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Experimental paper

The association of regional cerebral oximetry and neurologically intact survival in a porcine model of cardiac arrest

Mithun Suresh[a,*], *Susana Arango*[b], *Johanna Moore*[c,d], *Bayert Salverda*[d], *Michael Lick*[d], *Carolina Rojas-Salvador*[e], *Anja Metzger*[c], *Guillaume Debaty*[f], *Pouria Pourzand*[c,d], *Alexander Kaizer*[g], *Keith Lurie*[c,d]

Abstract

Background: The objective of this study was to determine if regional cerebral oximetry (rSO2) assessed during CPR would be predictive of survival with favorable neurological function in a prolonged model of porcine cardiac arrest. This study also examined the relative predictive value of rSO2 and end-tidal carbon dioxide (ETCO2), separately and together.

Methods: This study is a post-hoc analysis of data from a previously published study that compared conventional CPR (C-CPR) and automated head-up positioning CPR (AHUP-CPR). Following 10 min of untreated ventricular fibrillation, 14 pigs were treated with either C-CPR (C-CPR) or AHUP-CPR. rSO2, ETCO2, and other hemodynamic parameters were measured continuously. Pigs were defibrillated after 19 min of CPR. Neurological function was assessed 24 h later.

Results: There were 7 pigs in the neurologically intact group and 7 pigs in the poor outcomes group. Within 6 min of starting CPR, the mean difference in rSO2 by 95% confidence intervals between the groups became statistically significant ($p < 0.05$). The receiver operating curve for rSO2 to predict survival with favorable neurological function reached a maximal area under the curve value after 6 min of CPR (1.0). The correlation coefficient between rSO2 and ETCO2 during CPR increased towards 1.0 over time. The combined predictive value of both parameters was similar to either parameter alone.

Conclusion: Significantly higher rSO2 values were observed within less than 6 min after starting CPR in the pigs that survived versus those that died. rSO2 values were highly predictive of survival with favorable neurological function.

Keywords: Cardiac arrest, Cardiopulmonary resuscitation, Cerebral oximetry, Active compression-decompression, Impedance threshold device, Automated head-up positioning CPR

Introduction

Survival with favorable neurological function after out-of-hospital cardiac arrest is <10% worldwide.[1] In patients that never survive, inadequate cerebral circulation during the arrest and during cardiopulmonary resuscitation (CPR) causes neurological injury.[2] Regional cerebral oximetry (rSO2), is a promising non-invasive means for monitoring cerebral circulation. rSO2 values reflect the percentage of combined arterial and venous cerebral tissue oxygen level up to a depth of 2.5 cm.[3] Whether rSO2 can serve as an early indicator of the likelihood of neurologically intact survival is unknown. Furthermore, the relationship between rSO2, and other circulatory markers during cardiac arrest remains poorly understood.

We previously demonstrated that automated head up positioning CPR (AHUP-CPR) results in improved survival with favorable neurological function compared to conventional CPR (C-CPR) in a porcine model of cardiac arrest.[4] The primary objective of this study was to determine if rSO2 would be predictive of a favorable neurological outcome. The secondary objective was to examine the association between rSO2 and ETCO2, the non-invasive gold-standard for assessing circulation during CPR.

* Corresponding author at: CentraCare-St. Cloud Hospital, 1406 6th Ave N, St Cloud, MN 56303.

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Methods

Ethics

This is a post-hoc analysis of data from a previous study, and complete details of the experimental methodology were published.[4] A summary of this methodology is provided here. Care of the pigs followed the 2011 Guideline for the Care and Use of Laboratory Animals, and this study was approved by the Institutional Animal Care Committee (IACUC) of Hennepin Healthcare Research Institute (HHRI).

Study details

The pigs were mechanically ventilated (Narkomed, North American Drager, Telford, PA) to maintain oxygen saturation >92% and ETCO2 between 37–43 mmHg and monitored with a CO2SMO Plus (Novametrix Systems, Wallingford, CT) sensor. Ketamine and isoflurane were used for sedation and anesthesia, respectively. A near-infrared spectroscopy monitor (INVOS 5100C Cerebral/Somanetics Oximeter, Medtronic, Minneapolis, MN) on the pig's forehead measured rSO2, and 15% was the lowest value the monitor would display. The temperature was maintained between 36.5 °C–38.5 °C. Millar catheters (Mikro-Tip Transducer, Millar Instruments, Houston, TX) measured central aortic pressure (AoP) and right atrial pressure (RAP). Intrathoracic pressure (ITP) was assessed by measuring airway pressure, which served as a surrogate.[5] During the animal preparation, normal saline was given to achieve RAP between 7–10 mmHg, and intravenous heparin boluses were administered hourly. Arterial blood gases were measured using the Gem Premier 3000 blood gas analyzer (Instrumentation Laboratory, Lexington, MA). A digital system (BioPac MP 150, BioPac Systems, Inc., CA, USA) continuously recorded physiological parameters.

