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Effect of neuromonitor-guided titrated care on brain tissue hypoxia after opioid overdose cardiac arrest

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Abstract

Introduction—Brain tissue hypoxia may contribute to preventable secondary brain injury after cardiac arrest. We developed a porcine model of opioid overdose cardiac arrest and post-arrest care including invasive, multimodal neurological monitoring of regional brain physiology. We hypothesized brain tissue hypoxia is common with usual post-arrest care and can be prevented by modifying mean arterial pressure (MAP) and arterial oxygen concentration (PaO₂).

Methods—We induced opioid overdose and cardiac arrest in sixteen swine, attempted resuscitation after 9 minutes of apnea, and randomized resuscitated animals to three alternating 6-hour blocks of standard or titrated care. We invasively monitored physiological parameters including brain tissue oxygen (PbtO₂). During standard care blocks, we maintained MAP >65mmHg and oxygen saturation 94–98%. During titrated care, we targeted PbtO₂ >20mmHg.

Results—Overall, 10 animals (63%) achieved ROSC after a median of 12.4 minutes (range 10.8 to 21.5 minute). PbtO₂ was higher during titrated care than standard care blocks (unadjusted β = 0.60, 95% confidence interval (CI) 0.42 – 0.78, $P < 0.001$). In an adjusted model controlling for

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MAP, vasopressors, sedation, and block sequence, PbtO₂ remained higher during titrated care (adjusted $\beta = 0.75$, 95% CI 0.43 – 1.06, $P < 0.001$). At three predetermined thresholds, brain tissue hypoxia was significantly less common during titrated care blocks (44 vs 2% of the block duration spent below 20mmHg, $P < 0.001$; 21 vs 0% below 15mmHg, $P < 0.001$; and, 7 vs 0% below 10mmHg, $P = 0.01$).

Conclusions—In this model of opioid overdose cardiac arrest, brain tissue hypoxia is common and treatable. Further work will elucidate best strategies and impact of titrated care on functional outcomes.

Keywords

Cardiac arrest; resuscitation; critical care; neuromonitoring; precision medicine

Introduction

Sudden cardiac arrest affects more than 500,000 people in North America each year.¹ Rates of return of spontaneous circulation (ROSC) are improving over time,¹ but a majority of those hospitalized after cardiac arrest still succumb to sequelae of anoxic brain injury.² In the days after ROSC, patients are at risk for secondary brain injuries that may develop when the injured brain's physiology and autoregulation are deranged.³ Important mechanisms of secondary brain injury include both macro- and microvascular hypoperfusion and brain tissue hypoxia.^{4–7} Areas of no-reflow contribute to tissue hypoxia,⁶ as do alterations in pressure autoregulation and diffusion-limited oxygen delivery.^{5, 8}

After traumatic brain injury (TBI), augmenting mean arterial pressure (MAP) and increasing the partial pressure of arterial oxygen (PaO₂) can increase brain tissue oxygen tension (PbtO₂).⁹ In this population, goal-directed therapy improves brain tissue oxygenation and resulted in a trend towards improved outcomes in a Phase II clinical trial.¹⁰ However, the pathophysiology of non-traumatic post-arrest brain injury is distinct. The prevalence of brain tissue hypoxia after cardiac arrest is unknown, as is the degree to which it is responsive to changes in MAP or PaO₂. Since excessive afterload, catecholamine administration and arterial hyperoxia may all be injurious after cardiac arrest,^{11, 12} an individualized approach based on direct end-organ monitoring and titration of care may be preferable. Thus, considerable preclinical investigation is needed before a strategy of goal-directed therapy to treat brain hypoxia could be trialed after cardiac arrest.

We developed a porcine model of opioid overdose cardiac arrest and post-arrest care including invasive, multimodal neurological monitoring of regional brain physiology. Our focus on opioid overdose was motivated by the growing epidemic of opioid overdose in North America.¹³ The goal of our model was to test the primary hypotheses that brain tissue hypoxia is common with usual post-arrest care, and that it can be corrected by modifying MAP and PaO₂. Our secondary hypothesis was that surrogate electrophysiological and biochemical markers of neurological function would be improved by correction of brain tissue hypoxia.

