Monitoring the tissue perfusion during hemorrhagic shock and resuscitation: Tissue-to-arterial carbon dioxide partial pressure gradient in a pig model

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Abstract

Background: Transcutaneous CO₂ (tcPCO₂) and arterial CO₂ (artPCO₂) decoupling occurs during shock states. Our study aimed to test the hypothesis that the gradient between tcPCO₂ and artPCO₂ (tc-artPCO₂) can detect inadequate tissue perfusion during hemorrhagic shock and resuscitation.

Methods: This prospective animal study was performed by a qualified and experienced research team using female pigs (LWD, weighing 29–34 kg) at university-based experimental laboratory. Progressive massive hemorrhagic shock was induced in mechanically-ventilated pigs by stepwise blood withdrawal. Next, all the animals were then resuscitated by transfusing the stored blood in stages. A transcutaneous monitor was attached to the animals' ear to measure the tcPCO₂ and transcutaneous oxygen pressure (tcPO₂). The pulmonary artery catheter (PAC) and pulse index continuous cardiac output (PiCCO) were used to monitor several hemodynamic parameters.

Results: Hemorrhage and blood transfusion precisely impacted hemodynamic and laboratory data, such as cardiac output (CO), stroke volume, mean arterial pressure, heart rate, pulmonary artery wedge pressure, global end-diastolic volume, hemoglobin, and arterial lactate. The tc-artPCO₂ level markedly increased as CO decreased. In the analyses of the 42 paired measurements, there were significant correlations of tc-artPCO₂ with systemic oxygen delivery (DO₂) and CO (DO₂: $r = -0.83$, CO by PAC: $r = -0.79$; CO by PiCCO: $r = -0.74$; all $P < 0.0001$) levels. The critical level of oxygen delivery (DO_{2crit}) was 11.72 mL/kg/min according to tcPO₂ (at a threshold of 30 mmHg). The receiver operating characteristic curve analyses revealed that the area under the curves (AUCs) that predicted DO_{2crit} for tc-artPCO₂, shock index (SI), and lactate were 0.94 (95% confidence interval, 0.87-1.00); 0.78 (0.63-0.93); and 0.65 (0.47-0.82), respectively. The AUC for tc-artPCO₂ was greater in predicting DO_{2crit} than that for SI.

Conclusions: tc-artPCO₂ was strongly correlated with DO₂ during hemorrhagic shock and resuscitation. This less-invasive tc-artPCO₂ monitoring can sensitively detect inadequate systemic O₂ supply during hemorrhagic shock. Further evaluations are required in different forms of shock in other large animal models and in humans to assess its usefulness, safety, and ability to predict outcomes in critical illnesses.

Introduction

Hemorrhagic shock is a life-threatening condition, with a significant loss of intravascular volume, decreased cardiac output (CO), decreased tissue perfusion pressure, and cellular hypoxia, resulting in multiple organ damage and death [1, 2]. The ultimate goal of resuscitation for hemorrhagic shock is the rapid control of the source and the restoration of effective tissue perfusion, oxygenation, and cellular metabolism [2]. Thus, prompt assessment of the adequacy of tissue perfusion is essential for the early identification and intervention of shock.

The pulmonary artery catheter (PAC) provides continuous monitoring of comprehensive hemodynamic parameters, including stroke volume, CO, mixed venous oxygen saturation, and intracardiac pressure with several additional calculated variables to guide diagnosis and treatment [3]. The pulse index continuous cardiac output (PiCCO) is another efficient and advanced hemodynamic monitoring system that integrates various hemodynamic variables through intra-arterial and central venous catheterization [4]. However, these techniques are invasive, with no clear evidence of improved outcomes associated with their use to guide therapy [5, 6].

Transcutaneous partial pressure monitoring of oxygen (tcPO_2) and carbon dioxide (tcPCO_2), which can non-invasively assess the arterial partial pressure of oxygen (artPO_2) and carbon dioxide (artPCO_2), respectively, has been investigated for several decades [7–13]. However, in clinical practice, adherence with their use, remains low [7]. Both measures are indicators of tissue perfusion adequacy during shock [7, 12, 14, 15]. During low-flow shock, tcPO_2 can detect tissue hypoxia or inadequate perfusion [16, 17]. Particularly, tcPCO_2 and artPCO_2 mismatch and decoupling occurs during shock states [18], and increased tcPCO_2 is associated with poor outcomes in critically ill patients [12, 19]. These observations suggest that the gradient between tcPCO_2 and artPCO_2 (tc-artPCO_2) measured in a minimally invasive way (i.e., with only arterial puncture needed), is useful as a rapid and accurate measure during shock.

