ORIGINAL RESEARCH

Two-site regional oxygen saturation and capnography monitoring during resuscitation after cardiac arrest in a swine pediatric ventricular fibrillatory arrest model

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Abstarct

To investigate the use of two-site regional oxygen saturations (rSO_2) and end tidal carbon dioxide ($EtCO_2$) to assess the effectiveness of resuscitation and return of spontaneous circulation (ROSC). Eight mechanically ventilated juvenile swine underwent 28 ventricular fibrillatory arrests with open cardiac massage. Cardiac massage was administered to achieve target pulmonary blood flow (PBF) as a percentage of pre-cardiac arrest baseline. Non-invasive data, including, $EtCO_2$, cerebral rSO_2 (C-rSO_2) and renal rSO_2 (R-rSO_2) were collected continuously. Our data demonstrate the ability to measure both rSO_2 and $EtCO_2$ during CPR and after ROSC. During resuscitation $EtCO_2$ had a strong correlation with goal CO with $r = 0.83$ ($p < 0.001$) 95% CI [0.67–0.92]. Both C-rSO_2 and R-rSO_2 had moderate and statistically significant correlation with CO with $r = 0.52$ ($p = 0.003$) 95% CI (0.19–0.74) and 0.50 ($p = 0.004$) 95% CI [0.16–0.73]. The AUCs for sudden increase of $EtCO_2$, C-rSO_2, and R-rSO_2 at ROSC were 0.86 [95% CI, 0.77–0.94], 0.87 [95% CI, 0.8–0.94], and 0.98 [95% CI, 0.96–1.00] respectively. Measurement of continuous $EtCO_2$ and rSO_2 may be used during CPR to ensure effective chest compressions. Moreover, both rSO_2 and $EtCO_2$ may be used to detect ROSC in a swine pediatric ventricular fibrillatory arrest model.

Keywords Resuscitation · Regional oxygen saturation · Near-infrared spectroscopy (NIRS) · End tidal CO_2 · Return of spontaneous circulation · Non-invasive · Monitoring · Pediatrics

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1 Introduction

Cardiac arrest occurs in 2–6% of children admitted to Pediatric Intensive Care Units [1, 2]. The overall survival for pediatric patients with in-hospital cardiac arrest remains low at less than 40% [3, 4]. Although severe hypoxia and respiratory failure remain the most common cause of pediatric in hospital cardiac arrests, 10–15% have rhythm that requires defibrillation [5]. The outcome of cardiac arrest is dependent on critical interventions, especially early defibrillation, effective chest compressions and assisted ventilation [6, 7]. Invasive blood pressure and cardiac output monitoring provide an accurate means of assessing the effectiveness of chest compressions [8]. However, invasive monitoring at the time of either the arrest or initiation of resuscitation occurs in less than 50% of in-hospital pediatrics cardiac arrest cases and almost never occurs in out-of-hospital pediatric cardiac arrest cases [2]. The need for accurate, non-invasive, and real-time monitoring of both oxygenation and circulation during resuscitation is, therefore, paramount to the improvement of resuscitation outcomes.

Despite its limitations, end-tidal carbon dioxide ($EtCO_2$) monitoring remains the only noninvasive tool that has been used and advocated during CPR as a marker of effectiveness of resuscitation [9]. Furthermore, $EtCO_2$ has been suggested to correlate with cardiac output and cerebral perfusion, and it has also been reported to be a predictor of survival and prognosis in patients after cardiac arrest and resuscitation [10, 11]. However, measurement of $EtCO_2$ can be particularly unreliable in low-flow states such as during CPR or in the presence of significant pulmonary pathology. Moreover, the accuracy of $EtCO_2$ measurement depends on proper capnography waveforms that may be difficult to obtain during chest compressions [12, 13]. Finally, $EtCO_2$ does not provide any meaningful information about the quality of organ perfusion and oxygenation during resuscitation [14].