Methods

We utilized a prospective, randomized cross-over experimental design. Care and handling of the animals were in accord with NIH guidelines, and the University of Pittsburgh Institutional Animal Care and Use Committee approved all aspects of the study. We performed a randomized crossover study comparing usual post-arrest care modeled on standard clinical guidelines¹⁴ to titrated care guided by invasive monitoring of regional PbtO₂ (Figure 1). Sixteen female mixed-breed domestic swine (*Sus scrofa*) weighing 26–34 kg were used. Only female swine were used to minimize confounding from possible sex-based variations in animal response.

Instrumentation

We allowed animals full access to water on the night before the procedure but did not provide other oral intake. On the day of the procedure, we sedated the animal with intramuscular ketamine (10mg/kg) and xylazine (4mg/kg) to facilitate cannulation of a peripheral ear vein with a 20-gauge intravenous (IV) catheter. We infused normal saline at 20mL/hr to maintain vessel patency. Thereafter, we induced a surgical plane of anesthesia with an IV bolus of 50mcg/kg fentanyl followed by a continuous infusion of 200mcg/hr fentanyl and 40mcg/kg/min propofol, which we continued until induction of cardiac arrest. We serially assessed adequacy of sedation by assessing vital signs, salivation, and ensuring absence of spontaneous motor activity and corneal reflexes. We administered 1g ceftriaxone IV and 500mg metronidazole IV to minimize evolving septic physiology secondary to instrumentation or peri-arrest intestinal ischemia. We repeated the dose of metronidazole every 6 hours for the duration of the experimental protocol.

After achieving adequate anesthesia, we intubated the animal with a 5-0 cuffed endotracheal tube (ETT) via direct laryngoscopy. We initiated mechanical ventilation using an Ohmeda 7000 ventilator (Ohmeda, BOC Health Care, Madison, WI) in a volume control mode with an initial tidal volume of 10ml/kg, 12 breaths per minute, 5 cmH₂O of positive end expiratory pressure (PEEP) and 21% oxygen. We placed a mainstream capnometer (ZOLL M Series CCT) and titrated ventilator settings to maintain end-tidal carbon dioxide (EtCO₂) of 35–45 mmHg. We placed 5-lead electrocardiogram (ECG) monitoring and a pulse oximeter (Philips CMS Monitor, Philips Healthcare, Cleveland, OH). We recorded all physiological data continuously using a Moberg CNS Monitor (Moberg Research, Ambler, PA), and used the CNS Monitor's 12-channel DC-coupled amplifier to record electroencephalographic (EEG) data at 1024Hz.

Next, we gave a bolus of IV vecuronium 4mg to ensure neuromuscular blockade during surgical instrumentation. Under aseptic conditions, we placed 9Fr femoral arterial and venous introducer sheaths by cut-down through the dermis and then a modified Seldinger technique through the subcutaneous, fascial and femoral muscular tissue. From these, we transduced arterial and venous pressure waveforms (Edwards TruWave Pressure Transducer, Edwards Lifesciences, Irvine, CA).

Next, we injected 1% lidocaine with epinephrine 1:100,000 subcutaneously into the scalp. We incised the scalp and galea aponeurotica, drilled a burr hole into the skull overlying the

right frontal lobe and placed an intracranial access bolt (QFlow 500 Titanium Bolt, Hemedex, Cambridge, MA). Through this, we introduced a cerebral blood flow monitor (QFlow 500, Hemedex); an intracranial pressure, brain tissue temperature and oxygen monitor (Neurovent PTO, Raumedic, Mills River, NC); an 8-contact intracortical EEG probe (Spencer Depth Electrode, AdTech Medical, Racine, WI); and a microdialysis catheter (70 Bolt Catheter, M Dialysis, North Chlemsford, MA). We perfused the microdialysis catheter with CNS Perfusion Fluid (M Dialysis) at a flow rate of 0.33uL/min for the duration of the experiment, and collected 10uL aliquots of effluent every 30 minutes.

Cardiac arrest

After intracranial monitors had equilibrated to steady state (approximately 60 minutes), we discontinued propofol and collected a baseline arterial blood gas (ABG) sample (i-Stat 1, Abbott Point of Care, Inc.). We administered a rapid IV bolus of fentanyl (30mcg/kg) and vecuronium (10mg) to induce apnea, disconnected the ventilator and occluded the ETT. We recorded the total instrumentation from initial intramuscular sedation to ETT occlusion, and the time from ETT occlusion to cardiac arrest. We defined cardiac arrest as either degeneration to ventricular fibrillation or pulseless electrical activity below an arterial systolic pressure of 40mmHg.