Despite much evidence supporting the monitoring of the divergence of tcPCO_2 from artPCO_2 as an indicator of the shock status, data are limited on the systemic oxygen metabolism and hemodynamic parameters, which can be obtained by PAC or PiCCO in shock states. In this study, we tested the hypotheses that 1) significant associations between tc-artPCO_2 and a variety of hemodynamic parameters of PAC or PiCCO exist, and 2) tc-artPCO_2 could be an early and sensitive method to detect inadequate tissue perfusion in a pig model of progressive hemorrhage shock and resuscitation.

Methods

The experimental procedures were approved by the ethics committee for animal experiments at Rakuno Gakuen University (protocol number: VH19B14). Care and handling of the animals were performed in accordance with the guidelines of the National Institutes of Health.

Animal preparation

All studies were performed by a qualified and experienced research team using female pigs (LWD, weighing 29–34 kg). Food was withheld from the animals for 12 h prior to the start of the experiment; however, water was allowed 6 h prior. After getting used to the environment and following physical examination by a veterinarian, the animals were sedated by an intramuscular injection of medetomidine hydrochloride (40.0 $\mu\text{g}/\text{kg}$), midazolam (0.2 mg/kg), and butorphanol tartrate (0.2 mg/kg). Tracheal intubation was performed after induction of anesthesia using propofol, and general anesthesia was maintained with inhaled 2.0% sevoflurane (Sevoflo®, Dainippon-Sumitomo Pharma, Osaka, Japan). Anesthetics were adapted if the depth of anesthesia was insufficient. Following anesthesia induction, the

pigs were placed in a supine position and administered a fluid infusion of lactated Ringer's solution (LR, Terumo Co., Tokyo, Japan) at 10 mL/kg/h, through a 22-gauge catheter (Supercath, Medikit Co., Tokyo, Japan) placed in the right marginal ear vein. All animals were mechanically ventilated in volume-control mode (Flow-i, Maquet, Sonia, Sweden) after intravenous administration of 2 mg/kg vecuronium (Musculat®e, Fuji Pharma Co., Tokyo, Japan), followed by a constant-rate infusion at 0.1 mg/kg/h, administered through the left marginal ear vein. The ventilation settings were 8–10 mL/kg tidal volume with a respirator, with positive end expiratory pressure set at 5 cm H₂O. The fraction of inspired oxygen (F_IO₂) was set at 0.5, with an inspiration to expiration ratio of 1:2; the respiratory rate was adjusted to 16–20/min to maintain artPCO₂ 50 ± 5 mmHg. Body temperature was maintained at 37.0 ± 0.5°C using a heating pad.

Experimental protocol

After each catheterization was completed, all the animals were allowed to stabilize for 30 min, and each initial value was regarded as the baseline value. To induce a progressive hemorrhagic shock status, blood was withdrawn from the central venous catheter and stored in sterile bags with a volume of citrate-phosphate-dextrose-adenine (CPDA-1) appropriate for a 30 mL/kg of blood (14 mL CPDA-1 per 100mL of blood). After a 10 mL/kg of blood was withdrawn (BW10), the animals were allowed to stabilize for 10 min; thereafter, the hemodynamic parameters were measured when the BW10, 20 (BW20), and 30 (BW30) mL/kg of blood were withdrawn. Next, the animals were resuscitated by transfusing them with the stored blood, and the measurements were repeated when the 10 (BT10), 20 (BT20), and 30 (BT30) mL/kg of blood transfusion was completed (Fig. 1).