Regional oxygen saturation monitoring with near infrared spectroscopy (NIRS) has emerged as a noninvasive surrogate monitor of regional oxygen saturation (rSO_2) [15, 16]. During critical illness, NIRS probes are routinely placed on the forehead to measure cerebral rSO_2 (C-rSO_2) and the back to measure renal rSO_2 (R-rSO_2), referred to as two-site rSO_2. Two-site rSO_2 can provide a real-time indicator of the balance between oxygen supply and demand in the intraoperative and intensive care setting. Moreover, two-site rSO_2 represent two opposite poles of circulation, and the compensatory response to low cardiac output can be reflected in a decrease in R-rSO_2 while C-rSO_2 is preserved. This clinical information can help the provider to make treatment decisions and assess the effect of therapeutic interventions in settings of low cardiac output, such as cardiogenic, hemorrhagic and septic shock [17]. Moreover, NIRS does not require pulsatile flow, which makes it an ideal monitoring tool during cardiac arrest [18]. Although NIRS technology has been validated and used in many clinical scenarios, limited studies have examined the role of two-site rSO_2 monitoring during cardiac arrest to assess the effectiveness of chest compressions and detection of ROSC without interrupting resuscitation efforts [19–22].

2 Materials and methods

All applicable international, national, and institutional guidelines for the care of experimental animals for scientific purposes were applied throughout the study; the experimental protocol was approved by University of Wisconsin Institutional Animal Care and Use Committee, in accordance with the guidelines in the US Department of Health and Human Services and the National Institutes for Health. The choice of domestic pigs was based on the fact that the porcine heart closely resembles the human heart from the point of view of size, physiology and anatomy.

2.1 Animal preparation

This study was performed in eight healthy 2- to 3-month-old mixed-breed domestic swine (Sus scrofa) with weight of 23 ± 3 kg. Animals had free access to water but were fasted overnight. Each animal was pre-medicated with intramuscular telazol (4–7 mg/kg) and xylazine (2 mg/kg). Subsequently, a 20 g intravenous catheter was placed into an ear vein for additional anaesthetic agents (Propofol, 2–10 mg/kg) prior to the procedure. The animal was intubated with cuffed endotracheal tube and mechanically ventilated under general anaesthesia using mixture of room air and titrated isoflurane (0.5–1.5% inspired concentration). Volumetric capnography monitor (Philips, Carlsbad, CA) was connected to the ventilator circuit via a side stream capnostat sensor placed at the proximal end of the endotracheal tube (between the endotracheal tube and the ventilator circuit). Then animals were deeply sedated with adequate pain control throughout the experiment using fentanyl (3.0–10.0 µg/kg/h IV) as needed. The tidal volume was initially set at 8–10 mL/kg and the ventilator rate at 12 breaths per minute; ventilator settings then were adjusted to maintain $PaCO_2$ at 35 to 45 mm Hg. The femoral artery was accessed by percutaneous methods then a 6 Fr sheath was placed and advanced to the abdominal aorta to measure systemic pressure and to withdraw blood for blood gas analysis. A 6 Fr sheath was also placed in the femoral vein by percutaneous methods for further administration of medications. A median sternotomy was performed and the heart was exposed. Finally, an ultrasonic flow probe (PAU Series, ADInstruments, Dunedin, New Zealand) was placed around the pulmonary artery.

Following surgical procedures, adhesive, non-invasive NIRS probes were placed on a shaved portion of the left forehead scalp laterally from the midline, and left somatic (flank) region above the kidney. These locations were selected to reflect the locations used for clinical C-rSO_2 and R-rSO_2 monitoring in children. Then probes were connected to a Somanetics Invos 5100C Monitor (Oxy-AlertTM, Somanetics Invos 5100C, Somanetics Corporation, Troy, MI, USA). Baseline C-rSO_2 and R-rSO_2 readings were continuously obtained before VF induction and then was continuously monitored and recorded throughout the entirety of the experimental protocol.

Continuous monitoring included ECG, peripheral oxygen saturation, invasive arterial blood pressure monitoring, cerebral and renal saturation by near infrared spectroscopy (INVOS® Cerebral/Somatic Oximeter monitor, Somanetics, Troy, MI, USA), and the respiratory volumes, pressures, $EtCO_2$, volume of carbon dioxide monitoring, and tidal volume and dead space ratio by means of a volumetric capnography monitor. Blood gases, lactate, and

hemoglobin were analyzed using a blood gas analyzer (pHOx Basics; Nova Biomedical, Waltham, MA).

