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Buccal partial pressure of carbon dioxide outweighs traditional vital signs in predicting the severity of hemorrhagic shock in a rat model

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ABSTRACT

Background: Hemorrhagic shock (HS) is a leading cause of death in both military and civilian settings. Researchers have investigated different parameters as predictors of HS, but reached inconsistent conclusions. We hypothesized that buccal partial pressure of carbon dioxide (PCO_2) was a better predictor of HS than traditional vital signs.

Materials and methods: Twenty-four anesthetized Wistar rats were randomly divided into four groups: one control group (no bleeding) and three surgical groups (25%, 35%, and 45% blood loss). Hemorrhage was induced by withdrawing blood from the left femoral artery over a period of 30 min. After that, resuscitation was performed on animals in surgical groups using the Ringer lactate solution. Buccal PCO_2 was continuously measured by a newly designed sensor holder during the experiments. Traditional vital signs, cardiac output, base excess, and microvascular perfusion (MPF) were also measured or calculated.

Results: Buccal PCO_2 differed significantly among four groups beginning at 20 min, approximately 10 min earlier than the shock index and more earlier than the heart rate, systolic blood pressure, and mean arterial pressure. Buccal PCO_2 correlated well with cardiac index and the changes in MPF. The correlation coefficients with cardiac index, chest MPF, and upper-limb MPF for buccal PCO_2 were 0.781, −0.879, and −0.946, respectively. Besides, buccal PCO_2 showed a good value for predicting mortality. Furthermore, an approximate critical threshold of buccal PCO_2 was also identified for predicting the severity of HS.

Conclusions: Buccal PCO_2 was a noninvasive, sensitive indicator of HS than traditional vital signs and may help on-scene rescuers administer early treatment of injured patients.

1. Introduction

Hemorrhagic shock (HS) is defined as a reduction in the perfusion of vital organs, leading to the inadequate delivery of oxygen and nutrients necessary for normal tissue and cellular function [1]. HS gradually leads to multiple organ failure or even death if left untreated. Furthermore, HS is the leading cause of death among people aged 15–44 y, especially after

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traumatic injury [2]. By 2020, deaths from injury worldwide may increase to 8 million, with one-third resulting from HS [3]. Of these deaths, 33%–56% occur during the prehospital period. Moreover, up to 50% of combat deaths are related to HS, and most of these deaths occur in far-forward environments [4]. Therefore, it is important to evaluate the severity of hemorrhage quickly and accurately, so that on-scene responders can administer early treatment.

Traditional vital signs, such as blood pressure (BP) and heart rate (HR), are the initial parameters used to assess possible hemorrhage in trauma patients [5,6]. However, the early recognition of HS using only these vital signs may be difficult, even in the presence of significant blood loss, because of compensatory mechanisms [7–9]. Various studies have evaluated the severity of HS using different methods. Birkhahn *et al.* [10] and Nakasone *et al.* [11] both reported that shock index (SI), a simple ratio of HR to systolic BP (SBP), identifies patients with early acute hemorrhage better than HR, SBP, or diastolic BP (DBP) alone. Vandromme *et al.* [12] reported that SI is also useful for the identification of patients in the compensatory phase of HS.

In recent years, various studies have focused on diagnosing shock severity according to tissue perfusion and microcirculation. Tissue partial pressure of carbon dioxide (PCO_2) has been considered to be a good indicator of tissue hypoperfusion during hemorrhage. Many researchers have studied micro-invasive or noninvasive measurements of tissue PCO_2 in different body parts (e.g., end-tail, gastric, esophageal, sublingual, or buccal mucosal PCO_2) [13–17]. In recent years, a new technique, laser Doppler perfusion imaging, is capable of measuring superficial dermal capillary blood flow and thus could theoretically exploit the skin's compensatory mechanisms to detect early hemorrhage [18]. However, Pestel *et al.* [19] reported that traditional vital signs were more sensitive to acute hypovolemia than tissue oxygen tension measurements or regional perfusion in a swine model. Here the question arises that whether tissue perfusion parameters were more sensitive to acute hemorrhage than traditional vital signs?