Instrumentations

A 7 Fr PAC (Edward Lifesciences, Irvine, CA, USA) was inserted into the left internal jugular vein and advanced into the pulmonary artery. Assessment of pulmonary artery pressure and wedge waveforms confirmed the correct position of the PAC. Simultaneously, the right femoral artery was catheterized with a thermistor-tipped 4 Fr PiCCO catheter (PV2014L16, Pulsion Medical Systems AG, Munich, Germany) connected to a Pulsioflex (Pulsion Medical System, Munich, Germany). Arterial blood pressure was measured via the femoral artery using a PiCCO catheter. A 6 Fr double-lumen central venous catheter (UK catheter kit UB-0610-W, 21G, 10 cm, Unitika Medical, Osaka, Japan) was inserted into the right jugular vein and positioned at the cranial end of the superior vena cava for blood withdrawal and transfusion. The distal ports of the PAC were connected to the Pulsioflex monitor sensor for the same time measurement of CO via an injection of ice-cold physiological saline 0.9 % (Isotonic Sodium Chloride Solution®). All transducers were zeroed and positioned at the level of the right atrium.

Transcutaneous CO₂ and O₂ measurements

The transcutaneous monitoring system (TCM4; Radiometer, Copenhagen, Denmark) provides non-invasive and continuous tcPO₂ and tcPCO₂. Prior to the transcutaneous sensor (tc Sensor 84; Radiometer, Copenhagen, Denmark) fixation, the skin was cleaned, and an adhesive ring with two drops of contact gel was applied, according to the manufacturer's instructions. Measurements were performed in the supine

position with a skin probe positioned on the right ear. Calibration was conducted automatically, with the temperature of the skin probe set at 44°C. The tcPCO₂ and tcPO₂ values were obtained and recorded before the CO measurement, during each hemodynamic stage, by an investigator blinded to the experiments.

Measurements of hemodynamic parameters

CO was measured by pulmonary artery thermodilution (CO_{PATD}: using PAC) and transpulmonary thermodilution (CO_{TPTD}: using Pulsioflex); 10 mL of ice-cold physiological saline 0.9% (Isotonic Sodium Chloride Solution®) was used as an indicator and was injected through the left distal port of PAC. PATD and TPTD were measured simultaneously at each time point by the same operator (YE), who was blinded to the transcutaneous CO₂ and O₂ measurements and laboratory data. The number of measurements was less than four times at each measurement point. To unify the CO_{TPTD} measurement method and eliminate the nominative effects, CO_{TPTD} was measured by the following methods : 1) use of average of three time values, 2) the number of measurements were less than four times, 3) the indicator was injected by the same operator (YE) throughout the overall study period, 4) ΔT in TPTD (the change in blood temperature after indicator injection) was recorded; optimal = $\Delta T > 0.3$, good = $\Delta T > 0.2$, and bad = $\Delta T < 0.2$, to verify the reliability of the measurement method, and 5) the indicator was injected exactly for 2–3 sec (to avoid faster or slower injection); and 6) the temperature of the indicator was accurately controlled at 0°C using an ice and cooler box. In this study, $\Delta T > 0.3$ occurred 38 times, $\Delta T > 0.2$ occurred 4 times, and $\Delta T < 0.2$ did not occur at all, indicating that TPTD at all measurement points was quite accurate according to the TPTD instruction.

Hemodynamic parameters measured by PAC (pulmonary artery thermodilution [PATD]) included the central venous pressure (CVP), pulmonary artery wedge pressure (PAWP), stroke volume (SV_{PATD}), and CO (CO_{PATD}). Transpulmonary thermodilution [TPTD] parameters obtained by PiCCO technology (Pulsion Medical System, Munich, Germany) included the mean arterial pressure (MAP), SV (SV_{TPTD}), CO (CO_{TPTD}), global end-diastolic blood volume (GEDV), stroke volume variation (SVV), pulse pressure variation (PPV), cardiac function index (CFI, CO/GEDV), cardiac power output (CPO, mean arterial pressure [mmHg] $\times$ CO [L/min] $\times$ K, where K = 0.0022 [a conversion factor]). The shock index (SI), defined as heart rate divided by systolic blood pressure, at each measurement point was calculated. SI > 1.0 was indicative of worsening hemodynamic status and shock [20]. PATD and TPTD could be measured at each time point. SVV was not observed at two time points in one pig for an unknown reason, all other hemodynamic variables displayed each value.

Additionally, a perfusion index (PI), which was derived from pulse oximetry readings (Masimo SET Radical-7™, Masimo, Irvine, CA, USA), was monitored simultaneously. The Masimo Radical-7 uses transcutaneous, multi-wavelength analysis for non-invasive measurement of arterial oxygen saturation, PI, and pleth variability index (PVI), which are measures of local blood flow. The Masimo sensor type LNOP Neo-L was attached to the tail after clipping the hair. Esophageal temperature and heart rate were also recorded (BSM-6000; Nihon Kohden Inc., Tokyo, Japan).