2.2 Study protocol

Following baseline data acquisition, ventricular fibrillation was induced with current from a 9 V battery applied to the epicardial surface of the right ventricle for 3 s. Examination of the ECG tracing, absence of contractility, and the absence of pulses in the arterial pressure waveform was used to confirm VF. One minute following loss of pulse pressure, CPR was initiated by open manual cardiac massage. Cardiac massage was administered and was altered every 2 min during resuscitation to achieve target pulmonary blood flow (PBF) as a percentage of pre-cardiac arrest baselines (30%, 50%, and 70% of prearrest mean PBF) until ROSC or euthanasia. Non-invasive and invasive hemodynamic data was continuously monitored and collected through the whole experiment. Cardiac massage was at a rate of approximately 100 cycles per minute. Epinephrine, lidocaine, and defibrillation was administered per Pediatric Advanced Life Support (PALS) guidelines (Fig. 1). If there was no ROSC, the cycle was repeated per PALS protocol. ROSC was defined as restoration of perfusing rhythm, arterial systolic blood pressure of at least 50 mmHg and pulse pressure of 20 mmHg lasting at least 1 min. If there is no ROSC after 15 min resuscitation was discontinued.

After successful resuscitation, the animals was maintained on mechanical ventilation and continuous monitoring. Blood gases were obtained, metabolic acidosis was treated with normal saline and/or sodium bicarbonate and the ventilator was adjusted to achieve normal ventilation ($PaCO_2 = 35$–45 mmHg). Normal saline boluses were administered to treat hypotension. After 30 min of stability, the experiment was repeated in the animal up to four additional times.

2.3 Statistical analysis

Hemodynamic variables and levels of blood gases were summarized in terms of means ± standard deviations, stratified by event type. The correlations between measured cardiac output and rSO_2 and $EtCO_2$ parameters were evaluated using the nonparametric Spearman's rank correlation analysis. Receiver operating characteristics (ROC) curve analysis was conducted to evaluate whether cerebral, renal or $EtCO_2$ can predict ROSC. The strength of the prediction is quantified by calculating the area under the curve (AUC) which was reported along with the corresponding 95% confidence intervals. The Youden criterion was used to determine optimal threshold cutoff threshold for predicting ROSC [23]. Linear mixed effects modeling with animal-specific random effects was utilized when comparing outcome parameters between goal cardiac outputs. All reported P-values are two-sided and $P < 0.05$ was used to define statistical significance. Statistical analysis was conducted using SAS software (SAS Institute Inc., Cary NC), version 9.4.

3 Results

A total of 8 mechanically ventilated juvenile swine underwent 28 VF arrests with open cardiac massage (5 animals underwent 4 VF arrests, 2 underwent 3 VF arrests, and one animal underwent only 2 VF arrests). Hemodynamic variables and blood gases before cardiac arrest, during CPR and after ROSC are shown in Table 1. With onset of cardiac arrest, there was a sudden (within 30 s) decrease in $EtCO_2$, R-rSO_2 and C-rSO_2 by 17.1%, 20.4%, and 24.3% respectively. Correlations between R-rSO_2, C-rSO_2, and $EtCO_2$ before cardiac arrest, and after ROSC are shown in Table 2. There was a strong and statistically significant correlation between $EtCO_2$ and cardiac output after ROSC with $r = 0.74$ ($p = 0.03$) 95% CI [0.08–0.92]. During resuscitation, $EtCO_2$ had a strong correlation with goal CO, measured as a percentage of baseline PBF, with correlation coefficient of $r = 0.83$ ($p < 0.001$) 95% CI [0.67–0.92]. Both C-rSO_2 and R-rSO_2 had moderate and statistically significant correlation with measured CO with correlation coefficient of 0.52 ($p = 0.003$) 95% CI (0.19–0.74) and 0.50 ($p = 0.004$) 95% CI [0.16–0.73]. There were no significant differences detected in C-rSO_2, R-rSO_2 or $EtCO_2$ levels when goal cardiac output
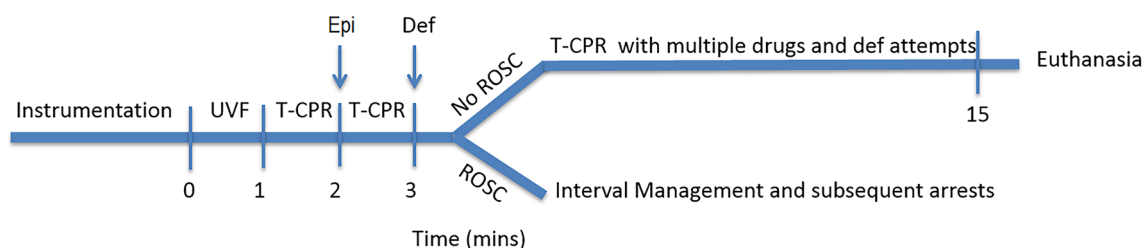

