal Care formulated by the National Society for Medical Research and the Guide for the Care and Use of Laboratory Animals, prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health. The laboratories of the Institute are fully accredited by the International American Association for Accreditation of Laboratory Animal Care.

Twenty male albino Sprague-Dawley rats, weighing 450–550 g, were investigated. The animals had free access to water before the study, but food was withheld for 12 h. Animals were anesthetized by intraperitoneal injection of pentobarbital (45 mg/kg) and placed on a surgical board in the supine position. The trachea was orally intubated with a 14-G cannula mounted on a blunt needle with a 145°-angled tip by the methods of Stark et al. (22). PteCO2 was monitored with a side-stream infrared CO2 analyzer (End-Til IL 200; Instrument Laboratory, Lexington, MA). A polyethylene catheter (PE-50, Becton-Dickinson, Sparks, MD) was advanced aseptically into the right carotid artery and connected to a peristaltic pump (Autoinfusor, ICM, Palm Springs, CA), which was utilized for blood shedding. After surgical exposure of the left femoral artery and vein, these vessels were cannulated with polyethylene catheters (PE-50) and advanced into the abdominal aorta and into the inferior vena cava, respectively. The inferior vena cava catheter served as a site for injection of additional doses of pentobarbital to maintain anesthesia and as a site for fluid infusion. The aortic catheter was connected to a high-sensitivity pressure transducer (model 42584–01; Abbott Critical Care System, Abbott Park, IL). A thermocouple microprobe, 10 cm in length and 0.5 mm in diameter (9030–12-D-34; Columbus Instrument, Columbus, OH), was inserted into the right femoral artery and advanced into the descending thoracic aorta. Blood temperature was measured with this sensor and maintained at 37 ± 0.5°C (mean ± SD) with the aid of a heating lamp.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
At the end of the surgical preparation, the animals were randomized into four groups to be bled in amounts equal to 25, 30, 35, or 40% of the estimated blood volume (8) over a period of 30 min. Thirty minutes after the end of the bleeding, the animals received infusion of lactated Ringer solution (B. Braun Medical, Irvine, CA) in amounts corresponding to twice the volume of blood removed. This volume was infused over an interval of 30 min, utilizing the same peristaltic pump.

Mucosal \( \text{PCO}_2 \) was measured with a miniature carbon dioxide electrode (MI-720 CO\text{2} electrode; Microelectrodes, Londonderry, NH), which was positioned with the aid of the “doughnut” designed by us. The doughnut (Fig. 1) maintains continuous contact with the mucosa without compromising local blood flow. The sensor was calibrated in a water-filled tonometer maintained at 37°C. A mixture of nitrogen and either 5 or 20% CO\text{2} gas (Air Liquide, Etiwanda, CA) was delivered to the tonometer. A thermocouple microprobe provided with the sensor was advanced between the tongue and the left cheek of the animals.

\( \text{PCO}_2 \) and hemodynamic data were recorded at baseline and continuously up to 1 h after the end of infusion. The animals were allowed to breathe spontaneously.

One hour after the completion of fluid infusion, animals were allowed to recover from anesthesia, and the catheters, including the endotracheal tube, were removed. The animals were then returned to their cages, and postresuscitation neurological deficit score, an adaptation for rats of the neurological score by Nemoto et al. (16), was recorded at 12-h intervals. Euthanasia followed an intraperitoneal injection of 150 mg/kg of pentobarbital after 72 h. Autopsy was performed for gross identification of any potential injuries caused by surgical interventions.

**Statistical analyses.** For measurements between groups, ANOVA and Scheffe’s multicomparison techniques were employed. Comparisons between time-based measurements within each group were performed with ANOVA repeated measurement. Categorical variables were analyzed with Fishers exact test. Measurements are reported as means ± SD. Values of \( P < 0.05 \) were considered significant.

**RESULTS**

Baseline hemodynamic and \( \text{PCO}_2 \) values did not differ among the four groups of animals. Autopsy revealed no coincidental abnormalities or injuries.