Arterial blood gas analysis

Arterial blood samples were withdrawn anaerobically from the PiCCO catheter and collected in a plastic syringe heparinized with 1,000 U/mL of sodium heparin (Novo-heparin for injection, Mochida Pharmaceutical Co., Tokyo, Japan), using an evacuation technique to minimize sample dilution. The blood samples were analyzed by an investigator blinded to the experiments immediately after collection (< 5 min), to measure artPO₂, artPCO₂, hemoglobin (Hb), and lactate, using a blood gas analyzer (ABL-90 FLEX; Radiometer, Copenhagen, Denmark).

Systemic oxygen delivery

An inappropriate level of systemic oxygen delivery (DO₂) capacity results in failure to satisfy the metabolic oxygen need in the tissue. It is well established that tissues exhibit a level of systemic DO₂, known as the critical DO₂ (DO_{2crit}), below which the extraction cannot increase sufficiently to sustain O₂ uptake; O₂ consumption then becomes supply-dependent [21–24]. DO₂ was calculated using the following equation: DO₂ (mL/kg/min) = CO × hemoglobin [Hb] × 1.36 × arterial oxygen saturation (SaO₂) + (partial pressure of oxygen [PaO₂] × 0.0031) [25]. In this study, tcPO₂ was used to define DO_{2crit} since tcPO₂ reflects tissue oxygenation under experimental conditions. Given that the lowest baseline tcPO₂ associated with survival was 28 mmHg [26], the lowest threshold for tcPO₂ was set as 30 mmHg. This is consistent with previous studies which demonstrated that tcPO₂ values < 25 mmHg reflects a 50% decrease in oxygen consumption, preceding cardiac arrest [27], and that a tcPO₂ value of 40 mmHg is a critical artPO₂ in the subcutaneous tissue [28, 29].

Statistical analysis

Values were expressed as the mean ± standard error of the mean. An unpaired two-tailed Student's t-test or Mann-Whitney U test was used to compare two independent groups, as appropriate. Linear regression and Bland-Altman analyses were used to determine the correlation between tcPCO₂ and artPCO₂. Repeated one-way analysis of variance (ANOVA) followed by Dunnett's correction, and Friedman test followed by Dunn's correction were used for post-hoc comparisons of normally and non-normally distributed data, respectively. Spearman's correlation coefficients (r) were calculated to evaluate the correlation between each parameter. To examine the accuracy of tc-artPCO₂, SI, and arterial lactate for predicting DO_{2crit}, receiver operating characteristic (ROC) curve analyses were performed. The area under the curve (AUC) between two pairs of potential predictors was compared using a nonparametric test. Statistical significance was defined as a two-sided p-value < 0.05. All statistical analyses were performed using GraphPad Prism version 8.3.0 (GraphPad Software, San Diego, CA) and Microsoft Excel (Microsoft 365, Microsoft Corporation, Redmond, WA).

Results

All six pigs were included, and 42 paired measurements of each of their variables were analyzed. No death occurred during the experiments.

Hemodynamics and blood gas analysis

Hemorrhage and blood transfusions impacted tc-artPCO₂, MAP, heart rate, CVP, SI, perfusion index, and comprehensive hemodynamic parameters obtained by PAC or PiCCO, such as CO and SV (Fig. 2). tc-artPCO₂ increased with increased volume of blood withdrawn, while tc-artPCO₂ decreased with increased blood transfusion volume (Fig. 2A). Hemorrhage and blood transfusions markedly induced changes in preload parameters, such as CVP, PAWP, GEDV, SVV, PPV, and pleth variability index. Blood gas analyses showed significant changes in pH, artPO₂, HCO₃⁻, Hb, lactate, CFI, and CPO, whereas artPCO₂ and base excess remained unchanged during the experiments (Fig. 3 and Table 1).

Table 1

Arterial blood gas changes during blood withdrawal and transfusion.