Fig. 1 Experimental timeline. *UVF* untreated ventricular fibrillation, *T-CPR* CPR to achieve target cardiac output as percentage of pre-cardiac arrest baseline, *Def* defibrillation, *ROSC* return of spontaneous circulation, *Epi* epinephrine standard dose

Table 1 Hemodynamic variables and blood gases before cardiac arrest, during CPR and after ROSC

Event	HR (BPM)	MAP (mmHg)	CO (L/min)	pH	$paCO_2$ (mmHg)	SaO_2 (%)	Lactate (mmol/L)
Baseline before CA	91.08 ± 52.2	74.28 ± 55.45	1.75 ± 0.34	7.43 ± 0.04	43.93 ± 6.95	97.71 ± 0.84	1.82 ± 0.63
CPR	116.4 ± 30.92	35.25 ± 17.05	0.63 ± 0.38	N/A	N/A	91.07 ± 14.6	N/A
ROSC	104.85 ± 34.57	61.81 ± 32.33	1.65 ± 0.71	7.39 ± 0.04	43.93 ± 3.06	95.82 ± 1.83	3.66 ± 2.14

Values are given as mean and standard deviation

CA cardiac arrest, *CO* cardiac output, *CPR* cardiopulmonary resuscitation, *EtCO2* end-tidal carbon dioxide, *HR* heart rate, *MAP* mean arterial pressure, *paCO2* partial pressure of carbon dioxide in arterial blood, *ROSC* return of spontaneous circulation, *SaO2* arterial oxygen saturation

Table 2 Correlations and p-values of $EtCO_2$, cerebral-rSO_2, and renal-rSO_2 with cardiac output before cardiac arrest, and after ROSC

Event	$EtCO_2$	Cerebral-rSO_2	Renal-rSO_2
Before CA	0.18 (−0.60 to 0.79); p=0.68	0.25 (−0.55 to 0.81); p=0.56	0.41 (−0.41 to 0.86); p=0.33
ROSC	0.74 (0.08–0.95); p=0.03*	0.62 (−0.16 to 0.92); p=0.11	0.50 (−0.31 to 0.89); p=0.19

Values are given as correlation coefficient (95% confidence interval); p-value

CA denotes cardiac arrest; *EtCO2* end-tidal carbon dioxide, *ROSC* return of spontaneous circulation, *rSO2* regional oxygen saturation