Ventricular fibrillation (VF) was induced by an electrophysiology catheter placed in the right ventricle. Mechanical CPR with adjustable ACD (Caztek Engineering, St Paul, MN) using a suction cup at a right angle to the pig's thorax was performed with 105 compressions per minute with a 50% duty cycle and depth of 22.5% of the antero-posterior chest diameter. During active decompression, the suction cup pulled upwards with a force of ~ 10 kg (~4 cm lift). In conventional CPR (C-CPR), the pigs remained flat, and no active decompression or impedance threshold device (ITD) was utilized. CPR that was performed with ACD + ITD and automated head and thorax positioning using a controlled sequential elevation device was termed AHUP-CPR. The inspiratory resistance valve within the ITD had an opening pressure of −16 cm H_20 (ITD-16) (ResQPOD-16™, ZOLL Medical, Chelmsford, MA). Details about the elevation sequence have been published previously.[4]

Following 10 min of untreated VF, CPR commenced, and the total CPR duration was 19 min. If a pig gasped during CPR, 100 mg intravenous succinylcholine was administered. Since the pigs were in VF, they were not conscious and they did not have a cardiac rhythm compatible with life. Accordingly, use of succinylcholine was approved by HHRI. After 18 min of CPR, amiodarone (50 mg), and if the decompression phase AoP was <30 mmHg at that time, and epinephrine (0.5 mg) were administered. We did not administer these medications earlier in order to avoid confounding with the hemodynamic comparison of the two CPR techniques in the original study.[4] Defibrillation occurred one minute later with 200 joules (X Series™ defibrillator, ZOLL Medical, Chelmsford, MA). If no ROSC after the first defibrillation attempt, two more cycles of medications and defibrillation were performed; if still no ROSC, then the study was terminated.

Following ROSC, anesthesia was reinitiated for four hours and subsequently weaned. An epinephrine infusion was administered intravenously as needed to maintain mean arterial pressures >65 mmHg. Weaning from anesthesia and mechanical ventilation proceeded in a stepwise fashion, and once oxygen saturation was adequate with no signs of respiratory distress, extubation occurred. Pigs were then returned to the kennel where monitoring continued by a member of the research team to ensure they remained stable (e.g., no signs of distress, no seizure activity, etc.). Pain was managed with buprenorphine, fentanyl, or flunixin. Survival and neurological status were evaluated 24 h after ROSC by a veterinarian blinded to the method of CPR. A cerebral performance category (CPC) score modified for pigs was assigned by the veterinarian, with 1 = normal, 2 = slightly disabled, 3 = severely disabled but conscious, 4 = vegetative state, and 5 = animals that did not achieve ROSC or died prior to 24-hour assessment. We also evaluated neurological function using a Neurological Deficit Score (NDS), which was adapted for pigs and captures several neurological parameters related to mental status, gait, and reflexes.[6] Values range from 0 to 260, with 0 indicating no deficits and 260 indicating brain death or death itself. Given that CPC is more widely recognized in the literature for neurological assessment post-resuscitation, we used CPC in our final analysis when assessing for favorable neurological function. Euthanasia was performed with intravenous potassium chloride followed by necropsy.

Statistical analysis

The pigs were separated into two groups: 1) pigs that survived for 24 h with a CPC score of 1 or 2 (neurologically intact group) and 2) pigs that did not survive or survived for 24 h with a CPC score of 3–5 (poor outcomes group). To form these groups, pigs from our previous study[4] where rSO2 was recorded were separated into the neurologically intact and poor outcomes groups. Accordingly, each group had pigs that received both C-CPR and AHUP-CPR. For sample size calculation, assuming a significance level (alpha) of 0.05, a power of 80%, and a projected survival rate of 10% in the C-CPR group and 75% in the AHUP-CPR group, the necessary sample size was calculated to be 16 pigs.[4] However, we only used 14 pigs in this study because for two of the pigs, rSO2 could not be measured. For comparisons of rSO2 between groups, a linear random effects model was used with a random intercept for each pig to account for the correlation over time with covariates included for baseline rSO2 values, time of measurement, survival status, and the interaction. Differences in rSO2 values at each time point were estimated with 95% confidence intervals (CIs). Contrasts were used to estimate the difference in rSO2 values at each time point with 95% confidence intervals (CIs). The predictive utility of the various measurements was summarized with estimates and 95% CIs for the area under the curve (AUC) of the receiver operating characteristics (ROC) curve and the sensitivity and specificity at the "optimal" threshold calculated by Youden's J index. DeLong's test was used to compare the AUC between ROC curves. Scatterplots with Pearson's linear correlation were provided to compare rSO2 and ETCO2 values. All analyses and figures were created in R v4.1.0 (Vienna, Austria). A p-value of less than 0.05 was considered statistically significant.