Status of circulating blood volume							
	BL	BW10	BW20	BW30	BT10	BT20	BT30
pH	7.51 ± 0.05	7.54 ± 0.04	7.50 ± 0.03	7.52 ± 0.08	7.46 ± 0.05	7.45 ± 0.05	7.43 ± 0.07*
artPCO ₂ , mmHg	46.3 ± 6.1	44.6 ± 4.5	44.6 ± 5.0	40.6 ± 10.6	49.0 ± 4.6	50.0 ± 5.8	55.0 ± 10.3
artPO ₂ , mmHg	267.3 ± 8.3	267.3 ± 6.2	275.2 ± 30.3	268.0 ± 18.1	246.2 ± 14.3*	248.3 ± 17.1	218.3 ± 42.5†
HCO ₃ ⁻ , mmol/L	36.8 ± 1.8	37.0 ± 2.0	35.1 ± 1.6	34.4 ± 2.0	35.0 ± 3.2	34.6 ± 1.9*	36.3 ± 3.2
BE, mmol/L	12.4 ± 2.1	13.0 ± 1.9	11 ± 1.0	10.7 ± 2.9	10.1 ± 3.5	9.6 ± 2.4	10.7 ± 3.3
BL, Baseline; BW10, 10mL/kg of blood withdrawal; BW20, 20mL/kg of blood withdrawal; BW30, 30mL/kg of blood withdrawal; BT10, 10mL/kg of blood transfusion; BT20, 20mL/kg of blood transfusion; BT30, 30mL/kg of blood transfusion; pH, arterial pH; artPCO ₂ , partial pressure of arterial carbon dioxide; artPO ₂ , partial pressure of arterial oxygen; HCO ₃ ⁻ , arterial bicarbonate; BE, arterial base excess.							
*P < 0.05, †P < 0.01 vs. baseline.							

Assessment of the agreement between tcPCO₂ and artPCO₂

To confirm that tcPCO₂ and artPCO₂ are coupled in normal conditions but decoupled during hemorrhagic shock, the agreements between tcPCO₂ and artPCO₂ were evaluated in euvolemic or hypovolemic status. Using 12 measurement points of the euvolemic status (i.e. at BL and BT30), linear regression demonstrated that there was a strong relationship between tcPCO₂ and artPCO₂ ($r = 0.86$, $P = 0.0004$). In a Bland-Altman analysis, the mean bias was 4.1 ± 5.4 mmHg. In contrast, using 30 measurement points of the hypovolemic status, there was no relationship between tcPCO₂ and artPCO₂ ($r = 0.29$, $P = 0.11$), and the mean bias by a Bland-Altman analysis was 16.2 ± 11.4 mmHg (Fig. 4).

Associations of CO with tc-artPCO₂ and tcPO₂

Linear regressions demonstrated significant negative correlations of tc-artPCO₂ with CO_{PATD} ($r = -0.79$), CO_{TPTD} ($r = -0.74$), and tcPO₂ ($r = -0.89$) (all $P < 0.0001$) (Fig. 5). Data for tc-artPCO₂ and tcPO₂, obtained at all measurement time points were divided into four groups according to CO categories: CO_{PATD} (L/min) < 2.5 , $2.5 \leq \text{CO}_{\text{PATD}} < 3.0$, $3.0 \leq \text{CO}_{\text{PATD}} < 4.0$, and $4.0 \leq \text{CO}_{\text{PATD}}$. There was a negative linear trend between tcPCO₂ and CO categories: with the lowest tc-artPCO₂ value (2.6 ± 1.0 mmHg) when $\text{CO} > 4.0$ L/min, and the highest (24.6 ± 2.9 mmHg) when $\text{CO} < 2.5$ L/min. Conversely, there was a positive linear trend between tcPO₂ and CO categories (Fig. 6).

Correlations between DO₂ and hemodynamic variables

Compared with DO₂ at baseline (15.9 ± 2.7 mL/kg/min), significant declines in DO₂ at BW10, BW20, BW30, and BT10 were observed (11.2 ± 2.1 , $P = 0.002$; 9.5 ± 2.1 , $P = 0.018$; 7.7 ± 2.1 , $P = 0.002$; and 11.2 ± 1.5 mL/kg/min, $P = 0.04$, respectively). After all the stored blood was transfused (BT30), DO₂ returned to baseline value (16.2 ± 1.9 mL/kg/min). There were significant positive correlations of DO₂ with tcPO₂ and MAP ($r = 0.72$, $P < 0.001$; $r = 0.75$, $P < 0.001$, respectively), and significant negative correlations of DO₂ with tc-artPCO₂, SI, heart rate, and lactate ($r = 0.77$, $P < 0.001$; $r = 0.64$, $P < 0.001$; $r = 0.30$, $P = 0.047$; $r = 0.24$, $P = 0.027$, respectively) (Fig. 7).