*Statistically significant
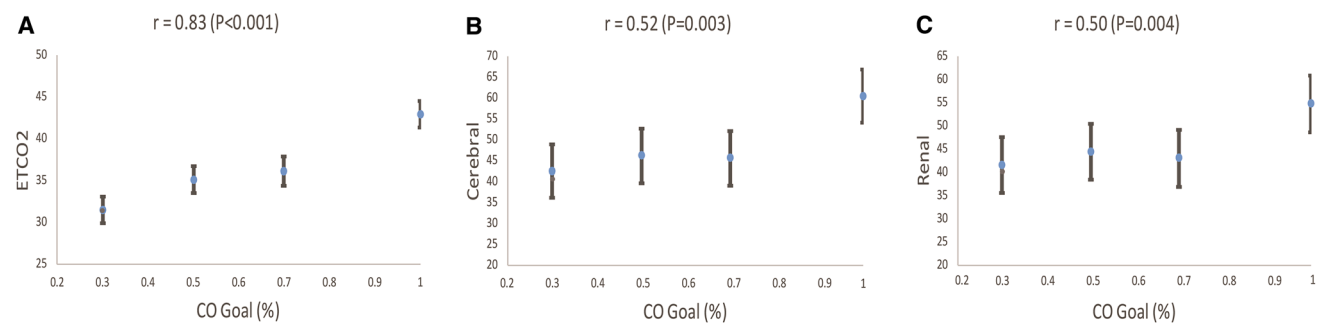
Fig. 2 Correlation of $EtCO_2$, C-rSO_2, and R-rSO_2 with cardiac output (CO) goal during CPR
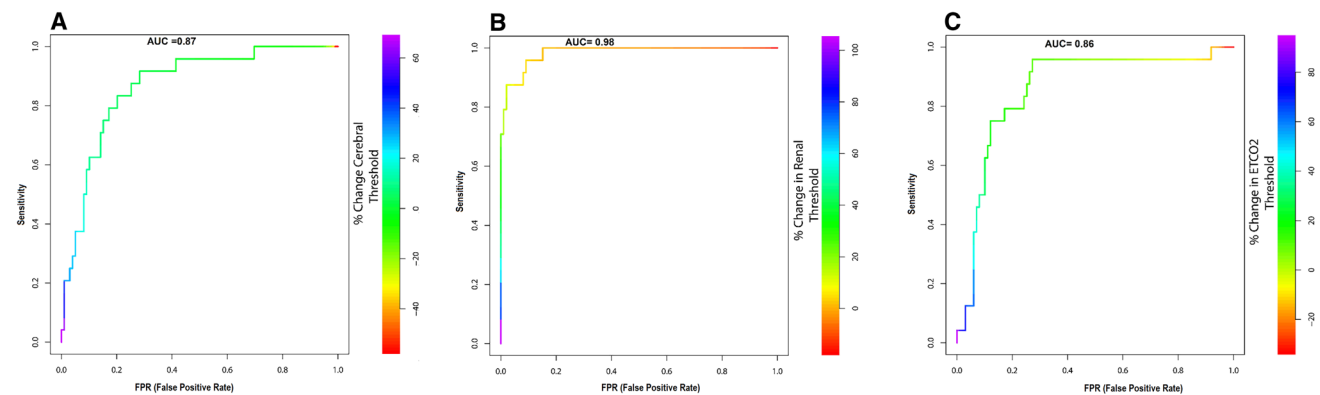
Fig. 3 Receiver operation for sudden increase in **a** C-rSO_2, **b** R-rSO_2, and **c** $EtCO_2$ to detect return of sponteneous circultion (ROSC). *AUC* area under ROC the curve

was increased from 50 to 70% (Fig. 2). The AUCs for sudden increase in $EtCO_2$, $C-rSO_2$, and $R-rSO_2$ at ROSC were 0.86 [95% CI, 0.77–0.94], 0.87 [95% CI, 0.8–0.94], and 0.98 [95% CI, 0.96–1.00] respectively (Fig. 3). The optimal threshold for percentage change cutoffs for $EtCO_2$, $C-rSO_2$, and $R-rSO_2$ were 9.3%, 4.0%, and 5.0% respectively. At these cutoffs, a sudden increase in $EtCO_2$, $C-rSO_2$, and $R-rSO_2$ had similar sensitivities (96%, 92%, and 96%). However, $R-rSO_2$ was the most specific when compared to $EtCO_2$ and $C-rSO_2$ (91% vs. 73% and 72%). Further analysis included only the first VF arrest for each animal showed that AUCs for sudden increase in $EtCO_2$, $C-rSO_2$, and $R-rSO_2$ at ROSC were 0.86 [95% CI 0.82–0.90], 0.72 [95% CI 0.66–0.78], and 0.84 [95% CI 0.79–0.89] respectively (Fig. 3). The optimal threshold for percentage change cutoffs for $EtCO_2$, $C-rSO_2$, and $R-rSO_2$ were 6.8%, 9.9%, and 7.5% respectively. At these cutoffs, a sudden increase in $EtCO_2$ was more sensitive than $C-rSO_2$ and $R-rSO_2$ (93% vs. 50% and 82%). However, $C-rSO_2$ and $R-rSO_2$ were more specific when compared to $EtCO_2$ (93% and 82% vs. 76%) (Fig. 4).