Cardiopulmonary resuscitation

After 9 minutes of ETT occlusion, we began cardiopulmonary resuscitation (CPR). We resumed positive pressure ventilation with 100% oxygen and otherwise unchanged ventilator settings, and began mechanical chest compressions at a rate of 100 per minute and depth of 2 inches using a LUCAS2 chest compression system (Physio Control, Redmond, WA). We administered IV bolus doses of epinephrine (0.1mg/kg), sodium bicarbonate (1mEq/kg) and vasopressin (40U). After 2 minutes of compressions, we attempted defibrillation of shockable cardiac rhythms with a 150J biphasic transthoracic shock. We continued CPR with additional epinephrine (0.015mg/kg) boluses and defibrillation, when indicated, every 5 minutes. We discontinued CPR when ROSC was achieved, or when both coronary perfusion pressure and EtCO₂ were sustained below 15mmHg for at least 5 minutes.

Post-arrest care

We stabilized animals with ROSC for 1 hour then randomized them to the order in which they received three alternating blocks of care (Figure 1). The randomization sequence was generated in permuted blocks of 2 and 4 by an independent research technician who did not participate in the resuscitations, and placed in sequentially numbered opaque envelopes that were opened at the time of randomization. During the stabilization period, in addition to general post-arrest care described below, we administered intravenous bolus doses of 0.5mg calcium chloride and/or epinephrine 100mcg IV for precipitous hypotension (MAP 40 mmHg) to support hemodynamics while we mixed and titrated vasopressor infusions. We additionally administered 1g magnesium sulfate IV to reduce the likelihood of recurrent cardiac dysrhythmias.

Thereafter, during standard care block we maintained MAP 65mmHg, oxygen saturation 94–98% and EtCO₂ levels 35–45%. We did not artificially lower MAP if animals

spontaneously generated MAP >65, and did not lower FIO₂ below 0.21 even if oxygen saturation was above 98%. We recorded intracranial monitoring data continuously during these blocks, but blinded the experimental team to the values. During titrated care blocks, the experimental team was unblinded to neuromonitoring data and titrated MAP, FiO₂ and PEEP as described below targeting a PbtO₂ 20mmHg. At the beginning of each titrated care block, we performed three physiological challenges to assess the responsiveness of PbtO₂ to PaO₂, MAP and CO₂ at that time, which we believed might vary between animals and over time.¹⁵ First, we increased FiO₂ to 1.0 for 10 minutes and considered a change in PbtO₂ 10mmHg to represent oxygen responsiveness. Next, we administered or increased the dose of a continuous norepinephrine infusion to raise MAP by 20mmHg and again evaluated for a change in PbtO₂ 10mmHg over 10 minutes. Finally, we reduced respiratory rate by 25% and assessed for a change in PbtO₂. We found all animals to be responsive to FiO₂ and MAP regardless of time-point, and so these were the parameters we titrated to achieve PbtO₂ goals. No animals were responsive to initial hypercapnea, so we did not further titrate this parameter.

For all animals, we resumed anesthesia at the time of ROSC with continuous infusions of fentanyl, which we titrated from 0 to 800mcg/hr to maintain a surgical plane of anesthesia. In animals that required fentanyl doses 400mcg/hr, we added an infusion of propofol titrated from 0 to 75mcg/kg/min. We allowed periodic boluses of fentanyl 200mcg and midazolam 10mg IV for signs of awareness (e.g. salivation or lacrimation) to bridge until increased infusion rates took effect. We did not actively modulate core temperature, however we administered 10mg midazolam IV or 10mg vecuronium IV as needed if overt shivering developed.

We supported MAP with boluses of crystalloid vasoactive infusions titrated to goals specified by the experimental arm. Animals with MAP or PbtO₂ below target, depending on care block type, a regular cardiac rhythm and arterial pulse pressure variation 13% received 10mL/kg boluses of 0.9% sodium chloride until MAP reached target or pulse pressure variation fell below 13%. In cases of irregular cardiac rhythms, we empirically administered 10mL/kg and considered an increase in MAP of 10mmHg to reflect fluid responsiveness. We administered additional fluid boluses in these animals until MAP or PbtO₂ reached target or the animal was no longer fluid responsive. After we optimized volume status, we sequentially added vasopressor infusions if MAP or PbtO₂ remained below target. Our first line vasopressor was epinephrine, which we titrated between 0 and 0.5mcg/kg/min. If epinephrine dose exceeded 0.1mcg/kg/min, we added norepinephrine titrated between 0 and 3mcg/kg/min, and if norepinephrine dose exceeded 0.5mcg/kg/min we added vasopressin titrated between 0 and 0.12U/min. Typically, maximal vasopressor doses were only required during the initial 1 hour stabilization period during which animals were observed to exhibit profound cardiogenic shock physiology.