Prediction of DO_{2crit}

The critical level of DO₂ (DO_{2crit}) was calculated as 11.72 mL/kg/min, according to the predetermined tcPO₂ threshold of 30 mmHg (see *Methods*). ROC curves were drawn to compare the predictive value of tc-artPCO₂, SI, and lactate for DO_{2crit} (11.72 mL/kg/min). The AUCs showed that the predictive values of tc-artPCO₂, SI, and lactate were 0.94 (95% confidence interval [CI], 0.87-1.00); 0.78 (0.63-0.93); and 0.65 (0.47-0.82), respectively, with respect to the prediction of DO_{2crit} for the transition from aerobic to anaerobic metabolism (Fig. 8A). The tc-artPCO₂ cut-off of 6.15 mmHg provided the optimal sensitivity (100%) and specificity (77%) for predicting DO_{2crit}, while an SI cut-off of 1.13 was identified as the optimal value (sensitivity = 70%, specificity = 82%) (Fig. 8B). The AUC for tc-artPCO₂ was greater for predicting DO_{2crit} than for predicting SI ($P = 0.04$) and lactate ($P = 0.001$) (Fig. 8B). Figure 9 shows the percentage changes in tc-artPCO₂, SI, and lactate at each time point, compared to baseline. The largest percentage change occurred in tc-artPCO₂ with hypovolemia (BW30, 353.3%) compared with SI and lactate BW30 (142.3% and 89.0%, respectively).

Discussion

In this study, we assessed the usefulness of tc-artPCO₂ as a rapid, yet sensitive, indicator of shock in a mechanically-ventilated pig model during progressive hemorrhagic shock and resuscitation. We verified the hypotheses that tcPCO₂ can non-invasively estimate and track artPCO₂ in euvolemic conditions, and that tcPCO₂ and artPCO₂ decoupled during hemorrhagic shock. This study showed, for the first time, (1.) strong associations of tc-artPCO₂ with DO₂ and CO, which were properly measured by both PAC and PiCCO; and (2.) significantly superior AUC for tc-artCO₂, compared to those for SI or arterial lactate which are independently associated with physiological and clinical outcomes in hemorrhagic shock [1, 20, 30–32]. Taken together, we concluded that tc-artCO₂ can be a valid indicator of impaired DO₂ during shock.

The primary purpose of tcPCO₂ monitoring is to measure artPCO₂ non-invasively and continuously, preventing the need to perform multiple blood gas analyses and helping to guide therapeutic interventions. In previous studies, tcPCO₂ and artPCO₂ became decoupled during circulatory failure and are associated with poor outcomes in critically ill patients [12, 18, 19]. Additionally, tc-artPCO₂ is less invasive, quick, and easy to use. Therefore, monitoring tcPCO₂ can be used as a common utility, especially in emergency departments and intensive care units. Particularly in patients under respirators, monitoring tcPCO₂ can estimate artPCO₂ and detect respiratory issues as a common utility, while tc-artPCO₂ can estimate low CO and/or low DO₂ for hemodynamic and metabolic assessments during shock.

Previous studies support elevated tissue PCO₂ as a marker of hypoperfusion [33–36]. The tissue hypercarbia during shock is explained by consequent reduced removal of CO₂ and anaerobic production of CO₂ [37]. Current technologies allow the estimation of CO₂ content in tissues (mucosal or cutaneous) based on the high diffusivity of CO₂ gas. In a pig model with acute lung injury, tcPCO₂ is an acceptable surrogate for artPCO₂ in hemodynamically stable states; however, tcPCO₂ and artPCO₂ decoupled during shock [38]. This is consistent with our results. In patients with septic shock, tcPCO₂ measured from the ear lobe at study inclusion was significantly higher in patients with septic shock than in controls. Additionally, there was a significantly greater gradient between tcPCO₂ and artPCO₂ or end-tidal CO₂ (etCO₂) in patients with septic shock than in controls [19]. Increased gastric-to-arterial PCO₂ is an early indicator of circulatory failure and a prognostic factor of increased morbidity in patients with cardiopulmonary bypass, after cardiac surgery [39]. Despite these observations, the equipment for tcPCO₂ is not widely used in clinical practice [7] and remain poorly evaluated in preclinical large animal models.