4 Discussion

Published guidelines for CPR increased the focus on ways to ensure that high-quality CPR is performed in all resuscitation attempts to improve outcomes from cardiac arrest [24, 25]. Recent adult studies have assessed the usefulness of $EtCO_2$ and $C-rSO_2$ as a guide to resuscitative efforts during CPR [26–28], yet there have been no studies that assessed the use of $R-rSO_2$, nor the role of two-site rSO_2 in assessing quality of resuscitation or ROSC. We report the potential use of two-site rSO_2, and $EtCO_2$ to monitor the effectiveness and quality of CPR, and ROSC. This is the first study to evaluate the relationship between changes in $C-rSO_2$, $R-rSO_2$, and $EtCO_2$ and CO during resuscitation and ROSC in swine pediatric VF arrest model.

In this study we demonstrate that $EtCO_2$ and two-site rSO_2 can be used to assess and guide effectiveness of chest compressions especially when resuscitation efforts are suboptimal. As $EtCO_2$ reflects PBF, and two-site rSO_2 reflects the balance between oxygen delivery and extraction at 2 two different vascular beds [28], the use of both monitoring devices during resuscitation may provide complementary information on the quality of resuscitation organ perfusion, and tissue oxygenation during CPR. Our result is consistent with the findings of Koyama et al. who reported that $C-rSO_2$ could reliably assess the quality of chest compressions and improve effectiveness of CPR in adult cardiac arrest patients. However, in that study only $C-rSO_2$ waveform (not the absolute value) was used to assess the quality of chest compression [26]. In our study the quality of chest compressions was controlled and continuously monitored and the absolute rSO_2 was monitored as well. In contrast to our results, Kämäräinen et al. found that $C-rSO_2$ remained low during high-quality resuscitation and that improvement in CPR was not significantly reflected in $C-rSO_2$ [27]. However, the assessment of $C-rSO_2$ was not monitored prior to initiation of CPR and therefore the $C-rSO_2$ before cardiac arrest was not known. Moreover, quality of CPR provided was monitored using defibrillator with CPR quality analysis features and no other direct or invasive measurements of CPR quality was measured. In regard to $EtCO_2$, a recent study using a lamb asphyxial cardiac arrest model, Chandrasekharan et al. demonstrated a relationship between $EtCO_2$ and adequate chest compression during resuscitation, and concluded that a rapid increase in $EtCO_2$ with a threshold of > 32 mmHg is 100 sensitive and 97% specific in predicting ROSC [29]. Moreover, a recent multicenter study of 583 adult patients with in- and out hospital CA showed that depth of chest compression was associated with higher $EtCO_2$ which suggest that $EtCO_2$ monitoring during CPR might be a useful tool to guide effective resuscitation after CA [30].
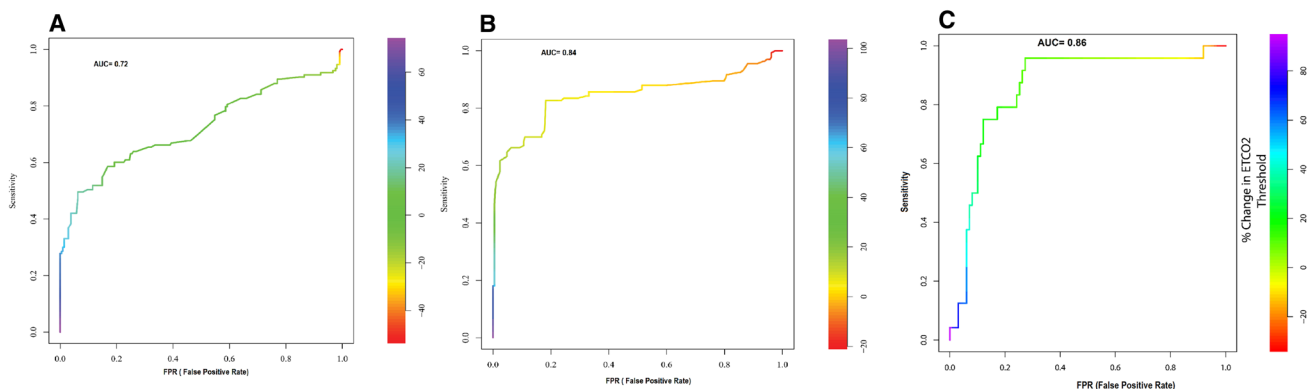