We titrated fraction of inspired oxygen between 0.21 and 1.0 and positive end expiratory pressure between 5 and 12cmH₂O to achieve oxygenation goals and titrated respiratory rate to maintain EtCO₂ 35–45mmHg in both arms. We checked ABGs at the beginning of each sequential care block to ensure the accuracy of our oxygen saturation and EtCO₂ measurements. We administered 10mEq potassium chloride IV for potassium levels

<4.0mEq/L on these ABGs and sodium bicarbonate 25mEq IV to maintain pH >7.1. While still anesthetized, we euthanized animals surviving to the end of the care protocol with a rapid bolus of 40mEq potassium chloride.

Experimental outcomes and statistical methods

We used descriptive statistics to summarize experimental conditions and outcomes. Our primary hypothesis had two main components. First, we hypothesized that brain tissue hypoxia is common during usual post-arrest care. To address this question, we simply calculated the proportion of time PbtO₂ was below thresholds of 20mmHg, 15mmHg and 10mmHg during blocks of usual care. Next, we used generalized linear models (GLMs) to test whether titrated care reduced the incidence of brain tissue hypoxia below each threshold. In these models, the predictor “block type” encompassed the aggregated effect of the bundle of hemodynamic and ventilator management on PbtO₂. Then, as an alternative means of modeling the data, we treated PbtO₂ as a continuous outcome and used a GLM to test answer the question: does titrated care result in higher PbtO₂?

After exploring the overall effect of a bundle of titrated care, we tested the association of individual physiological and care parameters on PbtO₂. We did this to identify individual, potentially modifiable determinants of PbtO₂. We first used unadjusted GLMs to identify measures significantly associated with PbtO₂. The effect of medications (e.g. vasopressors), non-pharmacological care (e.g. ventilator management) and intrinsic physiology (e.g. myocardial contractility) on PbtO₂ is likely to be complex and interdependent. Thus, we constructed an adjusted model to identify independent predictors of PbtO₂ by included univariable predictors significant at a p-value < 0.1. In our experimental setup, some parameters were easily quantified (e.g. medication doses or MAP) while others could not be measured more than infrequently, if at all (e.g. effects of ventilator management). A persistent independent association of care block with PbtO₂ in the adjusted model implies care differed between block types in unmeasured ways. In this model, we expected that to be primarily in terms of ventilator management, since PaO₂ and PaCO₂ could not be continuous sampled and were therefore not directly included in regression models.

Finally, we tested the effect of PbtO₂ on neurophysiological parameters. We calculated alpha-delta ratio (ADR) and EEG amplitude from the raw recordings as follows. We used MATLAB R2017a (The MathWorks Inc., Natick MA, USA) and the open source EEGLab toolbox (<https://sccn.ucsd.edu/eeglab/index.php>) to sum the bandpass-filtered spectral power in the 8–13Hz and 0–4Hz ranges estimated by fast Fourier transform in 1 second epochs, then calculated the ratio of these two values and averaged in 1 minute epochs. To determine amplitude, we found second-by-second peaks in the EEG data, used to calculate a 10-second running average then down-sampled to the mean value in 1 minute epochs. We used a GLM to correlate EEG amplitude and ADR with PbtO₂, and compare these EEG parameters between care blocks. We performed all statistical analyses using Stata v14.2 (StataCorp, College Station, TX), and all reported p-values are derived from GLMs that accounted for clustering of repeated measures within animals by using robust sandwich estimators.

It was our intent to compare microdialysis measures of lactate, pyruvate, glucose and glutamate between care blocks and correlate these values with PbtO₂. Samples were

collected as described above and shipped on dry ice to the manufacturer (M Dialysis Inc, North Chelmsford, MA) for analysis. However, the presence of microbubbles after thawing resulted in erroneous readings and no interpretable results were available.