Results

There were 7 pigs in the neurologically intact group and 7 pigs in the poor outcomes group. Pigs in the neurologically intact group had CPC scores of 1 (n = 4) or 2 (n = 3) 24 h after ROSC. In the poor outcomes group, 6/7 (86%) pigs did not achieve ROSC, and 1/7 (14%) pigs achieved ROSC, but died in less than 24 h after ROSC. Fig. 1 shows the mean ± standard deviation (SD) of coronary perfusion pressure (CorPP), decompression phase AoP, ETCO2, and rSO2. The values of these parameters separate such that soon after the start of CPR, higher values occurred in the neurologically intact group compared to the poor outcomes group within a few minutes and remained higher for the duration of CPR. Fig. 2 and Supplemental Table 1 show the mean difference in rSO2 by 95% CIs between the neurologically intact and poor outcomes groups. As the duration of CPR increased, the difference between the groups increased and became statistically significant <6 min after starting CPR, which is when the area between the CIs (gray shaded area) no longer overlaps the null (i.e., 0) value in Fig. 2. By contrast, the values of all four parameters slowly decreased as CPR continued in the poor outcomes group. A total of 6/7 pigs in the neurologically intact group received AHUP-CPR and 6/7 pigs in the poor outcomes group received C-CPR.

Scatterplots of rSO2 versus ETCO2 for each minute of CPR (Fig. 3) showed as the CPR duration increased, the values of the groups separate. Over time, lower values for both rSO2 and ETCO2 are observed in the poor outcomes group. Values for the neurologically intact group were more varied, but higher for both rSO2 and ETCO2. At 8 min, the pigs in the neurologically intact group were concentrated in the upper right (r = 0.862). When looking at the data points in totality, the correlation generally improved throughout the duration of CPR; Pearson's linear correlation values approached 1.0, indicating a stronger and positive correlation.

The potential sensitivity and specificity of rSO2, ETCO2, and rSO2+ETCO2 were assessed with ROC analyses (Fig. 4). The ROC curve for rSO2 achieved a near-maximal AUC value of 1.0 after approximately 4 min of CPR (Fig. 4a). After minor fluctuations over the next few minutes of CPR, the AUC value was 1.0 after 13 min of CPR and remained at this value for the remaining duration of CPR. The AUC value for the ETCO2 ROC curve (Fig. 4b) reached a peak value of ~0.9 after 3 min of CPR and remained relatively constant thereafter. The AUC value for the combined rSO2 + ETCO2