In a pig model with lethal hemorrhagic shock, Belenkiy et al. demonstrated that the noninvasive etCO₂ and tcPCO₂ gradient (NICO₂G) can serve as a proxy for the severity of hemorrhage-induced metabolic debt, as indicated by elevated arterial lactate levels [40]. Linear regression analyses of the parameters with lactate showed a low correlation for etCO₂ ($r^2 = 0.26$, $P < 0.001$); better for tcPCO₂ ($r^2 = 0.46$, $P < 0.001$); and best for NICO₂G ($r^2 = 0.58$, $P < 0.0001$). NICO₂G increased with hemorrhage and correlated

well with arterial lactate levels, even as artPCO₂ remained constant [40]. However, no hemodynamic monitoring was used with PAC or PiCCO technology, leading to a lack of information on DO₂ in their study. Furthermore, etCO₂ monitoring is not suitable for serial hemodynamic assessments in patients with lung injury, or under mechanical ventilation, if the respiratory settings are frequently needed to be adjusted to the patient's conditions. Additionally, etCO₂ can be decreased in shock states because of impaired pulmonary blood flow. These facts suggest the superiority of tc-artPCO₂ for detecting shock in ventilated patients, compared to NICO₂G. Moreover, it was reported that an increase in arterial lactate occurred later than the decreases in CO and DO₂ in a pig model with hemorrhagic shock, due to a time difference in the occurrence of tissue and circulating lactic acid [41]. Thus, DO₂ and/or CO could be more appropriate markers for shock than lactate level. Our efforts to measure hemodynamic parameters with two different established methods (i.e., PAC and PiCCO), and using DO₂ as a primary outcome, strengthened the results of this study.

Besides tcPCO₂, tcPO₂ measurement allows for continuous monitoring of tissue oxygenation, which is compromised during the early phase of hemorrhagic shock and is one of the last to be restored during resuscitation [42]. In this study, we further observed that tcPO₂ responded rapidly to changes in CO during hemorrhage and blood transfusion (Fig. 6). Consistent with our results, previous studies in piglet models have demonstrated a rapid decrease in and restoration of tcPO₂ in response to hemorrhage and fluid infusion [43, 44]. In a rat model of hemorrhagic shock and resuscitation, tcPO₂ was more rapidly responsive than tcPCO₂ and arterial lactate [45]. However, in clinical practice, the dependence of tcPO₂ cannot be overemphasized [12], since tcPO₂ depends on F_IO₂, which should be managed frequently during critical care. Thus, tcPO₂ monitoring without reference to F_IO₂ can be misleading [27].

Our study had several limitations that should be addressed in future investigations. First, the small sample size could have resulted in a type 1 error. Second, this study included only female animals, to minimize the heterogeneity. Future studies should include both male and female animals to investigate the role of sex in susceptibility to shock. Third, this study needs to be replicated for all types of shocks before extrapolating the data to other critical illnesses. Clinical trials aimed at testing the role of tc-artPCO₂ in patients with shock could be justified only if preclinical evidence suggests that the changes in tc-artPCO₂ might provide meaningful associations with outcomes, or changes in surrogate markers after shock and resuscitation.

Conclusions

In conclusion, we demonstrated, using this precise pig model, that continuous tc-artPCO₂ monitoring is a minimally invasive technique that could be a rapid, yet sensitive indicator of evolving hemorrhagic shock during mechanical ventilation, and that tc-artPCO₂ is superior to SI and arterial lactate levels. The present study results are encouraging, and the data clearly strengthen previous literature on techniques to monitor tissue O₂ and CO₂ partial pressures. Further evaluations are required in different forms of shock

in other large animal models and in humans to assess its usefulness, safety, and ability to predict outcomes in critical illnesses.