Results

Of 16 experimental animals, 10 (63%) achieved ROSC after a median of 12.4 minutes (range 10.75 to 21.5 minute). Median weight was 27.9 [IQR 26.7 – 29.5] kg and median duration from experiment start to arrest was 82 [IQR 61 – 95] minutes. Six animals were randomized to receive standard care first and 4 were randomized to receive titrated care first. During asphyxia, 10 animals' cardiac rhythms degenerated into ventricular fibrillation while the remaining 6 evolved from pulseless electrical activity to asystole. There was no difference in ROSC rates by initial arrest rhythm (6/10 with VF, 4/6 with asystole). In the peri-arrest period, we observed a consistent stress response characterized by a transient increase in MAP, cerebral blood flow and intracranial pressure as oxygen saturation, PbtO₂ and heart rate fell prior to circulatory arrest (Figure 2). Upon ROSC, hypertension and ventilation with 100% oxygen resulted in a brief but profound increase in cerebral blood flow and PbtO₂ that lasted between 20 to 40 minutes (Figure 2) after which both parameters fell below their pre-arrest baseline.

Overall, treated as a binary outcome, brain tissue hypoxia was common during usual care, and the burden of tissue hypoxia was significantly less with titrated care (44% vs 2% of the block duration spent below hypoxia threshold of 20mmHg, $P < 0.001$; 21% vs 0% below a threshold of 15mmHg, $P < 0.001$; and, 7% vs 0% below a threshold of 10mmHg, $P = 0.01$). Treated as a continuous outcome, PbtO₂ was higher during titrated care blocks than standard care blocks (unadjusted $\beta = 0.60$, 95% confidence interval (CI) 0.42 – 0.78, $P < 0.001$; adjusted for block sequence $\beta = 0.74$, 95%CI 0.17 – 1.31, $P = 0.01$) (Figure 3). Additional univariable predictors of PbtO₂ are presented in Table 1. In an adjusted model controlling for MAP, vasopressor infusions and fentanyl infusion, and block sequence, PbtO₂ remained significantly higher in titrated care blocks (adjusted $\beta = 0.75$, 95%CI 0.43 – 1.06, $P < 0.001$) (Table 2). There was moderate collinearity between MAP and care block type, but results did not substantively change when MAP was dropped from the model. There was no interaction between the duration of CPR and the effect of care block on PbtO₂.

Both with and without adjustment for anesthetic doses, PbtO₂ was associated with higher ADR (adjusted $\beta = 0.006$, 95%CI 0.003 – 0.008, $P < 0.001$) but was not with EEG amplitude ($P = 0.26$). There was a threshold in the relationship between PbtO₂ on ADR with the greatest effect at PbtO₂ values below 10mmHg. Block type itself did not independently affect ADR (0.27 [IQR 0.21 – 0.37] titrated vs 0.26 [IQR 0.20 – 0.41] standard) or EEG amplitude (128 [IQR 68 – 166] uV titrated vs 129 [80 – 164] uV standard). Treatment for shivering was needed in 36 instances, and it was associated with a significant increase in both mean PbtO₂ (40 vs 38mmHg, $P = 0.02$) and mean cerebral blood flow (44 vs 35mL/100g/min, $P = 0.03$) in the 10 minutes after treatment compared to the 10 minutes before treatment. At the same time, mean intracranial pressure was reduced (12.7 vs 13.8mmHg, $P < 0.001$). These effects were preserved whether midazolam or vecuronium was selected to

treat shivering. Mean MAP did not change after treatment of shivering (74 vs 75mmHg, $P = 0.58$), but mean oxygen saturation increased (99 vs 98%, $P = 0.03$).

Other physiological measures also differed between care types. Mean MAP during titrated care segments was higher (80 vs 74mmHg, $P = 0.004$), as was mean arterial oxygen saturation (100 vs 97%, $P = 0.005$). By contrast, mean cerebral blood flow was lower during titrated care arms (36 vs 47mL/100g/min, $P = 0.02$), while intracranial pressure did not differ (16.0 vs 14.7mmHg, $P = 0.15$). Infusion doses of epinephrine, norepinephrine, vasopressin and fluid boluses were all non-significantly higher during titrated care arms.