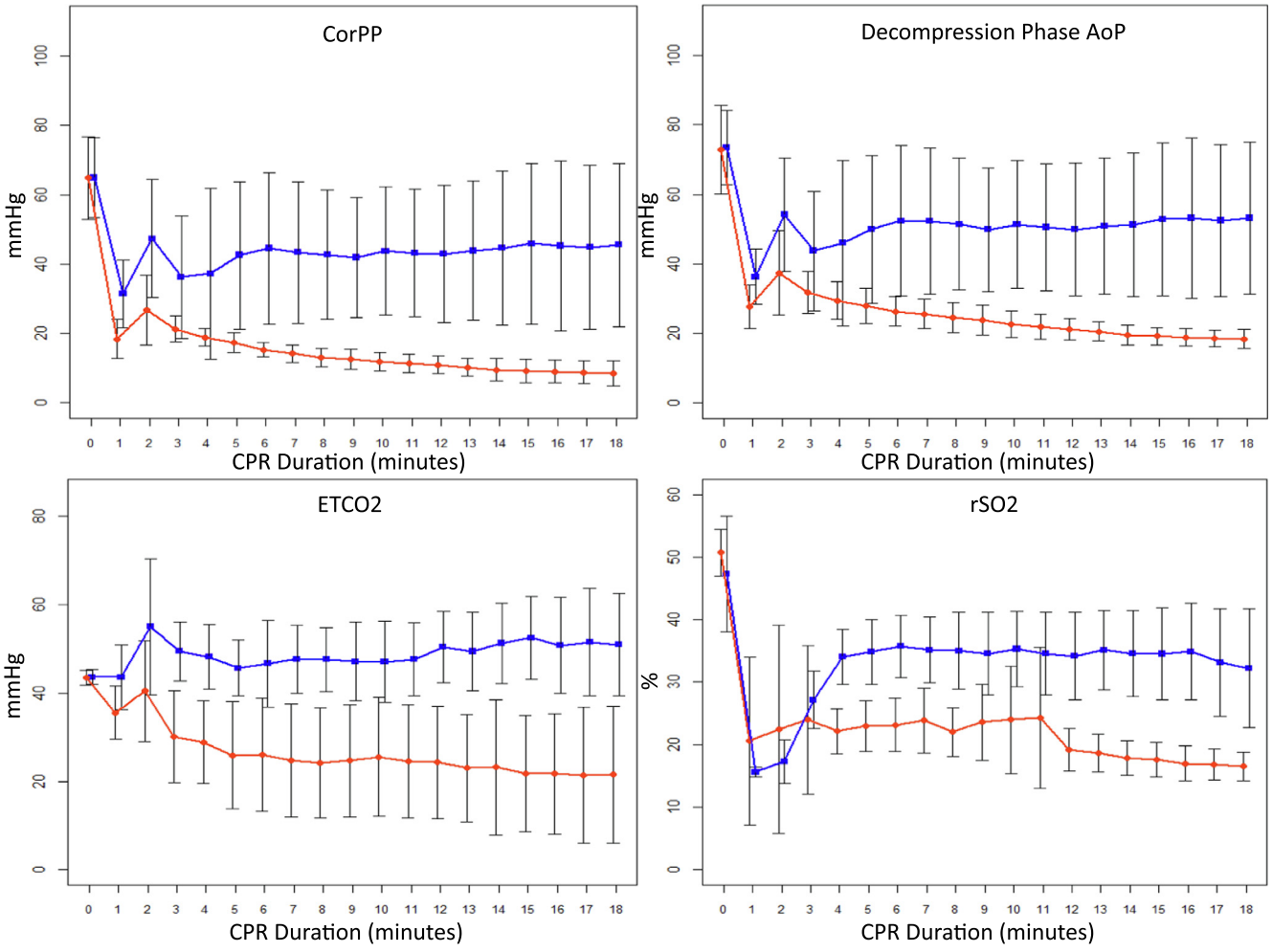

Fig. 1 – Parameters over time stratified by neurologically-intact (blue) and poor outcomes (orange) group status. CPR duration minute 0 is pre-arrest, 1 minute is 1 minute of CPR, 2 minutes is 2 minutes of CPR, etc. Panels are showing the mean +/- standard deviation of each parameter at each minute.