Abbreviations

artPCO₂, Arterial partial pressure of carbon dioxide

artPO₂, Arterial partial pressure of oxygen

CFI, Cardiac function index

CO, Cardiac output

COPATD, CO by pulmonary artery thermodilution

COTPTD, CO by transpulmonary thermodilution

CPDA-1, Citrate-phosphate-dextrose-adenine

CPO, Cardiac power output

CVP, Central venous pressure

DO₂, Oxygen delivery

DO_{2crit}, Critical DO₂

F_IO₂, fraction of inspired oxygen

GEDV, Global end-diastolic blood volume

Hb, Hemoglobin

MAP, Mean arterial pressure

PAC, Pulmonary artery catheter

PAP, Pulmonary artery pressure

PAWP, Pulmonary artery wedge pressure

PI, Perfusion index

PiCCO, Pulse index continuous cardiac output

PPV, Pulse pressure variation

PVI, Pleth variability index

SV, Stroke volume

SVPATD, SV by pulmonary artery thermodilution

SVTPTD, SV by transpulmonary thermodilution

SVV, Stroke volume variation

tc-artPCO₂, Gradient between tcPCO₂ and artPCO₂

tcPCO₂, transcutaneous partial pressure of carbon dioxide

tcPO₂, transcutaneous partial pressure of oxygen

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of supporting data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

Figure 1

(A) A schema of the pig hemorrhagic shock and resuscitation model and (B) experimental protocol.

Figure 2

Changes in (A) transcutaneous partial pressure monitoring of oxygen and carbon dioxide (tc-artPCO₂), cardiac output measured by pulmonary artery thermodilution (COPATD), cardiac output measured by transpulmonary thermodilution (COTPTD); (B) stroke volume by pulmonary artery thermodilution (SVPATD), stroke volume by transpulmonary thermodilution (SVTPTD); (C) mean arterial pressure (MAP), heart rate (HR); and (D) shock index, perfusion index during hemorrhagic shock and resuscitation. Data are presented as the mean $\pm$ standard error of the mean. *P < 0.05, †P < 0.01 vs. baseline (BL).

Figure 3

Changes in (A) central venous pressure (CVP), pulmonary artery wedge pressure (PAWP), global end-diastolic blood volume (GEDV), (B) stroke volume variation (SVV), pulse pressure variation (PPV), pleth variability index (PVI), (C) hemoglobin (Hb), lactate, (D) cardiac function index (CFI), cardiac power output (CPO) during hemorrhagic shock and resuscitation. BW, blood withdrawal (10, 20, 30 mL/kg); BT, blood transfusion (10, 20, 30 mL/kg). Data are presented as the mean $\pm$ standard error of the mean. * $P < 0.05$, † $P < 0.01$, § $P < 0.001$ vs. baseline (BL).

Figure 4

(A, B) Linear regressions and Bland-Altman analyses of tcPCO_2 and artPCO_2 in euvolemic states ($N = 12$) and (C, D) hypovolemic states ($N = 30$).

Figure 5

Linear regression analyses. (A) tc-artPCO₂ and cardiac output measured by pulmonary artery thermodilution (COPATD), (B) tc-artPCO₂ and cardiac output measured by transpulmonary thermodilution (COTPTD), and (C) tc-artPCO₂ and tcPO₂.

Figure 6

tc-artPCO₂ and tcPO₂ levels by cardiac output measured by pulmonary artery thermodilution (COPATD). Data are presented as the mean $\pm$ standard error of the mean. [†]P < 0.01 vs. baseline (BL).

Figure 7

Linear regression analyses of systemic oxygen delivery (DO₂) and (A) tc-artPCO₂, (B) tc-artPO₂, (C) shock index, (D) heart rate (HR), (E) mean arterial pressure (MAP), and (F) lactate. N = 42.

B

Prediction of DO₂crit

	ROC curve						P-value (vs. tc- artPCO ₂)
	AUC	95%CI	P-value	Cut-off value	Sensitivity	Specificity	
tc-artPCO ₂	0.94	0.87 to 1.00	<0.001	6.15	100%	77%	N/A
Shock index	0.78	0.63 to 0.93	0.002	1.13	70%	82%	0.04
Lactate	0.65	0.47 to 0.82	0.11	1.55	45%	82%	0.001

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; tc-artCO₂, gradient between tcPCO₂ and artPCO₂; tcPCO₂, transcutaneous CO₂; artPCO₂, arterial blood CO₂.

Figure 8

Receiver operating characteristic (ROC) curves comparing the ability of transcutaneous partial pressure monitoring of oxygen and carbon dioxide (tc-artPCO₂), shock index, and arterial lactate concentration to distinguish between the critical level of systemic oxygen delivery (DO₂crit) < 11.72 and DO₂crit ≥ 11.72 mL/kg/min.

Figure 9

Percent changes in indicators during hemorrhagic shock and transfusions.