Discussion

Treatment strategies to reduce secondary brain injury after cardiac arrest may save lives and improve neurologic outcomes. By measuring regional oxygenation, we demonstrated in this model of opioid overdose cardiac arrest that brain tissue hypoxia is both common and treatable in the first 18 hour after ROSC through titrated cardiovascular and pulmonary management. The observation that brain tissue hypoxia is common after cardiac arrest is not new, having previously been described in both animals and observational human data.^{4, 8, 16, 17} However, in this large animal model we demonstrated that titrated care effectively reverses tissue hypoxia, and that hypoxia reversal is associated with improvement in alpha-delta ratio, a neurophysiological measure of cortical energetics and function.

Mechanisms for development of brain tissue hypoxia after acute neurological illness are likely multifactorial. Poorly perfused capillary beds resulting from increased cerebral vascular resistance, increased critical opening pressure, and areas of no-reflow may increase the diffusion distance for oxygen transit from perfused capillaries to more remote brain tissue.^{4-7, 18} Perivascular edema may further compound this problem.⁹ Titrated care resulted in significantly higher PbtO₂ and a reduced burden of brain tissue hypoxia at all thresholds examined. A fall in PbtO₂ below 20mmHg results in cerebral ischemia and metabolic crisis,^{19, 20} while oxygen tensions below 8–10mmHg result in infarction.²¹ By contrast, severe hyperoxia may also be harmful because of increased oxidative stress and ischemia-reperfusion injury.^{12, 22} Effectively balancing these competing priorities in the face of deranged cerebrovascular autoregulation,⁵⁻⁷ heterogeneity both between patients, and changes within patients over time may be unrealistic without real-time monitoring. Similar arguments have been made in the case of TBI, where titrated care based on invasive PbtO₂ monitoring dramatically reduces the burden of brain tissue hypoxia.¹⁰

While PbtO₂ and MAP were higher during titrated care blocks, cerebral blood flow was significantly lower. Physiologically, this can only result from increased cerebrovascular resistance and likely reflects preservation of the hypoxic cerebral vasodilatory response.²³ Transient cerebral hyperemia develops early after resuscitation from cardiac arrest, a phenomenon that has been linked to development of vasogenic cerebral edema after focal brain ischemia.^{24, 25} Indeed, with our approach to multimodality monitoring we were able to directly observe the severity and duration early post-arrest hyperemia and brain tissue hyperoxia (Figure 2). In the post-arrest population, development of early cerebral edema is an ominous finding.²⁶ Whether brain tissue hypoxia and resulting decreases in

cerebrovascular resistance is a modifiable contributor to hyperemia, hyperoxia-mediated ischemia reperfusion injury, or early edema formation, is an interesting direction for future investigation.

Although we did not develop our model to test the effect of shivering on cerebral physiology, we observed a substantial increase in cerebral blood flow, arterial oxygen saturation and PbtO₂, decrease in intracranial pressure, and no change in MAP when shivering was abolished. This effect was preserved whether shivering was treated through sedation or peripheral neuromuscular blockade. In humans, continuous neuromuscular blockade is associated with improved outcomes after cardiac arrest,²⁷ an effect which has been attributed to improved lung mechanics and decreased global metabolic demand. To our knowledge, the potentially beneficial effects of treating shivering on intracranial physiology has not been previously reported.

Our ability to assert that preventing brain tissue hypoxia is beneficial after cardiac arrest is limited. Because we were unable to analyze microdialysis results, we can only speculate whether treatment reduced cerebral ischemia and infarction. We did observe that ADR increased when PbtO₂ rose above 10mmHg, a neurophysiological surrogate that has been linked to cerebral metabolic crisis and ischemia.²⁸ This threshold for ischemia and infarction is well established in other patient populations, and our data support a similar physiological effect after cardiac arrest. However, care type itself was not significantly associated with ADR. This may indicate that our model generated moderate, but not severe brain injury. Indeed, PbtO₂ only fell below 10mmHg during 7% of usual care. A larger sample size or more severe brain injury might allow a direct link between care type and ADR or other neurophysiological measures.