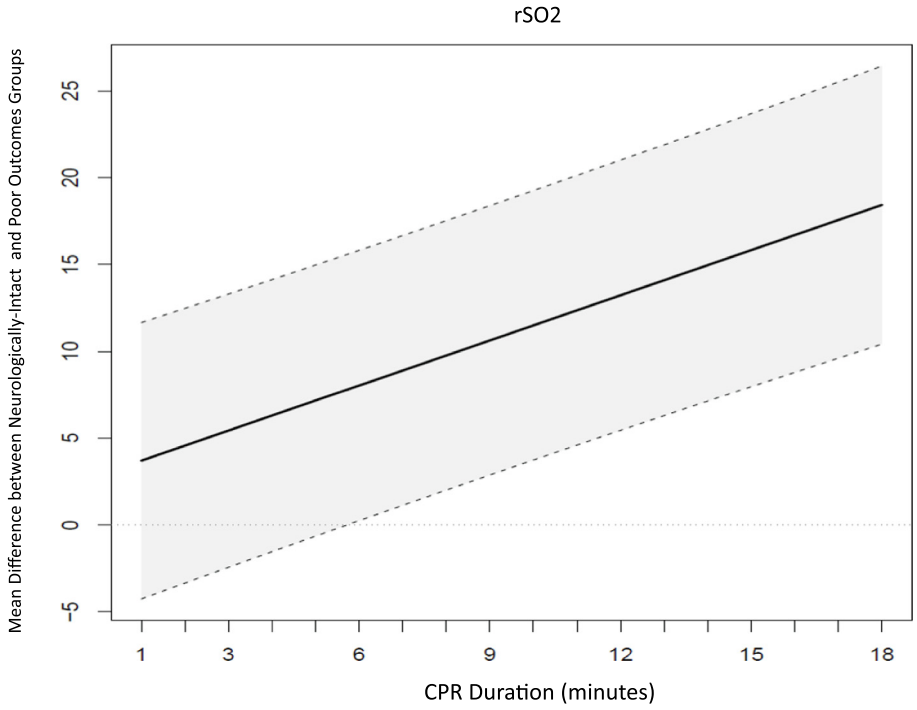

Fig. 2 – Mean difference between neurologically-intact and poor outcomes groups over time for rSO2 by 95% CIs. The solid black line shows the mean difference between the groups, and the dashed lines show the 95% CIs at each minute. When the area between the CIs (gray shaded area) does not overlap the null (i.e., 0), this implies that the mean difference in rSO2 by 95% CIs between the neurologically-intact and poor outcomes groups is statistically significant at the given time.

ROC (Fig. 4c) also reached a maximal value of 1.0 at 3 min of CPR. After minor fluctuations, this value reached 1.0 again after 12 min of CPR and remained at this value for the remaining duration of CPR. There were, however, no statistically significant differences in the AUC values on a minute-by-minute basis when comparing rSO2, ETCO2, and rSO2 + ETCO2 (Supplemental Table 2).

Discussion

Predicting the likelihood of survival with favorable neurological function would be helpful to optimize the care of patients in cardiac arrest. Results from this preclinical study suggest that the measurement of rSO2 and ETCO2 during CPR, separately and combined, were strongly predictive of survival with favorable neurological function with a high degree of sensitivity and specificity that improved over the duration of CPR (Fig. 4). Moreover, the differences in rSO2 values between the neurologically intact and poor outcomes groups were significant in less than 6 min of CPR.

Key invasive hemodynamic parameters were CorPP, decompression phase AoP, and compression phase AoP. These parameters were markedly different between the groups (Fig. 1 and Supplemental Fig. 1). Moreover, ETCO2 and rSO2 mirrored these invasive parameters, both in terms of the time course and relative magnitude of change between the groups. The differences in CorPP, decompression phase AoP, and compression phase AoP likely explains the large difference in the number of pigs that achieved ROSC in the groups, 7/7 pigs in the neurologically intact group versus 1/7 pigs in the poor outcomes groups. In totality, these results are consistent with the physiological precept that adequate circulation to the heart and perfusion to the brain are needed for ROSC[7] and meaningful neurological survival.[8] The improved hemodynamics and greater frequency of ROSC in the neurologically intact group were further corroborated by the number of pigs in each group that needed epinephrine to maintain decompression phase AoP $\geq$ 30 mmHg before defibrillation; 1/7 pigs in the neurologically intact group versus 7/7 pigs in the poor outcomes group.

These new observations led to the question, are ETCO2 and rSO2 complementary? As such, we investigated this possibility by combining the two parameters and determining their potential joint predictive value. When comparing the combination of rSO2+ETCO2 with each parameter individually, the performance characteristics of the combination appeared to have qualitatively less variability, especially between minutes 0 and 12 of CPR as shown in Fig. 4, and the fluctuations in AUC values were reduced when the parameters were combined. Perhaps more importantly, both rSO2 and ETCO2 may be clinically complementary, especially in the setting when they may not track in parallel or when critically important life and death decisions, such as whether or not to terminate resuscitation efforts, are being considered based upon these non-invasive surrogates of circulation. Based on these findings, ETCO2 and rSO2 appear to be complementary, and when combined, the AUC, sensitivity, and specificity of these parameters was similar to the individual parameters alone.

Another reason that rSO2 may be helpful is that measurement of ETCO2 by itself may not always be a reliable marker of circulation, as it can be affected by the underlying disease state.[9–11] or respiratory parameters.[12] Thus, concurrent measurement of rSO2 has the potential to provide beneficial and additional non-invasive clinical