In the present study, we established a rat model including both bleeding and infusion processes and designed a novel sensor holder for buccal PCO_2 measurement. During the experiments, we simultaneously measured HR, SBP, DBP, mean arterial pressure (MAP), rectal temperature (Trc), base excess (BE), cardiac output (CO), buccal PCO_2, and microvascular perfusion (MPF). After that, we compared buccal PCO_2 with traditional vital signs and further studied the relationship among buccal PCO_2, the changes in MPF, and the rats' mortality. On the basis of our results, we hypothesized that buccal PCO_2, a noninvasive tissue perfusion parameter, performed better than traditional vital signs in predicting HS severity in prehospital settings and might play a role for clinical application in the future.

2. Materials and methods

Normal male Wistar rats, weighing 280–330 g, were purchased from the Experimental Animal Center of the Academy of Military Medical Sciences (Beijing, China). All experiments, in this study, were performed in strict accordance with the Principles of Laboratory Animal Center, formulated by the National Society for Medical Research and the National Health Institutes Guide for the Care and Use of Laboratory Animals.

2.1. *Animal preparation*

A total of 24 male Wistar rats were randomly divided into four groups, including a control group that received only intubation without blood loss. The other three groups were subjected to controlled blood loss of 25%, 35%, or 45% of the calculated total blood volume over a 30-min period (total blood volume [mL] = body weight [g] × 0.061) [20]. According to the American College of Surgeons' Advanced Trauma Life Support for Doctors, blood losses of 25%, 35%, and 45% correspond to class II (15%–30%), class III (30%–40%), and class IV (> 40%) hemorrhage, respectively [21].

2.2. *Surgical procedures*

Animals were anesthetized with pentobarbital (45 mg/kg, intraperitoneally), and the chest and upper limbs were shaved. The animals were placed in a supine position on the operating table, and the Trc was maintained at 38 ± 0.5°C using a heating pad. After incising the peripheral tissue of the neck and the right and left periphery of the inguinal area, a polyethylene catheter (PE 60; Becton Dickinson, Sparks, MD) was aseptically advanced into the left femoral artery and connected to an infuse and withdraw syringe pump (Pump 11 Plus; Harvard Apparatus, Holliston, MA) for blood withdrawal. Two PE 60 catheters were inserted into the right femoral artery and vein, respectively. The femoral artery catheter was connected to a reusable BP transducer (MLT0380/D; AD Instruments, Sydney, Australia) for BP measurement. The femoral vein catheter served as a site for injection of overdose of pentobarbital to conduct euthanasia and a site for fluid infusion. All catheters were filled with a mixture of heparin sodium (Shanghai No. 1 Biochemical & Pharmaceutical Co Ltd, Shanghai, China) and normal saline. The left carotid artery was cannulated, and a thermocouple probe (MLT 1402; AD Instruments) was passed through the cannula for CO estimation using the thermodilution technique (Fig. 1A). Another polyethylene catheter (PE 10; Becton Dickinson) was advanced through the right external jugular vein and into the right atrium for the injection of cold isotonic saline (Fig. 1C). All incisions were then closed and bathed with 1% lidocaine (Beijing Zizhu Pharmaceutical Co Ltd, Beijing, China) to provide analgesia throughout the experiment. Blood samples were obtained from the left inguinal area for blood gas analysis.

2.3. *Experimental protocol*

During the experiments, the room temperature and humidity were maintained at 22 ± 2°C and 50 ± 10%, respectively. The experimental procedure is shown in Figure 2. The intubation procedure required approximately 20 min. The rats were rested for 10 min, after which a controlled-volume hemorrhage of 25%, 35%, or 45% of the total blood volume was performed from the left femoral artery over a 30-min period. The rats were observed for another 30 min before infusion. To mimic prehospital treatment during the first hour after injury,