During and after volume repletion, \( \text{PCO}_2 \) and the severity of neurological deficit discriminated between duration of survival of the groups (Figs. 2 and 3). One hour after the completion of fluid infusion, \( \text{PCO}_2 \) of the 40, 35, 30, and 25% bleeding groups averaged 85 ± 4, 70 ± 7, 57 ± 4, and 55 ± 3 Torr, respectively. The difference between 40 and 35% and those of 30 and 25% were statistically significant (Fig. 2).

However, mean arterial pressures failed to differentiate among the four groups of animals (Fig. 2).

**Statistical analyses.** For measurements between groups, ANOVA and Scheffe’s multicomparison techniques were employed. Comparisons between time-based measurements within each group were performed with ANOVA repeated measurement. Categorical variables were analyzed with Fishers exact test. Measurements are reported as means ± SD. Values of \( P < 0.05 \) were considered significant.

**RESULTS**

Baseline hemodynamic and \( \text{PCO}_2 \) values did not differ among the four groups of animals. Autopsy revealed no coincidental abnormalities or injuries.

During and after volume repletion, \( \text{PCO}_2 \) and the severity of neurological deficit discriminated between duration of survival of the groups (Figs. 2 and 3). One hour after the completion of fluid infusion, \( \text{PCO}_2 \) of the 40, 35, 30, and 25% bleeding groups averaged 85 ± 4, 70 ± 7, 57 ± 4, and 55 ± 3 Torr, respectively. The difference between 40 and 35% and those of 30 and 25% were statistically significant (Fig. 2).

However, mean arterial pressures failed to differentiate among the four groups of animals (Fig. 2).

Although \( \text{PETCO}_2 \) and blood lactate identified the most severe bleeding group after estimated 40% volume depletion, it failed to differentiate between lesser volume losses (Fig. 3).

![Fig. 1. Methods of tissue \( \text{PCO}_2 \) measurements.](image)

![Fig. 2. Comparison of measurements among four groups at baseline (BL), during bleeding, after bleeding, and after fluid infusion (Infus.). \( \text{PETCO}_2 \), end-tidal \( \text{PCO}_2 \); ■, 40% bleeding; □, 35% bleeding; ●, 30% bleeding; ○, 25% bleeding. Values are means ± SD.](image)

![Fig. 3. Comparison of neurological deficit scores and durations of survival. Open bars, 40% bleeding; light shaded bars, 35% bleeding; dark shaded bars, 30% bleeding; solid shaded bars, 25% bleeding. Values are means ± SD.](image)
DISCUSSION

Until recently, aggressive volume repletion was the mainstay for treatment of hemorrhagic shock, primarily guided by arterial pressure (1). Yet more recent studies in both experimental and clinical settings of hemorrhagic shock demonstrated that both aggressive fluid repletion during exsanguinating hemorrhage and/or attempts to restore normal blood pressure increased blood loss and mortality (2, 3, 7, 11, 23).

The present study provides evidence that continuous measurement of $PCO_2_{BU}$ identifies the severity of the volume deficit and prognosticates the likelihood of restoration of normal neurological outcomes and longer term survival. The data of this study are consistent with results on patients with values of sublingual $PcO_2$ higher than 70 Torr predictive of circulatory failure (24). $PETCO_2$ serves as a surrogate of pulmonary blood flow and, therefore, cardiac output. However, this measurement is not sensitive to tissue perfusion, which has proven to be a better biological marker of the severity of shock states (9, 17). Yet even blood lactate measurement, which is related to tissue perfusion, has at least two limitations. It is invasive, requires laboratory facilities, and, most of all, its utility to guide fluid management during low-flow states is constrained by the substantial delay in the clearance of lactate after reversal of perfusion failure (19).

We recognize several limitations in the interpretation of our findings. The study was performed with controlled bleeding on an animal model and in the absence of any type of blunt trauma. Accordingly, applicability to patients remains to be proven. However, experience with tissue $PcO_2$ in other circulatory shock states is consistent with the present findings (13, 14, 24).

Within these limitations, we conclude that measurement of $PCO_2_{BU}$ promises to serve as a useful measurement for diagnosis, triage, prognostication of the severity of hemorrhagic shock, and as a guide to fluid resuscitation.

GRANTS

This study was supported in part by the Rosse Family Foundation, Concord, MA.

REFERENCES