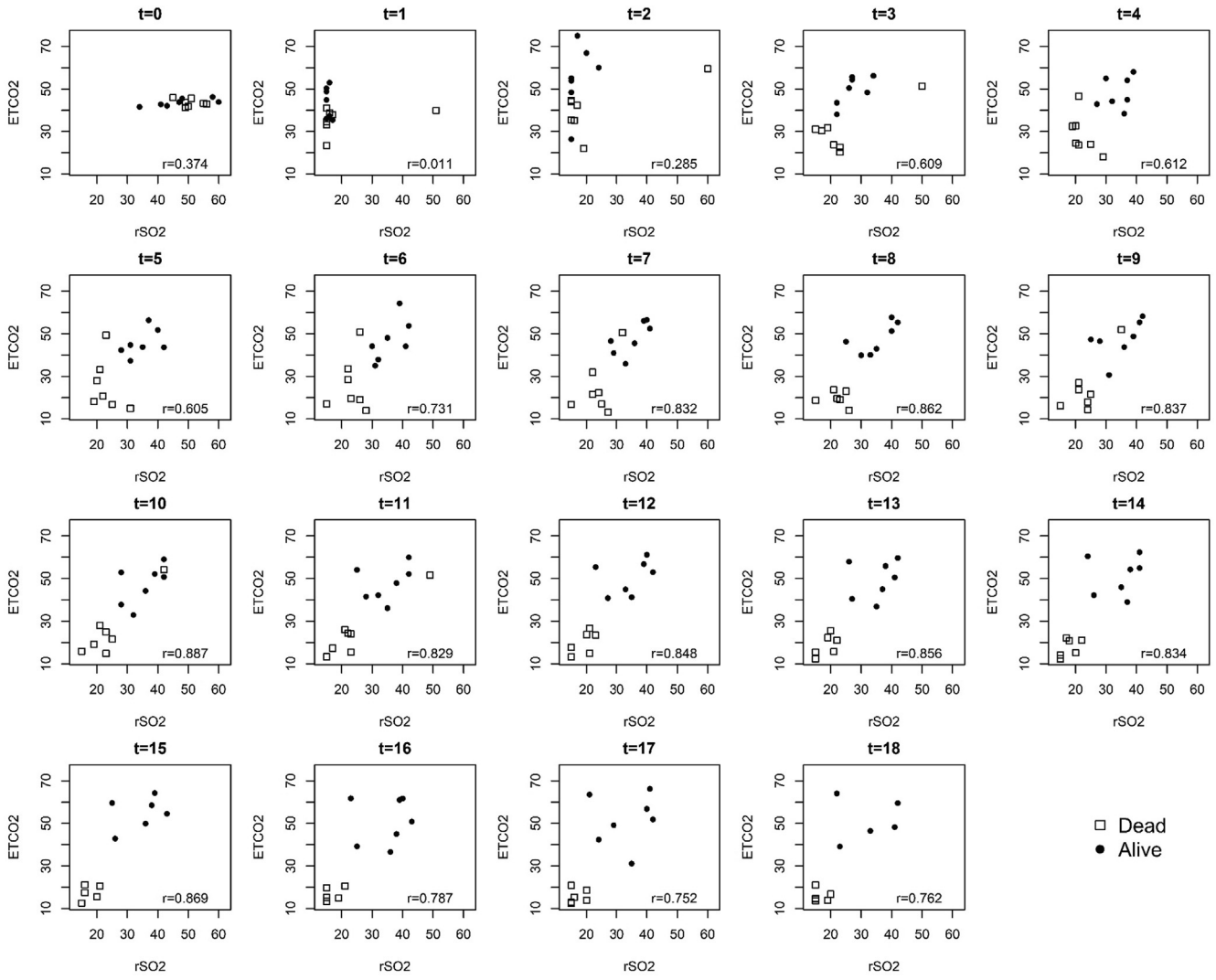

Fig. 3 – Scatterplots over time for rSO2 versus ETCO2 by neurologically-intact (alive) and poor outcomes (dead) group status. ETCO2 (y-axis) units are mmHg and rSO2 (x-axis) units are %. Time is indicated at the top of each scatterplot (t =), with t = 0 representing pre-arrest, t = 1 representing 1 minute of CPR, t = 2 representing 2 minutes of CPR, etc. Pearson's linear correlation values (r) for pre-arrest and at each minute of CPR are shown within each scatterplot.

information particularly when ETCO2 values may not be as reflective of circulation.[13] Notably, since only 1 pig achieved ROSC and no pigs survived more than 24 h in the poor outcomes group, this suggests that more broadly, rSO2 is predictive of survival, and not just survival with favorable neurological function.