Fig. 4 Receiver operation for sudden increase in **a** $C-rSO_2$, **b** $R-rSO_2$, and **c** $EtCO_2$ to detect return of spontaneous circultion (ROSC) after first VF cardiac arrests. *AUC* area under ROC the curve

Our data also suggest that both rSO_2 and $EtCO_2$ can detect ROSC during CPR without interrupting chest compressions. Although C-rSO_2, R-rSO_2, and $EtCO_2$ were all very sensitive tests to detect ROSC, R-rSO_2 was more specific than both C-rSO_2 and $EtCO_2$. Thus adding renal NIRS monitoring during resuscitation might not only guide resuscitation, but can be used to detect with more confidence ROSC. Our results is consistent with Pokorna et al. who showed that a sudden increase in $EtCO_2 > 10$ mmHg during out-of-hospital CPR could be used as an early indicator of ROSC [31]. Similarly, with the findings of Singer et al. who reported that during outside hospital CA, both mean C-rSO_2 and $EtCO_2$ during CPR can be used to predict ROSC [32]. They found that $EtCO_2$ was more sensitive and C-rSO_2 was more specific at predicting ROSC. However, they didn't assess the sensitivity and specificity of sudden increase in both to detect ROSC. Moreover, a growing number of recent studies demonstrated that a higher mean cerebral rSO_2 during CPR was observed in patients who achieved ROSC compared to non-survivors [14, 20, 32, 33]. We are not aware of any studies that assessed the ability of two-site rSO_2 to detect ROSC during CPR.

Finally, our results demonstrated that both rSO_2 and $EtCO_2$ rapidly decline after loss of pulse pressure. This is consistent with the findings of Reynolds et al. who reported that forelimb rSO_2 in a porcine VF arrest model rapidly declined by 28% in 1 min after loss of pulse pressure. However, they reported that $EtCO_2$ did not drop immediately [34]. Similarly, Putzer et al. found that C-rSO_2 decreased during periods of untreated cardiac arrest in an animal model of hypothermic cardiac arrest [35]. The recognition of acute sudden drop in rSO_2 and $EtCO_2$ in a hemodynamically unstable patient could be extremely vital in the recognition of cardiac arrest and early initiation of resuscitation efforts especially in patients who lack invasive lines.

Our study has obvious limitations. First, our study included animals with open chest without sufficient thoracic pump function, which may have affected venous return and cardiac output. We acknowledge that our model might not resemble the clinical situation of most critically ill patients who suffer cardiac arrest and require CPR, however, it might be clinically relevant in anaesthetized patients or patients who just undergone cardiac surgery and suffer a sudden, cardiac deterioration and arrest. Second, the cardiac massage was performed by hand and mean PBF goal was used during resuscitation. Also animals received normal saline and/or sodium bicarbonate after ROSC which might led to a transient increase in $EtCO_2$ without an actual increase in cardiac output during subsequent arrests, however, further analysis of the first VF arrest didn't indicate such effect, in the contrary, $EtCO_2$ was more sensitive than C-rSO_2 and R-rSO_2 to detect ROSC during the first VF arrests when compared to subsequent arrests (Fig. 4). Third, all animals

had relatively healthy lungs, which may not reflect common pediatric cardiac arrests. This latter point presents a concern as $EtCO_2$ is affected by alveolar dead space, which may be a confounding factor when assessing changes in CO. Finally, analgosedative drugs were administered, as necessary, to maintain adequate analgesia and anesthesia. The use of these drugs may have affected cardiovascular function and autonomic control during resuscitation.

5 Conclusions

In this swine pediatric VF arrest model, two-site rSO_2 obtained by NIRS technology, and $EtCO_2$ correlates with cardiac output changes during CPR and can be used to guide resuscitations efforts and detect ROSC without interrupting resuscitation efforts. Further studies are required to explore the use of two-site rSO_2 and capnography as a tool for early detection of CA, monitor effectiveness of chest compression, and detection of ROSC among critically ill pediatric patients who suffer from cardiac arrest.

Compliance with ethical standards

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