Additional insights may come from replicating this work in other models of cardiac arrest, both in terms of etiology and severity of brain injury. Opioid agonists may have neuroprotective properties when administered prior to cardiac arrest,²⁹ and brain injury phenotypes of cardiac arrest secondary to asphyxia may differ from arrest secondary to primary cardiac pathology.³⁰ While the incidence of opioid overdose and associated cardiac arrest is increasing exponentially over time²⁹ and is certainly meritorious of translational research in its own right, neuroprotective strategies are best validated in multiple animal models before translating to human research. Moreover, in this experiment we chose a fixed duration of hypoxia before initiating CPR. It is our anecdotal observation that longer periods of untreated circulatory arrest are not compatible with reasonable rates of ROSC, but this limitation in ability to resuscitate the heart prevents induction of more severe brain injury without use of extracorporeal support or induction of selective cerebral ischemia. Our work has several other important limitations that must be considered. We overdosed animals after instrumentation and antibiotic pre-treatment, neither of which fully replicated common clinical scenarios. To avoid the potential for failed re-intubation during CPR, we occluded the endotracheal tube after overdose and neuromuscular blockade rather than extubating animals, but this may not fully reflect the pathophysiology of human overdose where a patent upper airway may allow some agonal respirations and the process of establishing an advanced airway may affect CPR delivery.³¹ Additionally, we initiated resuscitation after 9 minutes, which may be faster than is common in the out-of-hospital setting,³² and to

minimize pain to the animals did not administer naloxone. Modulating the severity and pattern of brain injury are critical next steps needed to justify future human trials. A final potential limitation is the crossover experimental design we selected. We chose this method for this pilot work to maximize statistical power by allowing each animal to effectively function as its own control. However, physiological or pharmacological effects from early care, for example alveolar or cerebrovascular recruitment, may have persisted into subsequent care blocks. These unmeasured residual effects are a potential source of bias, which can be eliminated in future work by randomizing animals to only a single type of care for the duration of the experiment.

In conclusion, we demonstrated in a large animal model that brain tissue hypoxia is common and treatable after opioid overdose and cardiac arrest. Goal-directed therapy against brain tissue hypoxia may reduce cerebral hyperemia and improve electrographic evidence of neuronal function. Our work supports this strategy as a promising area for ongoing investigation.

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Figure 1.

Overall experimental protocol

Abbreviations: ROSC – Return of spontaneous circulation; O₂ – Oxygen; MAP – Mean arterial pressure; SaO₂ – Arterial oxygen saturation; EtCO₂ – End tidal carbon dioxide; PbtO₂ – Brain tissue oxygen tension; CBF – Cerebral blood flow.

Figure 2.
Peri-arrest cardiopulmonary and neurophysiology from a single experimental protocol

Figure 3.

Raw brain oxygen measures from two experiments with alternating order of care blocks. Data from the animal randomized to titrated care first is shown in blue, while data from the animal randomized to standard care first is shown in red..

Table 1

Unadjusted predictors of brain tissue oxygenation

Predictor	β coefficient (95% CI)	P value
Titrated care (vs standard care)	0.60 (0.42 – 0.78)	<0.001
Mean arterial pressure, per mmHg	0.009 (0.002 – 0.017)	0.04
Intracranial pressure, mmHg	0.000 (–0.02 – 0.02)	0.98
Cerebral blood flow, mL/100g/min	–0.003 (–0.008 – 0.002)	0.29
Epinephrine infusion dose, mcg/kg/min	–0.82 (–1.34 – –0.29)	0.002
Norepinephrine infusion dose, mcg/kg/min	–0.37 (–0.57 – –0.18)	<0.001
Vasopressin infusion dose, U/min	–10.1 (–18.8 – –1.35)	<0.001
Propofol infusion dose, mcg/kg/min	–0.002 (–0.006 – 0.003)	0.42
Fentanyl infusion dose, mcg/hr	–0.001 (–0.002 – –0.001)	<0.001

Table 2

Adjusted predictors of brain tissue oxygenation

Predictor	β coefficient (95% CI)	P value
Titrated care (vs standard care)	0.75 (0.43 – 1.06)	<0.001
Block number (vs 1)		
2	0.27 (–0.21 – 0.74)	0.27
3	0.36 (0.03 – 0.68)	0.03
Titrated care $\times$ block sequence		
2	–0.29 (–0.87 – 0.28)	0.32
3	0.22 (–0.42 – 0.86)	0.50
Mean arterial pressure, per mmHg	0.000 (–0.004 – 0.003)	0.90
Epinephrine infusion dose, mcg/kg/min	0.27 (–0.33 – 0.87)	0.38
Norepinephrine infusion dose, mcg/kg/min	–0.12 (–0.41 – 0.18)	0.43
Vasopressin infusion dose, U/min	–3.67 (–10.29 – 2.93)	0.26
Fentanyl infusion dose, mcg/hr	–0.002 (–0.003 – –0.000)	<0.001