While rSO2 is typically measured at depths up to 2.5 cm, one confounder could be that the measured signal is coming from the skin or extracranial blood. When drilling the hole for the intracranial bolt, we have noted in these ~40 kg pigs that the brain tissue is typically <2.0 cm from the skin surface. Frequently, rSO2 sensors consist of multiple detectors at different distances from the light source.[14] Using spatial resolution techniques, this allows the detectors that are farther from the light source to capture signals from tissues deeper than the skin, such as the brain.[15] In addition, rSO2 sensors utilize subtraction algorithms to help filter signals from extracranial blood, which also helps to improve the accuracy of rSO2 measurements.[16]

With regards to how well rSO2 works during CPR, previous studies have examined rSO2 and outcomes. Sanfilippo et al. reported ROSC to be associated with significantly higher initial rSO2 (mean difference −11.54, 95% CI [-20.96,-2.12], p = 0.02) and overall rSO2 (mean difference −10.38, 95% CI [-13.73,-7.03], p < 0.00001) values compared to when ROSC was not achieved.[17] For neurological outcomes, Cournoyer et al. reported higher mean rSO2 values (standardized mean difference = 2.12, 95% CI [1.14,3.10], p < 0.00001) in patients with good neurological outcomes.[18] Moreover, Schnaubelt et al. found that average mean (SD) rSO2 values for patients with CPC scores 1–2 was 47% (11%) compared to 38%(12%) for patients with CPC scores 3–5 (p = 0.018).[19] Finally, for rSO2 threshold values, Parnia et al., reported that time with rSO2 >50% during CPR was the best predictor of CPC scores 1–2 (AUC 0.79, 95% CI [0.70,0.88]). When >60% of CPR time resulted in rSO2 > 50%, the sensitivity and specificity were 77% and 72%, respectively, for CPC scores 1–2.[20] Our findings

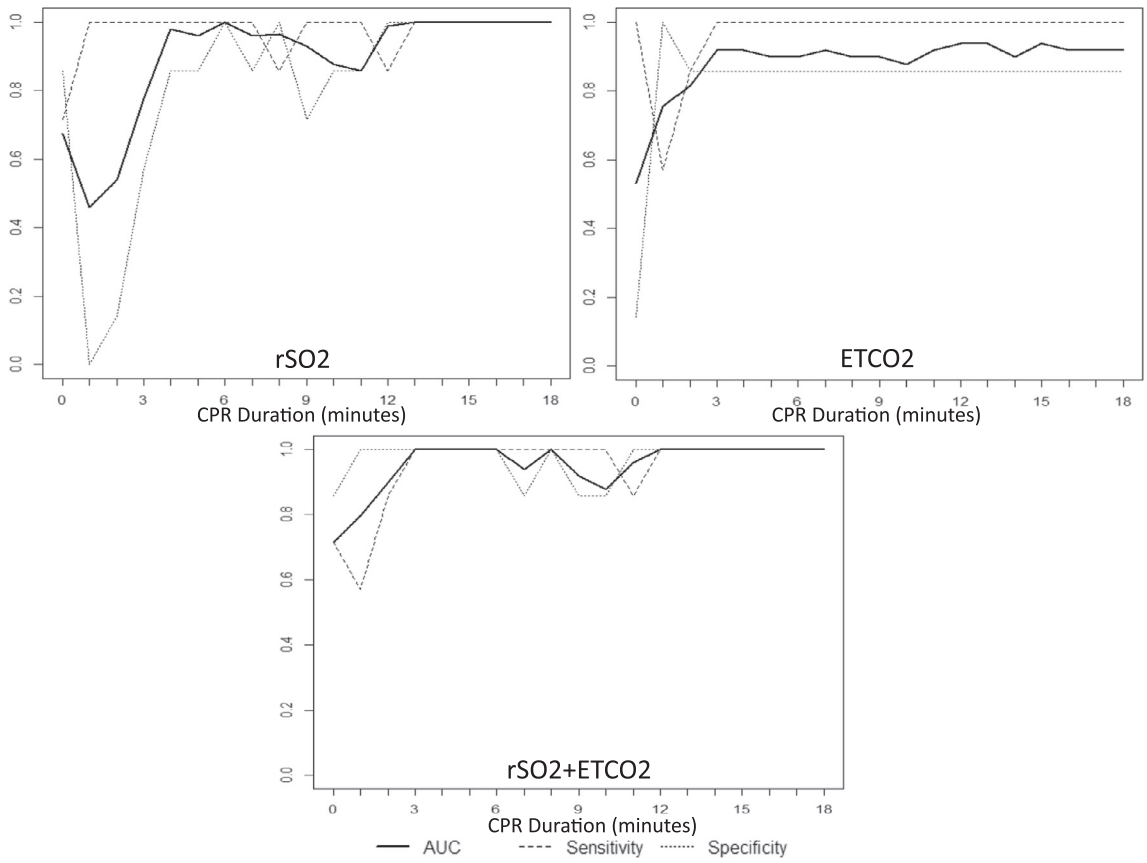

Fig. 4 – Predictive utility for survival with favorable neurological function over time based on AUC, sensitivity, and specificity with rSO2 (Fig. 4a), ETCO2 (Fig. 4b), and rSO2 + ETCO2 (Fig. 4c).

add to this body of literature by showing the minute-by-minute predictive value of rSO2 for favorable neurological function and its association with ETCO2, the gold-standard non-invasive parameter for assessing circulation during CPR.

Previous studies have examined FiO2 and the corresponding PaO2, and its impact on rSO2 and brain tissue oxygenation (PbO2); key findings from these important studies include showing that rSO2 and PbO2 are dependent on perfusion pressure and hemodynamics during CPR, but not necessarily FiO2 or PaO2.[21–23] The three physiological components that may influence rSO2 are oxygen content of the circulatory volume, hemodynamics, and oxygen extraction.[24] Accordingly, to maximize PbO2 and rSO2 during CPR, strategies to optimize all three of these components should be pursued. However, based on the findings of the aforementioned studies,[21–23] it appears that optimal circulation during CPR is important for maximizing cerebral oxygenation. Based on our prior work, this occurs with AHUP-CPR, as combining an ITD with ACD while performing controlled sequential elevation of the head and thorax serves to enhance cerebral hemodynamics and increase rSO2 more when compared to C-CPR.[4]

There are limitations with this study. First, this was a post-hoc analysis of a prior study where we compared AHUP-CPR and C-CPR; in this study, we focused on whether rSO2, measured during CPR, was predictive of favorable or unfavorable outcomes, regardless of the method of CPR used. Second, the pigs were young and healthy, which differs from patients that typically experience cardiac arrest. Another limitation is nearly all of the pigs in the neurologically intact group received AHUP-CPR whereas nearly all of the pigs in the poor outcomes group received C-CPR. The goal of this manuscript was not to compare AHUP-CPR and C-CPR. Consequently, no subgroup analysis was performed to examine whether rSO2 can predict survival with favorable neurological function with either AHUP-CPR or C-CPR by itself. Rather, by comparing all pigs with neurologically intact versus poor outcomes, these results provide new and important insights into the predictive capabilities of rSO2 alone or combined with ETCO2, which was the primary objective of this study, regardless of CPR technique. Moreover, it is now well-established in preclinical studies that AHUP-CPR provides significantly improved cerebral perfusion,[25–28] and higher rSO2 values occur in the AHUP-CPR group soon after the start of CPR and remain higher for the duration of CPR.[4] Finally, the pigs received CPR using the same resuscitation algorithm within their respective groups. This differs from the real world, where one cardiac arrest resuscitation may differ greatly from the next.

Conclusion

rSO2 predicted survival with favorable neurological function with high specificity and sensitivity within the first few minutes of CPR in a porcine model of cardiac arrest. Contemporaneous rSO2 and ETCO2 measurements were complementary, and the correlation between the parameters generally improved throughout the duration of CPR.

CRediT authorship contribution statement

Mithun Suresh: Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Susana Arango:** Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Johanna Moore:** Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Bayert Salverda:** Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Michael Lick:** Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Carolina Rojas-Salvador:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Anja Metzger:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Guillaume Debaty:** Writing – original draft, Writing – review & editing. **Pouria Pourzand:** Writing – original draft, Writing – review & editing. **Alexander Kaizer:** Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Keith Lurie:** Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Keith Lurie is the inventor of devices to elevate the head and thorax during CPR. He is the chief medical officer of Advanced CPR Solutions, a company that develops CPR technologies.].

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resplu.2023.100539.

Author details

[a]*Department of Medicine, CentraCare-St. Cloud Hospital, St. Cloud, MN, USA* [b]*Department of Anesthesiology, University of Minnesota, Minneapolis, MN, USA* [c]*Department of Emergency Medicine, University of Minnesota, Minneapolis, MN, USA* [d]*Hennepin Healthcare Research Institute, Minneapolis, MN, USA*[e]*Department of Medicine, University of Minnesota, Minneapolis, MN, USA* [f]*Department of Emergency Medicine, University of Grenoble Alps/CNRS/TIMC-IMAG UMR 5525, Grenoble, France* [g]*Department of Biostatistics and Informatics, University of Colorado, Aurora, CO, USA*

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